Obstetrics; *Maternal Fetal Medicine and Perinatology*

The Role of Aspartate Aminotransferase/Platelet Ratio Index Score in Predicting Intrahepatic Cholestasis of Pregnancy and its Relationship with Total Bile Acid Level: A Case-Control Study from a Tertiary Center

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ABSTRACT

OBJECTIVES: The aim of this study is to examine the value of the first-trimester aspartate aminotransferase to platelet ratio index (APRI) score in predicting intrahepatic cholestasis of pregnancy (ICP) occurring later in pregnancy. Another aim of the study is to determine the relationship between APRI scores and total bile acid (TBA) levels in pregnant women with ICP.

STUDY DESIGN: This retrospective case-control study was conducted by examining the hospital records of women diagnosed with ICP (n = 66) and healthy controls (n = 70) among women followed during pregnancy. Hemoglobin (Hb), platelet count (PLT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) values of all patients were obtained from routine blood test data taken in the first and third trimesters. The first and third-trimester APRI scores of the patients were calculated. Demographic data, laboratory findings, and APRI scores of women with and without ICP during pregnancy were compared. Using Roc analysis, the values of AST, ALT, PLT values, and APRI scores were examined in predicting ICP among the first trimester findings of the patients. In addition, TBA levels of patients with ICP at the time of diagnosis were obtained from hospital records. The relationship between the first and third-trimester APRI scores and TBA levels in patients with ICP was evaluated using correlation analysis.

RESULTS: In the first and third-trimester laboratory values, AST and ALT levels and APRI scores were found to be higher and PLT values were lower in patients with ICP compared to healthy controls. Among the first trimester measurements of these data, the APRI score had the highest predictive value in predicting ICP (AUC values are 0.648 for AST, 0.655 for ALT, 0.633 for PLT, and 0.705 for APRI). In an examination of patients with ICP, the APRI score calculated in the first and third trimesters showed a positive correlation with the TBA level at diagnosis ($r = 0.435$ $p < 0.001$ for the first trimester and $r = 0.433$ $p < 0.001$ for the third trimester in the Spearman analysis).

CONCLUSIONS: In the future, the APRI score calculated in the first trimester of pregnancy may be used as a tool to predict ICP that may occur in the following weeks. There may be a positive correlation between APRI score and serum TBA level in patients with ICP.

Keywords: Alanine transaminase; Aspartate aminotransferase to platelet ratio index; Aspartate aminotransferase; Intrahepatic cholestasis of pregnancy; Platelet; Total bile acid level

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disease characterized by pruritus, high bile acid level, and increased liver transaminases, usually in the late second trimester and third trimester. Although ICP can cause very serious perinatal complications, it usually resolves spontaneously within a few weeks after birth (1,2).

ICP increases the risk of many perinatal complications, including premature birth, intrauterine asphyxia, meconium staining of amniotic fluid, hemorrhages in the fetal central ner-

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vous system, fetal bradycardia, fetal distress, and fetal loss (1-4). In particular, total bile acid (TBA) concentration above 40 μmol / L indicates an increased risk of fetal complications in ICP (3,4). In pregnancies complicated with ICP, the risk of stillbirth increases when the serum TBA concentration is 100 μmol / L and above (5). The most common pharmacological treatment for ICP is the administration of ursodeoxycholic acid to lower bile acid levels and reduce maternal pruritus. However, if treatment fails, premature birth should be considered (4). Finding markers that can predict ICP in the first trimester, which carries serious perinatal risks and is generally detected in the third trimester, can reduce perinatal risks by close follow-up of the pregnant woman and timely initiation of treatment for ICP.

TBA level is considered the gold standard for the diagnosis and severity of ICP. However, it may not be easy to measure TBA levels in developing countries (3). Simpler laboratory parameters than TBA may be needed to predict and diagnose ICP and assess its severity.

The aspartate aminotransferase to platelet ratio index (APRI) score is one of the non-invasive tests thought to indicate liver damage and is calculated using blood tests (1-3,5,6,9). To date, several studies have been conducted in the field of obstetrics evaluating the relationship between APRI score and chronic liver disease in pregnancy (7,8), ICP (1-3,9), and HELLP syndrome (10).

Liver biopsy in women with ICP shows centrilobular cholestasis without inflammation and bile plugs without dilatation or injury to hepatocytes and canaliculi. In light of these pathological findings, ICP is a reversible liver disease (1). APRI score has been shown to be associated with liver fibrosis (5,6,11). In pregnant women with ICP, there may be a condition that does not manifest itself as macroscopic and microscopic fibrosis in the liver during pathological examination but is seen as molecular changes (2). These molecular changes may be associated with an increase in APRI scores.

