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Original Article / Orijinal Araştırma

Comparison of the Predictive Role of First Trimester APRI Score and De-Ritis Ratio in Intrahepatic Cholestasis of Pregnancy

Gebeliğin İntrahepatik Kolestazında Birinci Trimester APRI Skoru ve De-Ritis Oranının Prediktif Rolünün Karşılaştırılması

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Abstract

Aim: The APRI score and De Ritis ratio is associated with liver diseases. There is limited data in the literature on the predictive role of these markers in intrahepatic cholestasis of pregnancy. This study aimed to evaluate and compare the predictive role of first trimester APRI and De Ritis scores for intrahepatic cholestasis of pregnancy.

Material and Method: A total of 60 intrahepatic cholestasis of pregnancy and 60 healthy pregnant were included in this retrospective study. Demographic features, first trimester aminotransferases, complete blood count levels, fasting bile acid levels, coagulation tests, birth outcomes were recorded and compared between groups. Receiver operating curve was used to determine the predictive role of APRI and De-Ritis score for intrahepatic cholestasis of pregnancy.

Results: APRI score was significantly higher (p=0.017) whereas De-Ritis ratio was lower (p=0.002) in intrahepatic cholestasis group. Fasting bile acid was found to be positively correlated with APRI score (r=0.868, p<0.001). There was a weak positive correlation between APRI score and De Ritis ratio (r=0.219, p=0.016). APRI score >0.42 predicted intrahepatic cholestasis with 36.67% sensitivity and 98.33% specificity (AUC=0.626, p=0.016). De Ritis ratio ≤1.3 predicted intrahepatic cholestasis with 83.33% sensitivity and 51.67% specificity (AUC=0.664, p=0.001). No significant difference was found between two index for predicting intrahepatic cholestasis (p=0.065).

Conclusion: The first trimester APRI and De Ritis scores, which are cheap and easily available, can be used to predict intrahepatic cholestasis of pregnancy. Considering that there is no superiority between two markers, we suggest that both can be used for prediction.

Keywords: APRI score, De Ritis ratio, intrahepatic cholestasis of pregnancy

Öz

Amaç: APRI skoru ve De Ritis oranı karaciğer hastalıklarıyla ilişkilidir. Literatürde bu belirteçlerin gebeliğin intrahepatik kolestazındaki öngörücü rolü hakkında sınırlı veri bulunmaktadır. Bu çalışmada, gebeliğin intrahepatik kolestazındaki birinci trimester APRI ve De Ritis skorlarının öngörücü rolünü değerlendirmeyi ve karşılaştırmayı amaçladık.

Gereç ve Yöntem: Retrospektif çalışmamıza toplam 60 intrahepatik gebelik kolestazı ve 60 sağlıklı gebe dahil edildi. Demografik özellikler, ilk trimester aminotransferazları, tam kan sayımı düzeyleri, açlık safra asidi düzeyleri, pıhtılaşma testleri, doğum sonuçları kaydedildi ve gruplar arasında karşılaştırıldı. Receiver operating curve analizi, APRI ve De-Ritis skorunun intrahepatik gebelik kolestazı için öngörücü rolünü belirlemek için kullanıldı.

Bulgular: APRI skoru intrahepatik kolestaz grubunda anlamlı olarak daha yüksek (p=0,017) iken De-Ritis oranı daha düşüktü (p=0,002). Açlık safra asidinin APRI skoru ile pozitif korelasyon gösterdiği bulundu (r=0,868, p<0,001). APRI skoru ile De Ritis oranı arasında zayıf pozitif korelasyon vardı (r=0,219, p=0,016). APRI skoru >0,42, %36,67 duyarlılık ve %98,33 özgüllükle intrahepatik kolestazı öngördü (AUC=0,626, p=0,016). De Ritis oranı ≤1,3, %83,33 duyarlılık ve %51,67 özgüllükle intrahepatik kolestazı öngördü (AUC=0,664, p=0,001). İntrahepatik kolestazı öngörmede iki indeks arasında anlamlı fark bulunmadı (p=0,065).

