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Evaluation of Liver Function Indices in Intrahepatic Cholestasis of Pregnancy: Diagnostic Utility and Neonatal Outcomes

Gebelik İntrahepatik Kolestazında Karaciğer Fonksiyon Endekslerinin Değerlendirilmesi: Tanı Yararlığı ve Yenidoğan Sonuçları

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ABSTRACT

AIM: Intrahepatic cholestasis of pregnancy (ICP) is a hepatic condition that occurs in 0.2-2% of pregnancies. It is characterized by intense itching and increased levels of bile acids in the bloodstream. Precise identification and anticipation of adverse neonatal outcomes are crucial. This study evaluates the diagnostic performance of liver-related scores—APRI (aspartate aminotransferase- platelet), ALBI (albumin-bilirubin), PALBI (platelet- albumin-bilirubin), and FAR (fibrinogen/albumin ratio) —in ICP patients and examines their relationship to pregnancy outcomes.

MATERIAL AND METHOD: This study was a retrospective analysis of 180 patients who were treated at Ankara Etlik City Hospital between January 2023 and January 2024. 90 ICP patients (Group 1) and 90 control patients (Group 2) were compared. The PALBI, ALBI, APRI scores, and FAR were calculated using third-trimester laboratory values. Neonatal outcomes, including birth weight, APGAR scores, NICU (neonatal intensive care unit) admission, sepsis, RDS (respiratory distress syndrome), and neonatal death were recorded. Statistical analyses included ROC (Receiver Operating Characteristics) curve analysis and Spearman correlation.

RESULTS: The PALBI, ALBI, APRI scores, and FAR were significantly higher in ICP patients (p<0.001). The APRI score showed the highest diagnostic performance (area under curve 0.870). Cut-off values were >-2.58 for PALBI (sensitivity 62%, specificity 81%), >-2.47 for ALBI (sensitivity 67%, specificity 81%), and >0.3 for APRI (sensitivity 78%, specificity 68%). Neonatal outcomes did not differ significantly between the groups. There was no correlation between fasting bile acid levels and liver damage markers with negative outcomes in newborns.

CONCLUSION: In facilities where it is not possible to test fasting bile acid levels, PALBI, ALBI, APRI scores and FAR value offer an alternative approach to the evaluation of individuals with intrahepatic cholestasis of pregnancy (ICP). Future studies with larger patient groups are needed to increase the reliability of these parameters.

Keywords: Intrahepatic cholestasis of pregnancy; PALBI score; fasting bile acids

ÖZET

AMAÇ: Gebelikte intrahepatik kolestaz (ICP), gebeliklerin %0,2-2'sinde görülen bir karaciğer hastalığıdır. Yoğun kaşıntı ve kan dolaşımında safra asitlerinin artmasıyla karakterizedir. Olumsuz neonatal sonuçların kesin olarak tanımlanması ve öngörülmesi çok önemlidir. Bu çalışma, ICP hastalarında karaciğerle ilgili APRI (aspartat aminotransferaz-trombosit), ALBI (albümin-bilirubin), PALBI (trombosit-albümin-bilirubin) ve FAR (fibrinojen/albümin oranı) değerinin tanısal performansını değerlendirmekte ve bunların gebelik sonuçlarıyla olan ilişkisini incelemektedir.

GEREÇ VE YÖNTEM: Bu çalışma Ocak 2023-Ocak 2024 tarihleri arasında Ankara Etlik Şehir Hastanesi'nde tedavi gören 180 hastanın retrospektif analizidir. 90 ICP hastası (Grup 1) ile 90 kontrol hastası (Grup 2) karşılaştırıldı. PALBI, ALBI, APRI skorları ve FAR üçüncü trimester laboratuvar değerleri kullanılarak hesaplandı. Doğum ağırlığı, APGAR skorları, yenidoğan yoğun bakım ünitesine kabul, sepsis, solunum sıkıntısı ve neonatal ölümü içeren neonatal sonuçlar kaydedildi. İstatistiksel analiz, ROC (Receiver Operating Characteristics) eğrisi analizi ve Spearman korelasyonu ile yapıldı.

BULGULAR: ICP hastalarında PALBI, ALBI, APRI skorları ve FAR anlamlı olarak yüksekti (p<0,001). APRI puanı en yüksek tanısal performansı gösterdi (AUC: 0.870). PALBI skoru için cut-off değeri >-2,58 (sensivite %62, spesifite %81), ALBI skoru için >-2,47 (sensitive %67, spesifite %81), APRI skoru için >0,3 (sensivite %78, spesifite %68) idi. Yenidoğan sonuçları gruplar arasında anlamlı farklılık göstermedi. Yenidoğanlarda açlık safra asidi düzeyleri ve karaciğer hasarı belirteçleri ile olumsuz sonuçlar arasında bir korelasyon yoktu.