The main purpose of this study was to examine the value of the first-trimester APRI score calculated with the help of routine blood tests in predicting ICP occurring in the later stages of pregnancy. We also aimed to evaluate whether the APRI score has a place in the diagnosis of ICP and the relationship between the APRI score and TBA level in pregnant women with ICP. In this context, we planned to compare the first and third-trimester APRI scores of pregnant women with ICP and healthy pregnant women and to examine whether there is a relationship between the first and third-trimester APRI scores of women with ICP and the TBA levels at the time of diagnosis.

Material and Method

This case-control study was conducted by examining the hospital records of women diagnosed with ICP and healthy controls among the women followed during pregnancy in the gynecology and obstetrics outpatient clinic between 2022 and 2023. The study was conducted in accordance with the principles stated in the Declaration of Helsinki and was approved by the Kocaeli City Hospital Scientific Research Ethics Committee (protocol number: 2023 - 43).

Women between the ages of 18 and 45, whose pregnancies were followed from the first trimester and who were or were not diagnosed with ICP during pregnancy follow-up were included in the study. Patients with multiple pregnancies, liver or biliary tract disease, diabetic disease, positive hepatitis A, B, or C serology, known dermatological disorders, hematological diseases, preeclampsia or HELLP syndrome, patients diagnosed with gestational thrombocytopenia and insufficient hospital records were excluded from the study.

A total of 66 cases diagnosed with ICP formed the study group (n = 66), and 70 cases with completely normal pregnancy follow-up without cholestasis or any other disease formed the control group (n = 70). ICP was diagnosed according to the following criteria: [1] pruritus localized predominantly on the hands and feet; [2] abnormalities in liver function tests suggestive of ICP; [3] high fasting serum bile acid levels above 10 mmol / L; [4] absence of skin lesions caused by systemic diseases that may cause itching; and [5] spontaneous resolution of clinical symptoms and laboratory findings after birth (2,13). All patients diagnosed with ICP included in the study were treated with ursodeoxycholic acid.

Demographic data including age, gravida, and parity of all patients included in the study were obtained from data records. In addition, hemoglobin (Hb), platelet count (PLT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) values were obtained from routine blood test data taken in the first trimester and third trimester. The first and third-trimester aspartate aminotransferase to platelet ratio index (APRI) scores of the patients were calculated. APRI scores were calculated using the formula: “[(AST / upper limit of normal) / platelet count (109L -1) × 100]” (2,5). The normal upper limit for AST was considered to be 40 U / L, as many studies have suggested that the upper limit of normal for both ALT and AST levels is 40 U / L (12).

Demographic data, laboratory findings, and APRI scores of women who had and did not have ICP during pregnancy were compared. Using Roc analysis, the values of AST, ALT, PLT values, and APRI scores among the patients' first trimester findings in predicting ICP were examined. In addition, TBA levels at the time of diagnosis (before ursodeoxycholic acid treatment) of patients who had ICP were also obtained from hospital records. Whether there was a relationship between first and third-trimester APRI scores and TBA levels in patients with ICP was evaluated by correlation analysis.

Statistical Package for the Social Sciences (SPSS) Version 20.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Whether the variables showed normal distribution was evaluated using the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Numerical variables with a normal distribution were expressed as mean ± standard deviation, while numerical variables without a normal distribution were expressed as median (interquartile range). The difference between the groups was determined by the student-t test for numerical variables with normal distribution, and by the Mann-Whitney U test for numerical variables without normal distribution. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive performance of AST, ALT, PLT values, and APRI scores in the first trimester of the development of ICP. The Youden index was used to determine optimum cutoff values. Spearman's rank correlation was used to assess the relationship between quantitative variables. For two-sided hypotheses, $p < 0.05$ was considered significant.

Results

Data from 66 patients with ICP and 70 controls were evaluated. The demographic and clinical characteristics of the groups are shown in Table I and necessary comparisons were made. No significant difference was observed between patients with ICP and the control group in terms of age, gravida, and first and third-trimester hemoglobin values ($p > 0.05$, for all). It was observed that AST and ALT levels, as well as APRI scores, were higher, while PLT values were lower in patients with ICP in the first and third trimesters compared to controls ($p < 0.05$, for all). In addition, the mean TBA level of patients with ICP at the time of diagnosis was calculated as 41.55 μmol / L as shown in Table I.