Sonuç: Ucuz ve kolay hesaplanabilen ilk trimester APRI ve De Ritis skorları, gebeliğin intrahepatik kolestazını tahmin etmek için kullanılabilir. İki belirteç arasında bir üstünlük olmadığı düşünüldüğünde, her ikisinin de tahmin için kullanılabileceğini düşünmekteyiz.

Anahtar Kelimeler: APRI skoru, De Ritis oranı, gebeliğin intrahepatik kolestazı

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy complication characterized by itching localized especially in the hands and feet, worsening at night, and elevations in fasting bile acids and serum transaminases. It especially occurs in late second or third trimester.[1] The prevalence of ICP is between 0.5% and 1%, with variations among ethnicities and geographic regions due to differences in genetic susceptibility and environmental factors.[2] Since the etiology of ICP has not been sufficiently elucidated, management decisions are quite difficult due to insufficient data regarding diagnosis, treatment and adverse perinatal outcomes.[3] It is claimed that the mechanism of occurrence is due to increased circulating steroid levels in the maternal serum due to pregnancy, which leads to liver enzyme dysfunction and disorders in the transportation of the bile acids. Although pruritus disappears and liver function tests return to normal values after birth, patients with ICP may experience hepatobiliary and cardiovascular complications in later life. Moreover it is related to neonatal complications.[4,5] Considering these adverse outcomes, the early prediction of ICP is crucial.

Aspartate aminotransferase to platelet ratio index (APRI) and aspartate to alanine aminotransferase (De Ritis) ratio have been studied in various conditions. Aspartate aminotransferase to platelet ratio index was found to be a predictor for complicated dengue fever, cardiovascular risk for metabolic subject, cholestatic liver diseases in children and HELLP syndrome.[3,6-8] Aspartate to alanine aminotransferase ratio was first described in 1957 by Fernando De Ritis and used in the diagnosis of viral hepatitis, infectious mononucleosis, cirrhosis, Wilson disease and insulin resistance.[9-11]

There is limited data in the literature on the predictive role of these markers in intrahepatic cholestasis of pregnancy, and there are no studies comparing their predictive properties. Here, we aimed to evaluate and compare the predictive role of first trimester APRI and De Ritis scores for intrahepatic cholestasis of pregnancy.

MATERIAL AND METHOD

This is a retrospective case-control study performed at a university affiliated research and training hospital between January 2022 and December 2023. The local ethics committee approved the study with a decision number of 2024-TBEK 2024/08-13. It was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients for the use of data from medical records.

Study Population

The study was conducted with 120 pregnant women grouped as ICP (n=60) and healthy pregnant women (n=60). The inclusion criteria of the study were as follows: being 16 to 45 years old, having singleton pregnancy, having available regular antenatal follow-up and delivery data. Exclusion criteria were composed of multiple pregnancy, having prepregnancy systemic disease including dermatologic and hematologic disorders, known presence of coagulopathy, infectious diseases, gestational diabetes mellitus, hypertensive disorders of pregnancy, intrauterine growth restriction, placental pathologies, liver or biliary disease, drug and alchool use, patients who have acute viral hepatitis and unavailable medical records.

Demographic features such as age, gravida, parity, body mass index (BMI), first trimester aspartate aminotransferase (AST), alanine aminotransferase (ALT), complete blood count levels such as hemoglobin, white blood cell, platelet, third trimester serum bile acid levels, coagulation blood tests, birth week, birth weight and delivery mode, Apgar scores were obtained from medical records.

In our clinic, intrahepatic cholestasis is routinely diagnosed based on clinical findings of pruritus which is especially located on feet and hands, elevated serum AST, ALT and serum bile acids, negative viral hepatic serology normal hepatobiliary ultrasonography findings. The upper limit of normal was accepted as 34 IU/L for AST, 55 IU/L for ALT and 10µmol/L for fasting bile acids.

