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# DOES ASPARTATE AMINOTRANSFERASE PLATELET RATIO INDEX PREDICT GESTATIONAL DIABETES MELLITUS? A RETROSPECTIVE COHORT STUDY

## *ASPARTAT AMİNOTRANSFERAZ TROMBOSİT ORANI İNDEKSİ GESTASYONEL DIABETES MELLITUS ÖNGÖRÜR MÜ? RETROSPEKTİF BİR KOHORT ÇALIŞMASI*

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**ABSTRACT**

**Objective:** Our aim was to determine the significance of aspartate aminotransferase platelet ratio index (APRI), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) in predicting gestational diabetes mellitus (GDM) at first trimester screening in a retrospective study of pregnant women.

**Method:** In this study, a retrospective analysis of pregnant women (n=216) screened at the antenatal clinic and diagnosed with gestational diabetes between 24-28 weeks of gestation was performed. APRI score, NLR and PLR were calculated in the blood of these pregnant women in the first trimester and compared with the results of patients in the control group (n=250).

**Results:** The ROC -analysis for APRI yielded an AUC value of 0.489 (p=0.684). Maternal age was found to be an independent risk factor for GDM. The risk increased 1.162-fold with increasing maternal age (p<0.001). The optimal cutoff value for NLR was 3.55, sensitivity was 65%, specificity was 49%, and the area under the ROC curve was 0.544.

**Conclusion:** In the results we compared with those of the control group, we found no significant change in APRI value and PLR. However, we found that NLR has a predictive value for GDM.

**Keywords:** Gestational diabetes mellitus, aspartate aminotransferase platelet ratio index, liver fibrosis, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio.

**ÖZ**

**Amaç:** Bu retrospektif çalışmada amacımız, aspartat aminotransferaz trombosit oran indeksi (APRI), nötrofil lenfosit oranı (NLR) ve trombosit lenfosit oranının (PLR) birinci trimester taramasında gestasyonel diyabeti (GDM) öngörmedeki önemini belirlemekti.

**Yöntem:** Bu çalışmada antenatal polikliniğinde taranan ve 24-28. gebelik haftaları arasında gestasyonel diyabet tanısı alan gebelerin (n=216) retrospektif analizi yapılmıştır. Bu gebelerin ilk trimesterdeki kanlarında APRI skoru, NLR ve PLR hesaplandı ve kontrol grubundaki hastaların (n=250) sonuçları ile karşılaştırıldı.

**Bulgular:** APRI için ROC analizi, 0,489'luk bir AUC değeri verdi (p=0,684). Anne yaşı GDM için bağımsız bir risk faktörü olarak bulundu. Artan anne yaşı ile risk 1,162 kat arttı (p< 0,001). NLR için optimal kesme değeri 3,55, duyarlılık %65, özgüllük %49 ve ROC eğrisinin altındaki alan 0,544 idi.

**Sonuç:** Kontrol grubu ile karşılaştırdığımız sonuçlar da APRI değeri ve PLR'de anlamlı bir değişiklik bulamadık. Ancak NLR'nin GDM için prediktif bir değere sahip olduğunu bulduk.

**Anahtar Kelimeler:** Gestasyonel diabetes mellitus, aspartat aminotransferaz trombosit oranı indeksi, karaciğer fibrozisi, nötrofil-lenfosit oranı, trombosit-lenfosit oranı.

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## Introduction

Obesity and its consequences are an important global health problem, and women of childbearing age also represent an important population.[1] Gestational diabetes mellitus (GDM) and macrosomia during pregnancy are known to be associated with subsequent obesity and adverse pregnancy outcomes.[2,3] GDM develops due to a metabolic disorder in women with normal carbohydrate metabolism before pregnancy.[3] It is known that when GDM develops during pregnancy, in addition to insulin resistance, secretion of some diabetogenic placental hormones and pancreatic dysfunction increase accordingly.[4] Some inflammatory markers known to support this process have already been studied and shown to be effective in this pathogenesis (e.g. visfatin).[4] GDM is a clinical condition that must be correctly diagnosed and monitored because it causes polyhydramnios, increased cesarean section rates, maternal complications such as preeclampsia, and other complications such as macrosomia, birth trauma, and intrauterine growth retardation.[5] The 75-g glucose test recommended by the American Diabetes Association (ADA) and the 50-g glucose test recommended by the American College of Obstetricians and Gynecologists (ACOG) are now standard.[6] The sensitivity of the 50-g glucose test, which is widely used in the diagnosis of GDM, ranges from 60% to 80%.[7] This test is used in pregnant women between 24 and 28 weeks of gestation, and in the next phase, the 100-g oral glucose tolerance test (OGTT) is used in patients whose blood glucose is 140 mg/dl or more in the first hour after sugar loading without fasting.[8,9]