The effectiveness of the patients' first trimester AST, ALT, PLT values, and APRI scores in predicting ICP was examined with the help of ROC analysis and shown in Table II. In this evaluation, the area under the curve (AUC) values were calculated as follows: 0.648 for AST, 0.655 for ALT, 0.633 for PLT, and 0.705 for APRI scores. In other words, it was determined that the first-trimester APRI score had the highest predictive value among these values in predicting ICP. The Youden index was used to determine the optimum cut-off values of these values in the diagnosis of ICP, and the optimum cut-off points are shown in Table II. Accordingly, the optimum cut-off value for the first-trimester APRI score in ICP prediction was determined as 0.212 with 55% sensitivity and 81% specificity. In addition, for the evaluation of first-trimester laboratory data in ICP prediction, the ROC curves of AST and ALT values and APRI scores are shown in Figure 1, and the ROC curve of PLT value is shown in Figure 2.

Table I: *The demographic and clinical characteristics of the groups*

	ICP (n = 66)	Control (n = 70)	p
Age	27.98 ± 5.12	29.49 ± 5.04	0.087[a]
Gravida	1 (2)	2 (2)	0.067[b]
1st Hb (g/dL)	12.08 ± 1.18	12.07 ± 1.24	0.954[a]
1st AST (IU/L)	19 (9)	16 (5)	**0.003**[b*]
1st ALT (IU/L)	18 (19)	13 (6)	**0.002**[b*]
1st PLT (10^3/uL)	232.71 ± 80.39	263.70 ± 61.09	**0.013**[a*]
1st APRI score	0.236 (0.19)	0.162 (0.07)	**< 0.001**[b*]
3rd Hb (g/dL)	11.59 ± 1.18	11.68 ± 1.01	0.626[a]
3rd AST (IU/L)	64.50 (57)	18.80 (6)	**< 0.001**[b*]
3rd ALT (IU/L)	70.5 (82)	13 (8)	**< 0.001**[b*]
3rd PLT(10^3/uL)	229.35 ± 66.75	261.66 ± 62.92	**0.004**[a*]
3rd APRI score	0.687 (0.87)	0.188 (0.13)	**< 0.001**[b*]
3rd Fasting TBA (μmol/L)	41.55 ± 35.04 // 30.50 (39.6)		

*Variables are given as mean ± standard deviation and median (interquartile range). a: Student t test, b: Mann Whitney U test, * signifies statistical significance. Abbreviations: ICP, intrahepatic cholestasis of pregnancy; SD, standard deviation; IQR, interquartile range; 1st, first trimester; 3rd, third trimester; Hb; hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet; APRI, aspartate aminotransferase to platelet ratio index; TBA; total bile acid*

Table II: *ROC analysis to evaluate the effectiveness of patients' first trimester AST, ALT, PLT values, and APRI scores in predicting ICP*

	AUC (95% CI)	Cutoff value	Specificity, %	Sensitivity, %	p
1st APRI score	0.705 (0.618 - 0.793)	≥ 0.212	55	81	< 0.001
1st AST (IU / L)	0.648 (0.555 - 0.741)	≥ 19.50	49	79	0.003
1st ALT (IU / L)	0.655 (0.561 - 0.750)	≥ 19.50	46	85	0.002
1st PLT (10^3 / uL)	0.633 (0.539 - 0.728)	≤ 220.00	46	80	0.007

AUC: Area under the curve; CI: Confidence interval; APRI: Aspartate aminotransferase to platelet ratio index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PLT: Platelet; ROC: Receiver operating characteristic; ICP: Intrahepatic cholestasis of pregnancy

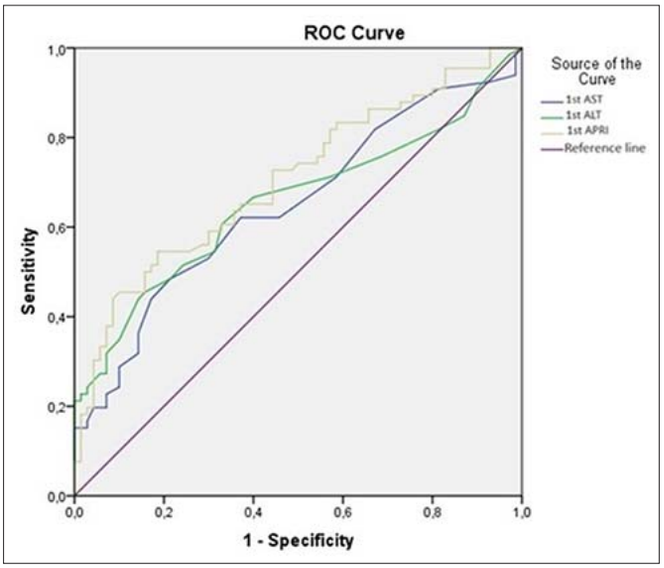

Figure 1: *ROC curves of AST and ALT values and APRI score in the first trimester for ICP prediction*