The aspartate aminotransferase to platelet ratio index was calculated by using the formula ([AST/upper limit of the normal values] x 100/ number of platelets (10^3/µL) while first trimester AST/ALT ratios was calculated using the following formula [AST(IU/L)] / ALT (IU/L).

Statistical Analysis

The normality of distribution were tested by Shapiro Wilk test. Variable were expressed as mean ± standart deviation for normally distributed variables, median (minimum-maximum) for nonnormally distributed variables and frequency (percentage) for categorical variables. Normally distributed variables were compared between two groups with Student t test and nonnormally distributed ones were compared with Mann-Whitney U test. Chi-square and Fisher's Exact test were performed for group comparison of categorical variables.

Receiver operating curve analysis was used to determine the predictive role of APRI and De-Ritis score for intrahepatic cholestasis of pregnancy. The sensitivity, specificity, Youden index and the cut-off values were analyzed for each index. Also, the predictive role of these indexes were compared with receiver operating curve analysis. Statistical analysis were carried out with SPSS version 22.0 and MedCalc 18 softwares. A p value ≤0.05 was accepted as statistically significant.

RESULTS

The demographic and obstetric characteristics of patients were demonstrated in **Table 1**. There was no statistically significant difference between ICP and control groups in terms of age, BMI, gravida, parity, first and fifth minutes scores. Birth week and weight were lower and cesarean section rate was higher in ICP group.

Table 1. The demographic and obstetric characteristics of patients

	Intrahepatic cholestasis of pregnancy (n=60)	Control (n=60)	p
Age (years)	32 (19-43)	29.5 (17-40)	0.151
Body mass index (kg/m^2)	27.89 (22.43-37.88)	28.93 (23.44-38.29)	0.213
Gravida (n)	2 (1-9)	2 (1-8)	0.909
Parity (n)	1 (0-4)	1 (0-7)	0.143
Birth week (week)	37 (28-38)	38 (31-41)	<0.001
Birth weight (gram)	2735 (945-4220)	3260 (1985-4300)	<0.001
Birth mode (n,%) Vaginal Cesarean section	 13 (21.7%) 47 (83.3%)	 30 (50%) 30 (50%)	0.001
First minute Apgar score	9 (4-9)	9 (5-9)	0.242
Fifth minute Apgar score	10 (5-10)	10 (8-10)	0.140

The laboratory parameters of patients were shown in **Table 2**. No significant difference was found between two groups according to hemoglobin, WBC, platelet, activated partial thromboplastin time and INR levels. Prothrombin time was significantly longer, AST and ALT levels were higher in ICP group. The median fasting bile acid levels was 26.6 (11.2-76.2) µmol/L in ICP group. APRI score was 0.33 (0.10-1.72) in ICP group and 0.23 (0.10-0.99) in control group which was statistically significant (p=0.017). De Ritis ratio was lower in ICP group as compared to control group (0.85 (0.50-4.05) vs 1.32 (0.5-2.4), p=0.002).

Table 2. The laboratory parameters of patients

	Intrahepatic cholestasis of pregnancy (n=60)	Control (n=60)	p
Hemoglobin (g/dL)	10.89±1.69	11.1±1.54	0.494
WBC (x10^3/mm^3)	12.9 (7-24)	12.3 (6.2-27.1)	0.125
Platelet (x10^3/µL)	198 (125-380)	225 (139-373)	0.092
Prothrombin time (sn)	13.3 (11.5-65.2)	12.8 (10.3-23.2)	0.001
Activated partial thromboplastin time (sn)	27.8 (22.4-33.8)	28.3 (19.9-37.6)	0.640
INR	0.98 (0.9-1.1)	0.95 (0.8-1.2)	0.109
Aspartate aminotransferase (IU/L)	21.5 (10-85)	18 (8-64)	0.038
Alanine aminotransferase (IU/L)	23 (6-87)	15 (8-34)	<0.001
APRI score	0.33 (0.10-1.72)	0.23 (0.10-0.99)	0.017
AST to ALT ratio	0.85 (0.50-4.05)	1.32 (0.5-2.4)	0.002

APRI: aspartate aminotranferase to platelet ratio index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AST to ALT ratio: aspartate aminotransferase to alanine aminotransferase ratio, WBC: white blood cell

The correlations between fasting bile acid, APRI score and De Ritis ratio was shown in **Table 3**. Fasting bile acid was found to be positively correlated with APRI score (r=0.868, p<0.001) while no correlation was detected between fasting bile acid and De Ritis ratio. There was a weak positive correlation between APRI score and De Ritis ratio (r=0.219, p=0.016).