SONUÇ: Açlık safra asidi düzeylerinin test edilmesinin mümkün olmadığı merkezlerde PALBI, ALBI, APRI skorları ve FAR değeri intrahepatik gebelik kolestazı olan bireylerin değerlendirilmesinde alternatif bir yaklaşım sunmaktadır. Bu parametrelerin güvenilirliğini arttırmak için daha geniş hasta gruplarıyla gelecek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Gebelikte intrahepatik kolestaz; PALBI skoru; açlık safra asitleri

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a common liver disease that occurs in 0.2-2% of women during pregnancy.[1,2] It is more common during the latter stages of pregnancy and can be reversed.[3] The condition is marked by severe itching, especially on the soles of the feet and palms of the hands, and increased levels of bile acids in the blood.[4,5]the association between LMPI values, total bile acid (TBA It poses significant risks to neonatal health, with sudden intrauterine death being the most severe outcome.[3]

Genetic, hormonal, and environmental factors significantly contribute to the development of ICP.[6] While serum bile acid measurement is a reliable biochemical indicator for diagnosing and following intrahepatic cholestasis of pregnancy (ICP), it cannot be measured in every center and necessitates fasting overnight.[7] Moreover, bile acid levels are not elevated in all ICP patients and can also rise in other liver diseases, highlighting the need for further research into ICP's pathogenesis and diagnostic methods.[8] This situation raises the need for further research into the pathogenesis and diagnostic methods in ICP patients. Although the pathogenesis of ICP is not clear, the primary organ affected is the liver. ALBI (albumin-bilirubin) score, APRI (aspartate aminotransferase- platelet) score, PALBI (platelet- albumin-bilirubin) score and FAR (fibrinogen/albumin ratio) are indices related to liver function and fibrosis.[9–12]the severity of which is currently assessed by the Child-Pugh (C-P PALBI score, APRI score, PALBI score and FAR can be easily calculated from routine laboratory values and are inexpensive.

Precise identification of intracranial pressure (ICP) and the anticipation of unfavorable newborn consequences are essential for efficient prenatal and postnatal healthcare.[3] This study investigates the diagnostic performance of liver-related scores (APRI, ALBI, PALBI, and FAR) in ICP patients and examines their relationship to negative pregnancy outcomes.

MATERIAL AND METHOD

This retrospective study was conducted between January 2023 and January 2024 in the Perinatology Clinic of Ankara Etlik City Hospital. The study protocol received approval from the Ethics Committee of Ankara Etlik City Hospital (approval number: AESH-EK1-2023-771, 20.12.2023), and the study followed the guidelines outlined in the Declaration of Helsinki by the World Medical Association.

The study population comprised 180 patients, divided into two groups: 90 patients diagnosed with intrahepatic cholestasis of pregnancy (ICP) (Group 1) and 90 control patients (Group 2) selected according to randomization rules and who met the inclusion criteria.

The diagnosis of ICP was based on the presence of pruritus on the palms and soles, particularly at night, a fasting bile acid level >10 µmol/L, and the exclusion of other causes of liver dysfunction.[13] The exclusion criteria were prolonged illness in the mother, multiple pregnancies, smoking, alcohol consumption, congenital malformations, and inaccessible medical records. Demographic data such as age, gravidity, parity, and body mass index (BMI) were collected for all patients. The gestational age of the study patients was calculated on the basis of the first day of the patient's last menstruation and confirmed by ultrasound. The control patients were selected according to the rules of randomization and in accordance with the maternal age and gestational age of the patient group. AST (aspartate aminotransferase), ALT (alanine aminotransferase), total bilirubin, direct bilirubin, creatinine, urea, albumin, GGT (gamma-glutamyl transferase), ALP (alkaline phosphatase), LDH (lactate dehydrogenase), APTT (activated partial thromboplastin time), PT (prothrombin time), INR (international normalized ratio), fibrinogen, hemoglobin, WBC (white blood count), platelet, neutrophil, lymphocyte and monocyte levels were examined from maternal venous blood. The PALBI score, the ALBI score, the APRI score and the FAR values were calculated on the basis of the laboratory test results of the ICP patients and the control patients in the third trimester.