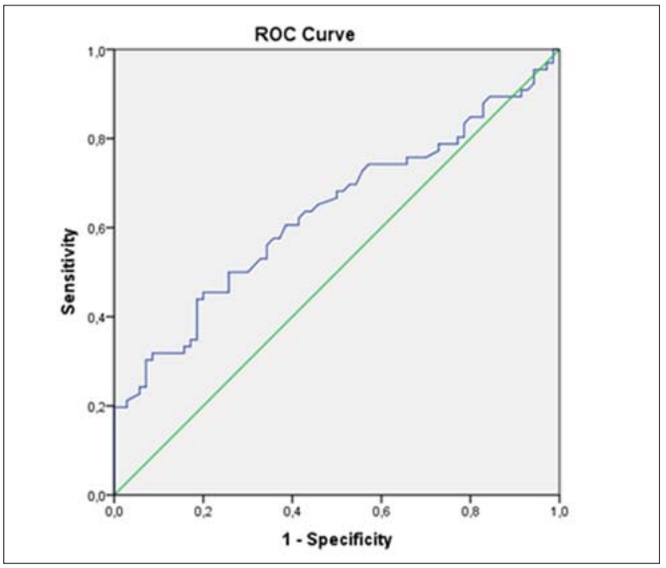

Figure 2: *ROC curve of PLT value in the first trimester for ICP prediction*

Table III examines whether there is a relationship between TBA levels at diagnosis and first and third-trimester APRI scores in patients with ICP. It was observed that there were moderate positive correlations between APRI scores calculated in the first and third trimesters and the TBA level at diagnosis. Using Spearman correlation analysis, the relationship between the first-trimester APRI score and TBA was calculated as $r = 0.435$ and $p < 0.001$, while the third-trimester APRI score showed a similar correlation with TBA ($r = 0.433$, $p < 0.001$).

Table III: *Examining whether there is a relationship between TBA levels at diagnosis and first and third-trimester APRI scores in patients with ICP with the help of Spearman correlation analysis*

	r	p
1st APRI score-3rd Fasting TBA	0.435**	< 0.001
3rd APRI score-3rd Fasting TBA	0.433**	< 0.001

ICP: Intrahepatic cholestasis of pregnancy. APRI: Aspartate aminotransferase to platelet ratio index. TBA: Total bile acid

Discussion

ICP is a pregnancy-specific liver disease associated with pruritus and high total bile acid (TBA) levels that are usually detected in the third trimester of pregnancy, leading to adverse neonatal outcomes (13). In general, the cut-off point for the total concentration of serum TBA for the diagnosis of ICP is considered to be 10 µmol / L. Serum TBA concentration exceeding this value is significant for the diagnosis of ICP. As the TBA level in maternal serum increases, the risk of harmful effects of ICP on the fetus increases (4). It has been observed that pregnancies with maternal serum TBA concentrations of 40 µmol / L or more are more likely to be complicated by spontaneous preterm birth, meconium-stained amniotic fluid, and fetal asphyxia (14). In addition, it has been shown that the risk of stillbirth increases in pregnancies where the maternal serum TBA concentration is 100 µmol / L (4,15). Early diagnosis and monitoring of ICP may help reduce ICP-related complications. For this purpose, some studies have been conducted to identify biomarkers that can predict ICP, which is generally diagnosed in the third trimester of pregnancy, at an early stage. The study conducted by Hançerlioğulları et al. (16) in 2015 and the study conducted by Tayyar et al. (17) in 2018 showed that the decrease in the first-trimester PAPP-A value indicates an increase in the risk of ICP development. Unlike these two studies, in the study published by Aksan et al. (18) in 2016, no significant difference was found between the maternal serum PAPP-A MoM levels of the ICP group and the healthy control group. In their study evaluating the relationship between maternal lipid levels and pregnancy complications, Zhang et al. (19) observed that total cholesterol levels of patients with ICP were higher than other patients, starting from the first trimester of pregnancy. More studies are needed to investigate biomarkers that can predict ICP during the first trimester of pregnancy. Additionally, identifying biomarkers that may be associated with high TBA levels, severe ICP, or poor perinatal outcomes in ICP may also help prevent pregnancy complications due to ICP.