Table 3. The correlations between fasting bile acid, APRI score and De Ritis ratio

Correlations

	Fasting bile acid	APRI score	De Ritis ratio
Spearman's rho			
Fasting bile acid			
Correlation Coefficient	1.000	.868**	.066
Sig. (2-tailed)	.	.000	.616
N	60	60	60
APRI score			
Correlation Coefficient	.868**	1.000	.219*
Sig. (2-tailed)	.000	.	.016
N	60	120	120
De Ritis ratio			
Correlation Coefficient	.066	.219*	1.000
Sig. (2-tailed)	.616	.016	.
N	60	120	120

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

The receiver operating curve evaluating the predictive role of APRI for ICP was presented in **Figure 1**. APRI score >0.42 was found to predict ICP with 36.67% sensitivity and 98.33% specificity (AUC=0.626, p=0.016).

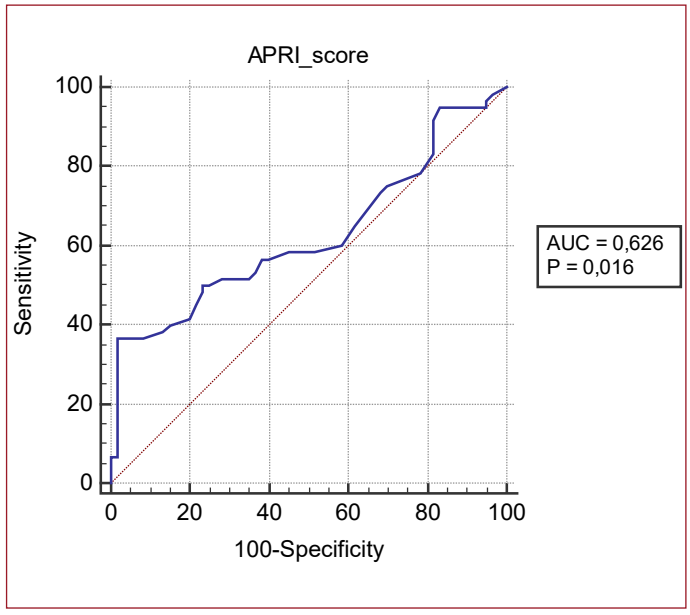

Figure 1. The receiver operating curve evaluating the predictive role of APRI for intrahepatic cholestasis of pregnancy

The receiver operating curve evaluating the predictive role of AST to ALT ratio for ICP was demonstrated in **Figure 2**. AST to ALT ratio ≤ 1.3 was found to predict ICP with 83.33% sensitivity and 51.67% specificity (AUC=0.664, p=0.001).

The receiver operating curve comparing the predictive role of APRI and AST to ALT ratio for ICP were shown in **Figure 3**. No significant difference was found between two index for predicting ICP (p=0.065).