The aspartate aminotransferase platelet ratio index (APRI), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are inflammatory markers used in many studies and in various fields.[10-15] They have recently gained popularity because they can be easily calculated from routine blood values and are inexpensive.[10] NLR and PLR have been used as prognostic markers in metastatic cancer, inflammatory bowel disease, and ischemic heart disease.[16] The same markers have also been used as screening tests for complications of diabetes mellitus (DM).[17] To determine the systemic inflammatory response, hematologic parameters such as NLR and PLR from blood counts have been useful to determine the presence and severity of disease in cardiovascular, oncologic, and metabolic disorders. NLR and PLR have been shown to be predictors of mortality, particularly in patients with coronary artery disease and acute coronary syndromes. Recent studies have also shown that these markers can predict pregnancy-related complications such as preeclampsia.[11] In studies performed to date, APRI has predictive value for conditions such as PE, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), and cholestasis, in which liver function is impaired.[14,15] These inflammatory markers may be indirect markers for hepatic and pancreatic insufficiency, in which gluconeogenesis occurs.

In view of this information, these markers were not studied together in the GDM group. Our objective was to determine the value of APRI, NLR, and PLR values in predicting first-trimester screening GDM in a retrospective study of pregnant women diagnosed with gestational diabetes mellitus.

## Methods

The study was approved by the board of the Health Sciences University Etlik Zubeyde Hanım Women's Health Education and Research Hospital on July 26, 2022, as number 09. Because it was a study with human participants, it complied with the principles of the Declaration of Helsinki.

In this study, participants admitted to obstetric department between 2015 and 2020. The study group included 216 patients with gestational age between 24-28 weeks and GDM as a result of glucose tolerance test. Venous plasma cutoff values for the 75 g OGTT were accepted as fasting ≥ 95 mg/dl, 1st hour ≥ 180 mg/dl, 2nd hour ≥155 mg/dl. Patients with a high value of 1 as a result of the test were diagnosed with GDM. According to Carpenter and Coustan (C&C) criteria, the cut-off values in venous plasma for the 100-g-OGTT fasting were ≥ 95 mg/dl; 1 hour ≥ 180 mg/dl; 2nd hour ≥ 155 mg/dl; 3rd hour was accepted as ≥ 140 mg/dl.18 GDM is diagnosed when there are two or more cut-off values for the 100-g-OGTT. One patient with a value above 200 was diagnosed with GDM. These patients were retrospectively analyzed, and the APRI score, NLR, and PLR were calculated using first-trimester screening blood values. There were no problems in pregnancy in 250 patients, and these patients formed the control group. The control group was selected from patients who presented to the outpatient clinic during the first two days of the month and met the inclusion criteria during the same period. Inclusion criteria were age between 18 and 40 years and singleton pregnancy. Exclusion criteria were multiple pregnancy, fetal anomalies, chronic diseases (diabetes, thyroid dysfunction, uncontrolled endocrine diseases or renal dysfunction, autoimmune diseases, chronic inflammatory diseases), intrauterine exitus, placental anomalies, pregnancy by assisted reproductive technology, active smokers.

Accordingly, 216 patients were included in the study group. The total number of patients was 466, and data were obtained from the patients' computerized medical records, which are continuously updated in real time during delivery and throughout the hospital stay. Data included various demographic, general medical, obstetric, and neonatal variables. In addition, patient data such as age, weeks of gestation, birth weight, diagnosis, operative time, transfusions, and results of swab specimen cultures were obtained from medical records.

Venous blood samples from patients were collected into tubes containing ethylenediaminetetraacetic acid (EDTA) after admission. Blood samples were centrifuged at 1500

g/min for 10 minutes and analyzed using the automated hematology instrument (Mindray BC-6000) available in our laboratory.

The Statistical Package (SPSS 23.0, Inc. Chicago, IL, USA) was used to analyze the data. Receiver operating characteristic curve analysis (ROC) was used to determine the optimal cut-off value for the independent markers, and sensitivity and specificity were calculated. Data were expressed as arithmetic mean, standard deviation, median, and minimum-maximum values. For normally distributed data, the independent-samples t test was used, and for nonnormally distributed variables, the Mann Whitney U test was used. For analysis of categorical variables, the chi-square test or the Fisher extract test was used.

In the study, a p value of less than 0.05 was considered statistically significant.