Recently, researchers have begun evaluating the relationship between APRI scores, a simple and noninvasive test based on routine blood tests, and liver diseases seen during pregnancy (1-3,7-10). Şaşmaz et al. (10) found in their study that the APRI scores predicted HELLP syndrome more strongly than AST alone. In the last few years, studies evaluating the relationship between APRI scores and ICP have begun to be conducted (1-3,9). In our study, we aimed to determine the value of the APRI score measured in the first trimester in predicting ICP. We found that AST, ALT levels, and APRI scores were higher, while PLT values were lower in the first-trimester laboratory values in patients with ICP compared to healthy con-

trols. Among these values, we found that the first-trimester APRI scores had the highest predictive value in predicting ICP. Additionally, we evaluated the relationship between TBA level at the time of ICP diagnosis and first-trimester and third-trimester APRI scores. We found that the APRI scores in both trimesters were positively correlated with the TBA level. It is generally thought that as the TBA level increases, the severity of ICP also increases (4,14,15). In light of this situation, we believe that there may be a positive correlation between the APRI scores and the severity of ICP, depending on the positive correlation we found between the APRI scores and TBA level. However, to reach a clearer decision on this issue, we needed to examine the relationship between APRI scores and poor perinatal outcomes associated with ICP.

There are two important studies in the literature, one by Tolunay et al. (1) and the other by Gok et al. (2), investigating the role of the first-trimester APRI scores in ICP prediction. In their pilot study with 103 pregnant women in 2021, Tolunay and colleagues compared the first-trimester APRI scores of the study group of 37 pregnant women with ICP and a control group of 66 healthy pregnant women. In the study by Tolunay et al., the first-trimester APRI scores of patients with ICP were significantly higher compared to controls, and a significant positive relationship was detected between the first-trimester APRI scores and the third-trimester fasting TBA level (1). In the study conducted by Gok et al. with 111 patients in 2023, the effectiveness of AST, ALT, and PLT values measured in the first trimester, as well as the first-trimester APRI scores, in predicting ICP were investigated. In this study, the first-trimester APRI scores and AST and ALT values in patients with ICP were found to be statistically significantly higher than the control group. In addition, first-trimester PLT values in patients with ICP were found to be statistically significantly lower than in the control group. It was determined that the development of ICP could be predicted by the first-trimester APRI scores, AST, ALT, and PLT levels. Among these values, the first-trimester APRI scores were observed to have the highest predictive value (2). In our study, similar to the findings of Tolunay et al. (1) and Gok et al. (2), we observed that first-trimester APRI scores can predict ICP. Additionally, as noted in Gok et al.'s studies, increases in AST and ALT levels, along with decreases in PLT, are also predictive of ICP, with the APRI scores demonstrating the highest predictive value among these factors. As in the studies of Tolunay et al., we found a positive correlation between the first-trimester APRI scores and the third-trimester TBA level. In addition, we found a positive correlation between the third-trimester APRI scores and the third-trimester TBA level. We believe that the APRI scores may be related to the severity of ICP, as the TBA level in maternal serum also may be associated with the harmful effects of ICP.