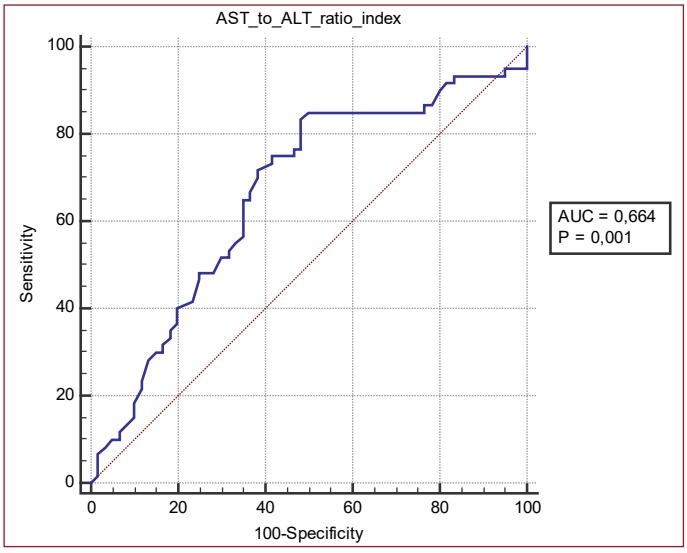

Figure 2. The receiver operating curve evaluating the predictive role of AST to ALT ratio for intrahepatic cholestasis of pregnancy

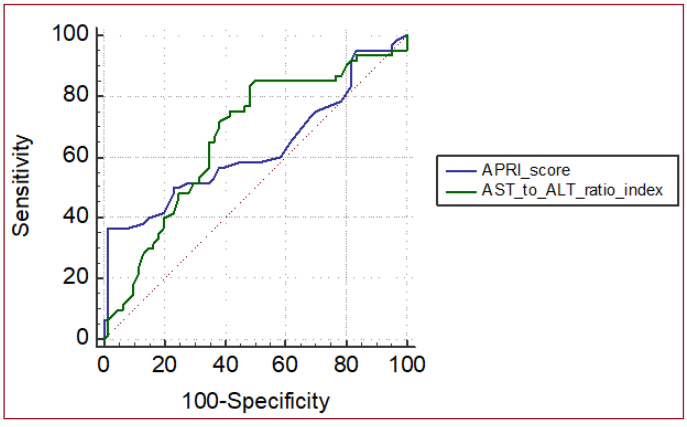

Figure 3. The receiver operating curve comparing the predictive role of APRI and AST to ALT ratio for intrahepatic cholestasis of pregnancy

DISCUSSION

Intrahepatic cholestasis of pregnancy has claimed to be related to the serious neonatal complications such as fetal demise, fetal distress, preterm birth and low birth weight. [12,13] Due to the increased perinatal mortality and morbidity, researchers have focused on finding predictive markers for intrahepatic cholestasis of pregnancy. Aneuploidy screening markers, lipid profile parameters such as total cholesterol and LDL cholesterol levels and sulfated metabolites were found to be a predictor in previous studies.[14-16] Besides these, scoring systems based on laboratory tests were used for the diagnosis and prediction of ICP.[17,18]

The APRI score presents hepatic fibrosis and cirrhosis. When cell damage to the liver fibrosis occurs, AST tends to increase. Then platelet count begin to decrease due to the portal hypertension. As a result, increased APRI scores appear. [19,20] Recently, an APRI score above 3 has been accepted as a noninvasive marker of liver damage.[17] In a meta-analysis including 40 studies, APRI score above 1 predicted cirrhosis with 76% sensitivity and 72% specificity while APRI score above 0.7 predicted liver fibrosis with 77% sensitivity and 72% specificity.[21] In intrahepatic cholestasis of pregnancy, morphologic changes of liver fibrosis is not an expected situation whereas molecular changes of fibrosis are present. This raises the question of whether the APRI score has a place in the prediction of intrahepatic cholestasis.