In the third trimester, the PALBI score, ALBI score, APRI score, and FAR values were calculated for both ICP and control patients using the following formulas: ALBI score = -0.085 × (albumin g/L) + 0.66 × (total bilirubin µmol/L) and this score is graded as ≤ −2.60 Grade 1, between −2.60 and −1.39 Grade 2, and > −1.39 Grade 3.[9]the severity of which is currently assessed by the Child-Pugh (C-P PALBI score= (2.02 × Log10 bilirubin µmol/L) + [−0.37 × (Log10 bilirubin)2] + (−0.04 × albümin g/dL) + (−3.48 × Log10 platelet 10^3/µL) + [1.01 × (Log10 platelet^2 10^3/µL)] and this score was calculated as Grade 1 when it was ≤−2.53, Grade 2 when it was between −2.53 and −2.09, and Grade3 when it was >−2.09.[14] APRI score= [(Aspartate aminotransferase (AST) (U/L) /upper limit of AST) /platelet count 10^3/µL] × 100 (upper limit of AST= 33 U/L in our hospital)[15]but the data is limited. As dengue epidemics are common in our country with limited healthcare resources, we believe APRI can help emergency physicians/primary physicians in predicting the severity of dengue and plan for the appropriate use of limited healthcare resources.\n\nObjective:\n1 and FAR= fibrinogen/albumin ratio. Neonatal outcomes such as birth weight, APGAR scores at 1 and 5 minutes, need for neonatal intensive care, neonatal sepsis, presence of respiratory distress syndrome (RDS), and neonatal death were recorded.

All statistical studies were conducted using RStudio (version: 2024.09.1+394 -Boston, USA) to analyze the data. The variables were assessed for normal distribution using visual techniques such as graphs and chance maps, as well as analytical methods like the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Levene test was employed to evaluate the uniformity of the variance. The descriptive analyses were conducted by calculating the means and standard deviations for variables that followed a normal distribution. The independent sample t-test was used to compare these parameters among the groups. Analyzed the irregularly distributed data using medians and quartiles (Q1-Q3) for descriptive analysis. The Mann-Whitney U test was conducted to compare these parameters among the groups. Frequency and percentage were used to offer descriptive analyses for the categorical variables. The Chi-square test or Fisher's exact test were used to investigate the relationship between categorical variables. The Fisher's exact test was employed in cases where the assumptions of the Chi-square test were not satisfied due to low anticipated cell numbers. The capacity of various parameters that can be used to predict ICP and adverse neonatal outcomes were analyzed using ROC (Receiver Operating Characteristics) curve analysis. When a significant cut-off value was observed, the sensitivity, specificity and AUC (Area Under Curve) were presented. The Spearman test was used to calculate the correlation coefficients and their significance for exploring the relationships between non-normally distributed variables. A p-value below 0.05 was accepted for statistical significance.

RESULTS

Ninety ICP patients and ninety control patients were included in the study. Table 1 presents the maternal characteristics and perinatal outcomes of the participants.