In recent years, two important studies have examined the relationship between the APRI scores, ICP severity, and neonatal outcomes of ICP (3,9). In a study published in 2021 by Eyisoy et al., the APRI scores of 72 patients with mild ICP and 29 patients with severe ICP were compared (3). Those with TBA levels below 40 μmol / L were considered mild ICP, and those above 40 μmol / L were considered severe ICP. It was found that APRI scores, as well as AST, ALT, and total bilirubin levels, were higher in the severe ICP group. No significant difference was detected in PLT values between the two groups. ROC curve analysis determined the APRI score cut-off value for distinguishing mild from severe ICP. The optimal APRI cut-off value for distinguishing severe from mild ICP was 1.06, with 82% sensitivity and 72% specificity. In the study, a significant, moderately positive correlation was detected between the fasting TBA level and the APRI score at the time of diagnosis in patients with ICP. In this study by Eyisoy et al., 101 ICP patients were classified based on the APRI cut-off value of 1.06 (APRI < 1.06 n = 56 and APRI ≥ 1.06 n = 45). Patients with an APRI score of 1.06 or higher had a lower gestational age at birth than patients with an APRI score of less than 1.06. The presence of meconium-stained amniotic fluid, preterm birth, and NICU admission rates was higher in patients with APRI scores of 1.06 and above than in patients with APRI scores below 1.06 (3). In the study by Peker et al., published in 2023, APRI scores from 198 patients diagnosed with ICP and 204 healthy pregnant women were compared across the first, second, and third trimesters (9). APRI scores were significantly higher in the ICP group in all trimesters. The ICP group was divided into those with and without composite adverse outcomes. The group with at least one complication - such as fetal growth restriction, amniotic fluid disorders (oligohydramnios and polyhydramnios), premature birth (spontaneous), premature rupture of membranes, or meconium-stained amniotic fluid-was considered to have composite adverse outcomes. APRI scores in all three trimesters were higher in patients with ICP with composite adverse outcomes than in those without. In addition, in the study by Peker et al., the ICP group was divided into two subgroups according to serum TBA levels at diagnosis: mild ICP group (serum TBA level < 40 μmol / L) and severe ICP group (serum TBA level ≥ 40 μmol / L). APRI scores in the first, second, and third trimesters did not differ significantly between these two subgroups. In other words, in Peker et al.'s study, no correlation was documented between APRI scores and serum TBA levels. There was also no statistical difference in composite adverse outcomes between the mild and severe ICP groups. Peker et al. speculated that this may be due to the compounding adverse outcomes seen in cases with low serum TBA levels. They stated that serum TBA levels alone may not be sufficient to predict ICP prognosis and that additional predictors of prognosis should be investigated (9). In our study, similar to the study of Peker et al., APRI scores were observed to be higher in patients with ICP compared to the control group in both the first and third trimesters. A significant difference between our study and Peker et al. was that we ob-

served a positive correlation between first and third-trimester APRI scores and TBA levels at diagnosis in patients with ICP. It is known that poor perinatal outcomes in ICP are associated with elevated TBA levels. Although we did not examine the relationship between APRI score and poor perinatal outcomes in our study, we think that a high APRI score may be associated with poor perinatal outcomes due to the correlation between the APRI score and TBA level we found. The relationship between high APRI scores and poor perinatal outcomes was shown in both the study of Eyüboğlu et al. (3) and the study of Peker et al. (9).

To our knowledge, our study is one of the first to examine the relationship between APRI scores in different trimesters and ICP development and TBA levels. This situation reveals the strength of our study. As in a few studies conducted to date, the APRI score was valuable in predicting ICP in our study. However, there are differences between the findings of the studies in the literature to date in terms of the relationship between the APRI score and TBA levels. TBA levels are thought to be related to the severity of ICP. We found that the APRI score in the first and third trimesters correlated with TBA levels at the time of diagnosis. Therefore, the results of our study in this respect raise the question of whether the APRI score is meaningful in assessing the severity of ICP and predicting severe ICP. Further studies with larger populations are needed to evaluate the relationships among APRI scores, TBA levels, ICP severity, and perinatal outcomes.

The limitations of our study are the retrospective nature of the study, the small sample size, and the fact that the relationship between poor perinatal outcomes of ICP and the APRI score was not examined.

Conclusion

In conclusion, we found that AST, ALT levels, and APRI scores were higher, while PLT values were lower in the first-trimester laboratory values of patients with ICP compared to healthy controls. Among these values, the first-trimester APRI scores were found to have the highest predictive value for ICP. The take-home message from our study is that the first-trimester APRI score is valuable in predicting ICP. In the future, the APRI score from the first trimester may serve as a tool to predict ICP in the subsequent weeks. Additionally, this study found that there was a positive correlation between TBA levels at diagnosis and first and third-trimester APRI scores in patients with ICP.

Declarations

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Ethics approval and consent to participate: All participants signed consent for the use of their data before inclusion in this retrospective study. The study was conducted in accordance with the principles stated in the Declaration of Helsinki and was approved by the Kocaeli City Hospital Scientific Research Ethics Committee (protocol number: 2023-43).

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests. Authors' contributions: Concept: MD., Design: MD., Data Collection or Processing: ES., Analysis, and Interpretation: MD., ES., Literature Search: MD., ES., Writing: MD., ES., Critical Review: MD. All authors read and approved the final manuscript.

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