In the literature, the first study evaluating the association between APRI score and ICP was performed by Tolunay et al. Tolunay et al reported higher first trimester APRI scores in ICP and claimed that APRI score 0.57 predicted ICP with 86.5 % sensitivity and 77.3 % specificity.[17] Then, in a study of Gok et al searching the predictive value of APRI score in 49 ICP cases and 62 healthy control claimed that first trimester APRI score above 0.15 predicted ICP with 79.6% sensitivity and 56.5% specificity.[18] In 2024, Cemortan et al reported higher APRI scores in ICP cases. Also, APRI score above 0.55 was reported to be a predictor with 66.2% sensitivity and 92.9% specificity. [22] Not only first trimester APRI scores were associated with intrahepatic cholestasis of pregnancy, but also second and third trimester APRI scores predicted intrahepatic cholestasis of pregnancy. Sakcak et al claimed that second trimester APRI score above 0.09 predicted ICP with 78% sensitivity and 79% specificity.[23] In a study of Saadi et al, third-trimester APRI score above 0.42 predicted ICP with 65.3% sensitivity and 73.2% specificity.[24] Peker et al evaluated the optimal cut-off values of APRI scores to predict ICP for the first, second, and third trimesters and found that APRI score above 0.101 predicted ICP with 79.7% sensitivity and 79.6% specificity in first, above 0.103 predicted ICP with 78.4% sensitivity and 76.3% specificity in second, and above 0.098 with 72.5% sensitivity and 72% specificity in third trimester.[25] In our study, first trimester APRI score was evaluated. We found APRI score as 0.33 (0.10-1.72) in ICP group and 0.23 (0.10-0.99) in control group which was statistically higher in ICP group. APRI score above 0.42 was found to predict ICP with 36.67% sensitivity and 98.33% specificity. Our study results were consistent with the literature. We suggest that different cut-off levels and sensitivity could be due to the severity of the disease or diagnostic criteria used in the studies. All of these studies, including our study, were far from investigating the severity of intrahepatic cholestasis of pregnancy. Only one study investigated the role of APRI score according to the severity of intrahepatic cholestasis. That study reported higher APRI scores in severe cases. Moreover, APRI score above 1.06 was found to predict severe ICP with 82% sensitivity and 72% specificity.[26]

Although the APRI score is associated with parenchymal damage, fasting bile acid levels circulating in extrahepatic biliary system were found to be correlated with APRI scores in some previous studies. Tolunay et al reported significant positive correlation between first trimester APRI scores and third trimester fasting bile acid levels in ICP (17). Similarly, Eyisoy et al and Cemortan et al reported positive association between APRI scores and fasting bile acid levels.[22,26] Likewise,

in the present study, we found positive correlation between third trimester fasting bile acids and APRI score. The mechanism to explain this correlation is not fully understood.

Another noninvasive marker investigated in liver diseases is De Ritis ratio. In a study of Parmar et al, decreased De Ritis ratio was reported in viral hepatitis while increased De Ritis ratio was present in alcholic liver diseases. No significant difference was reported in cholestasis. De Ritis ratio 1.5 and above claimed to be associated with intrahepatic cholestasis while levels below 1.5 was associated with extrahepatic conditions.[10] There is only one study searching De Ritis ratio in intrahepatic cholestasis of pregnancy. In this study, lower first trimester De Ritis ratio was detected in ICP as compared to healthy pregnants. De Ritis ratio below 1.07 predicted ICP with 64% sensitivity and 62% specificity. Furthermore, the study evaluated the predictive roles of both APRI and De Ritis ratios similar to our study. As previous studies, first trimester APRI scores were higher and APRI score above 0.191 predicted ICP with 66% sensitivity and 66% specificity.[3] In addition to this study, we compared the predictive role of these markers and found no difference between these markers. Also, we found that De Ritis ratio 1.3 and below predicted ICP with 83.33% sensitivity and 51.67% specificity.

The current study has several limitations. First, it was conducted in a single centre and has a retrospective design. Second, liver biopsy results were not available to assess liver fibrosis. Finally, the severity of ICP, which could have affected the results, was not assessed.

CONCLUSION

The first trimester APRI and De Ritis scores, which are cheap and easily available, can be used to predict ICP. Considering that there is no superiority between two markers, we suggest that both can be used for prediction. Early prediction, appropriate monitoring and treatment can reduce the maternal and fetal mortality and morbidity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bursa Yuksek Ihtisas Research and Training Hospital Ethics Committee (2024-TBEK 2024/08-13).

Informed Consent: Although the study design is retrospective, written informed consent is routinely obtained from all patients at admission for using their data from medical records.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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