## Results

In the study, 216 patients with gestational diabetes mellitus and 250 pregnant women in the control group were observed. The demographic characteristics of these patients are shown in Table 1. The mean age of the patients included in the study was 30.07± 5.54 years, and the body mass index was 30.93±3.44 kg/m2. The NLR value was higher in the study group (3.65±1.17) than in the control group (p=0.001). However, this difference could not be statistically demonstrated for APRI and PLR values.

**Table 1.** Clinical characteristics of patients and control group

| | Control Group (n: 250) mean±SD | Study Population (n: 216) mean±SD | p |
|---|---|---|---|
| **Age (years)** | 27.93±5.80 | 32.22±5.28 | **<0.001** |
| **BMI (kg/m²)** | 31.08±3.62 | 30.78±3.27 | 0.335 |
| **Birth weeks (weeks)** | 38.3±0.09 | 39.2±0.07 | **<0.001** |
| **Birth weight (gram)** | 3291.25±33.25 | 3251.17±30.15 | 0.117 |
| **White Blood cell (cells/mL)** | 8362.32±2158.40 | 8375.80±2149.78 | 0.946 |
| **Platelet (cells/µL)** | 258.444±56.61 | 266.580±64.28 | 0.147 |
| **APRI** | 0.168±0.108 | 0.170±0.176 | 0.923 |
| **PLR** | 161.54±61.30 | 160.62±63.11 | 0.873 |
| **NLR** | 3.30±1.05 | 3.65±1.17 | **0.001** |

SD: Standard deviation, BMI: Body mass index, APRI: Aspartate aminotransferase platelet ratio index, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio

In the ROC analysis for APRI, the AUC value was 0.489 (p=0.684). In univariate analysis, only maternal age was found to be an independent risk factor. Increasing maternal age increased the risk of a positive diagnosis by 1.144-fold (p<0.001). APRI and BMI were not found to be independent risk factors in multivariate analysis (p values 0.484 and 0.609, respectively). The risk increases 1.162-fold with increasing maternal age (p<0.001), (Table 2). The optimal cutoff value for NLR was 3.55, sensitivity 65%, specificity 49%, and area under the receiver operating characteristic curve 0.544 (Table 3, Figure 1).

**Table 2.** Multiple logistic regression analysis between the control and study groups

| | | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|
| | Control (n=250) | Study (n=217) | OR (95% CI) | p | OR (95% CI) | p |
| **APRI** | 0.169±0.108 | 0.17±0.177 | 1.064 (0.301-3.761) | 0.923 | 1.62 (0.419-6.261) | 0.484 |
| **BMI** | 31.08±3.629 | 30.78±3.275 | 0.975 (0.925-1.028) | 0.350 | 0.985 (0.93-1.044) | 0.609 |
| **Maternal Age** | 27.93±5.801 | 32.22±5.289 | 1.144 (1.104-1.186) | **<0.001** | 1.162 (1.114-1.212) | **<0.001** |

**Table 3.** ROC result between control and GDM groups

| | Cut-off | AUC (95% CI) | Sensitivity | Specificity | p |
|---|---|---|---|---|---|
| **NLR** | 3.55 | 0.544 (0.512-0.575) | 65 | 49 | **0.007*** |