Table 1. Maternal Characteristics and Perinatal Outcomes

	ICP n: 90	Control n: 90	p
Maternal age (year)	28 (24-31)	28 (24-32)	0.790
Blood sample collection time (week)	33 (31-35)	34 (33-35)	0.094
BMI	28.4 (25.7-31.3)	29.5 (27.0-33.7)	0.100
Weight gained during pregnancy (kg)	10 (8-13)	10 (8-15)	0.177
Gravida	2 (1-3)	2 (1-3)	0.287
Parity	0 (0-1)	1 (0-1)	0.106
Glucose (mg/dl)	86 (76-97)	86 (73-96)	0.700
AST (U/L)	47 (22-86)	13 (11-17)	**<0.001**
ALT (U/L)	65 (22-137)	10 (8-13)	**<0.001**
Total bilirubin (mg/dl)	0.44 (0.28-0.70)	0.24 (0.18-0.36)	**<0.001**
Direct bilirubin (mg/dl)	0.28 (0.14-0.42)	0.11 (0.09-0.14)	**<0.001**
Creatinine (mg/dl)	0.53 (0.47-0.59)	0.48 (0.44-0.54)	**0.008**
Urea (mg/dl)	15.2 (12.0-20.7)	13.6 (11.1-16.2)	**0.012**
Albumin (g/dL)	35 (12-32.8)	36.0 (34.7-38.1)	**0.005**
GGT (U/L)	16 (10-28)	8 (6-11)	**<0.001**
ALP (U/L)	169 (132-227)	120 (94-144)	**<0.001**
LDH (U/L)	219 (184-255)	197 (178-217)	**0.003**
APTT (sn)	26.6 (24.4-28.0)	26.3 (24.9-27.9)	0.799
PT (sn)	7.93 (7.64-8.21)	8.22 (7.97-8.53)	**<0.001**
INR	0.90 (0.86-0.93)	0.88 (0.86-0.92)	0.112
Fibrinogen (mg/dL)	562 (489-610)	481 (433-529)	**<0.001**
Hemoglobin (g/L)	11.30 (10.30-12.43)	11.55 (10.38-12.60)	0.409
WBC (10^3/µL)	10.29 (8.74-12.41)	10.14 (8.81-12.11)	0.828
Platelet (10^3/µL)	251±73.9	249±57.8	0.831
Neutrophil (10^3/µL)	6.63 (5.72-8.38)	7.32 (6.18-8.89)	0.069
Lymphocyte (10^3/µL)	1.83 (1.37-2.39)	1.95 (1.62-2.17)	0.387
Monocyte (10^3/µL)	0.66 (0.50-0.80)	0.71 (0.60-0.82)	0.049
PALBI score	-2.44 (-2.77; -2.12)	-2.92 (-3.14; -2.62)	**<0.001**
ALBI score	-2.38 (-2.61; -2.16)	-2.64 (-2.83; -2.50)	**<0.001**
APRI score	0.7 (0.3-1.4)	0.2 (0.1-0.3)	**<0.001**
FAR	15.5 (13.8-18.0)	13.2 (11.8-14.9)	**<0.001**
History of ICP	6 (6.7)	0 (0)	**0.029**
Antenatal corticosteroid therapy	31 (34.4)	6 (6.7)	**<0.001**
Preterm birth (<37 week)	28 (31.1)	9 (10)	**0.001**
Fetal distress	3 (3.3)	8 (8.9)	0.213
Gestational age at delivery (week)	37 (36-37)	39 (38-40)	**<0.001**
Birth weight (gram)	2858±376.9	3245±412.6	**<0.001**
Birth method			
Normal spontaneous vaginal birth	34 (37.8)	46 (51.1)	
Primary cesarean section	35 (38.9) *	20 (22.2) *	**0.048**
Previous cesarean section history	21 (23.3)	24 (26.7)	
APGAR Score at 1st minute	9 (8-9)	9 (9-9)	**0.029**
APGAR Score at 5th minute	10 (9-10)	10 (10-10)	**0.049**
NICU admission	22 (24.4)	10 (11.1)	**0.032**
Neonatal hypoglycemia	0 (0)	3 (3.3)	0.246
TTN	8 (8.9)	5 (5.6)	0.565
Respiratory distress syndrome	6 (6.7)	1 (1.1)	0.118
Need for CPAP	8 (8.9)	6 (6.7)	0.781
Need for mechanical ventilator	6 (6.7)	1 (1.1)	0.118
Need for phototherapy	10 (11.1)	7 (7.8)	0.610
Neonatal sepsis	5 (5.6)	0 (0)	0.059

ICP: Intrahepatic cholestasis of pregnancy, BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, APTT: Activated partial thromboplastin time, PT: Prothrombin time, INR: International normalized ratio, WBC: White blood count, PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio, NICU: Neonatal intensive care unit, TTN: Transient tachypnea of the newborn, CPAP: Continuous positive airway pressure

* There is a significant difference between the groups only in the primary cesarean section.

Data are expressed as mean±SD, median and quartiles (Q1–Q3), or number (percentage) where appropriate. A p value of <0.05 indicates a significant difference.