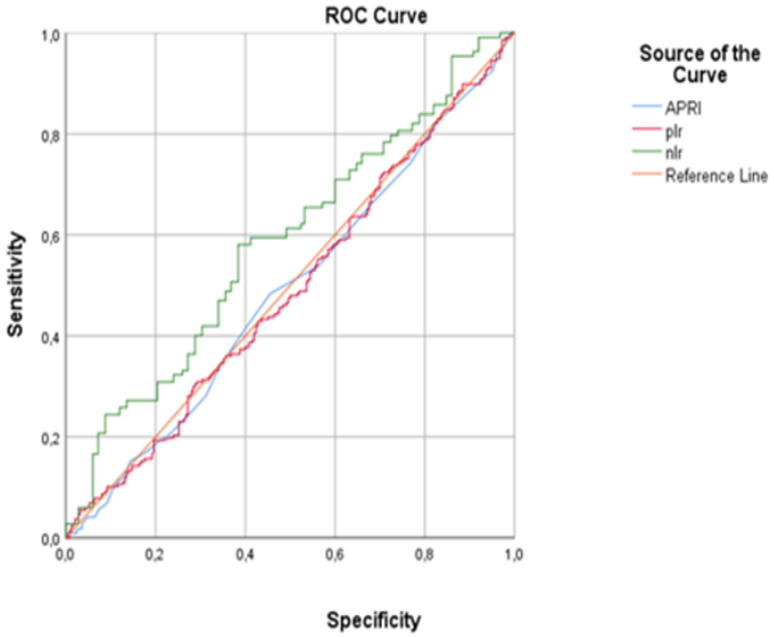


**Figure 1.** ROC analysis for APRI, PLR, NLR in GDM

## Discussion

In this study, we retrospectively evaluated patients diagnosed with GDM in our hospital and investigated whether the APRI score, PLR score, and NLR score predict this condition in the context of first-trimester screening. In the results we compared with the control group, we found no significant change for the APRI score and the PLR score. However, we found that the NLR score measured in the first weeks was predictive of future GDM.

Complete blood count, renal and liver function tests: these are routine, readily available, automated and inexpensive tests. When used for early diagnosis, prediction, or prognostic monitoring of disease, these parameters are of great importance to clinicians because they allow easy access and use of the test. During the literature search on PLR and NLR, it was found that there are many studies and many different results. Adipose tissue plays an important role in glucose and lipid metabolism.[19] The proliferation of this tissue triggers inflammatory cytokines that lead to obesity ( DM, PE).[19] In one study, it was found that the value tested in the first trimester that is important for predicting GDM is the leukocyte count.[20] In another study, a leukocyte count above 15,000 in the second trimester blood count was found to be important in predicting GDM.[21] In a study that examined PE, it was found that NLR was higher and PLR was lower in blood parameters measured in the last trimester than in the control group.[22] One study highlighted that NLR and PLR parameters were not sufficient to predict preeclampsia.[23] In the study conducted by Sargın et al, NLR and PLR were found to be inadequate for predicting GDM.[24] In our study, NLR was found to be the only independent variable suitable for predicting GDM in blood parameters measured in the first trimester.

Literature search did not find any study that investigated the association between gestational diabetes and APRI. However, the APRI score is considered a promising parameter, especially in pregnancy-related conditions such as HEELP syndrome and cholestasis, in which liver functions are impaired.[25] In a 2020 retrospective study by Şaşmaz et al, a multivariate regression analysis between study groups with HELLP syndrome (n=40) and normotensive patients (n=124) concluded that APRI score predicted HELLP syndrome better than AST alone.[15] In the ROC curve, the sensitivity of AST was 71.1% and the specificity was 91.2% to discriminate HELLP patients from the control group.[15] When the cut-off value of APRI score in the study was set at 0.339, the sensitivity was 82.6% and specificity was 87.6%. It is suggested that there is an association between diabetes mellitus and liver dysfunction. However, liver biopsy, an invasive procedure, is the method that best detects deterioration of liver function in the general population.[26] Therefore, there is great interest in introducing approved noninvasive fibrosis markers into clinical practice. A population-based study that demonstrated the association between type 2 DM and liver fibrosis showed a weak correlation with APRI.[27] However, there is a stronger association between overweight and obese diabetics and APRI.[27] On the other hand, many complications due to liver dysfunction occur in macrosomic infants who develop due to GDM. For this reason, the association between maternal APRI blood level at the beginning of pregnancy and macrosomia might be stronger. However, in our study, this difference between the study group and the control group could not be clearly demonstrated because treatment for GDM was started at the time of diagnosis.

The main limitation of this study is the small sample size and retrospective design. In addition, the sample size had to be kept smaller in this study because we had to use the pre-pandemic values COVID -19 and it was not known

whether the pandemic would affect the complete blood count and liver function parameters. Now that the effects of the pandemic are diminishing, it is appropriate to conduct prospective studies on this topic.

## Conclusion

This study explores the association between APRI and GDM. Although the association has not been fully proven, more extensive studies are needed to examine the complications associated with GDM. APRI score, thanks to its ability to detect early; it is considered a promising marker because it can reduce mortality and morbidity in pregnant women. NLR score is a parameter that can be used to predict GDM, according to the literature. Our findings pave the way for randomized, controlled, prospective studies with larger numbers of cases.

**Compliance with Ethical Standards**

This study followed the Declaration of Helsinki on human-subject research. The present study was approved by the Ethics Committee for Ankara Etlik Zubeyde Hanim Women's Health Training and Research Hospital on July, 2022, with approval number 09.

**Conflict of Interest**

The authors declare no conflicts of interest.

**Author Contribution**

MCI, HNO, CI: Study idea, hypothesis, study design; BS: Material preparation, data collection and analysis; MCI: Writing the first draft of the article; YEU: Critical review of the article finalization and publication process.

**Financial Disclosure**

None.

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