There were no significant differences between the two groups regarding maternal age, time of blood sampling, BMI, weight gained during pregnancy, gravidity, and parity (p = 0.790, p = 0.094, p = 0.100, p = 0.177, p = 0.287, p = 0.106, respectively.) Laboratory values, including glucose, APTT, INR, hemoglobin, WBC, platelets, neutrophils, lymphocytes, and monocytes, were similar in both groups (p = 0.700, p = 0.799, p = 0.112, p = 0.409, p = 0.828, p = 0.831, p = 0.069, p = 0.387, p = 0.049, respectively). However, AST, ALT, total bilirubin, direct bilirubin, creatinine, urea, GGT, ALP, LDH, and fibrinogen levels were higher in the ICP group, while albumin and PT levels were higher in the control group (p < 0.001 for AST, ALT, total bilirubin, direct bilirubin, GGT, ALP, fibrinogen; p = 0.008 for creatinine; p = 0.012 for urea; p = 0.003 for LDH; p = 0.005 for albumin; p < 0.001 for PT). The average fasting bile acid level in the ICP group was 17.4 µmol/L (range: 12.0-32.8). The ICP group had significantly greater PALBI, ALBI, APRI scores, and FAR compared to the control group (p <0.001 for all). Perinatal outcomes did not differ significantly between the two groups in terms of fetal distress, neonatal hypoglycemia, TTN (transient tachypnea of the newborn), respiratory distress syndrome, need for CPAP (continuous positive airway pressure), need for mechanical ventilation, need for phototherapy, and neonatal sepsis (p=0.213, p=0.246, p=0.565, p=0.118, p=0.781, p=0.118, p=0.610, p=0.059). Antenatal corticosteroid therapy, preterm birth, primary cesarean section, and NICU admission were significantly higher in the ICP group, while gestational age at birth, birth weight, and APGAR scores at the first and fifth minutes were significantly lower (p < 0.001 for antenatal corticosteroid therapy, preterm birth, gestational age at birth, birth weight, APGAR scores; p = 0.001 for neonatal intensive care unit (NICU) admission; p = 0.048 for primary cesarean section; p = 0.032 for gestational age at birth; p = 0.029 for birth weight).

Table 2. Receiver Operating Characteristic (ROC) Analysis to Evaluate PALBI Score, ALBI Score, APRI Score and FAR in Detecting ICP Patients

	Cut-off	Sensivity	Specificity	AUC	CI	P value
PALBI score	>-2.58	62%	81%	0.749	0.679-0.811	**<0.001**
ALBI score	>-2.47	67%	81%	0,756	0.687-0.817	**<0.001**
APRI score	>0.3	70%	91%	0.870	0.812-0.916	**<0.001**
FAR	>13.68	78%	68%	0.713	0.663-0.796	**<0.001**

ICP: Intrahepatic cholestasis of pregnancy, PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio, AUC: Area under the curve, CI: Confidence interval

Table 2 shows the ROC (receiver operating characteristic) analysis of the PALBI, ALBI, APRI scores, and FAR values in detecting ICP patients. The cut-off value for the PALBI score was>-2.58, with a sensitivity of 62% and a specificity of 81% (p <0.001). For the ALBI score, the cut-off value was >-2.47, with a sensitivity of 67% and a specificity of 81% (p <0.001). The APRI score had a cut-off value of >0.3, with a sensitivity of 78% and a specificity of 68% (p <0.001), and the highest AUC (area under the curve) was 0.870 for the APRI score

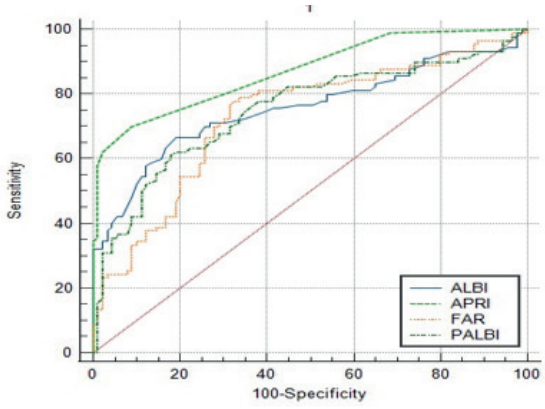

Figure 1. Receiver operating characteristic (ROC) curves to assess the usefulness of APRI (Aspartate aminotransferase-platelet) score, ALBI (Albumin-bilirubin) score, FAR (fibrinogen/albumin ratio) and PALBI (platelet-albumin-bilirubin) score

When the cut-off values and AUCs are compared with the ROC analysis, the APRI score is higher than the ALBI score (p = 0.04), the

PALBI score (p = 0.05) and FAR (p = 0.02).

Table 3. Receiver Operating Characteristic (ROC) Analysis to Evaluate Fasting Bile Acid, PALBI Score, ALBI Score, APRI Score and FAR in Predicting Adverse Neonatal Outcomes in ICP Patients

	Cut-off	Sensivity	Specificity	AUC	CI	P value
Fasting bile acid	>67.1	18%	97%	0.500	0.393-0.608	0.997
PALBI score	>-2.7	55%	28%	0.502	0.395-0.609	0.980
ALBI score	>-2.29	55%	71%	0.539	0.431-0.645	0.625
APRI score	≤ 0.2	27%	84%	0.518	0.410-0.625	0.809
FAR	>16.59	50%	71%	0.545	0.437-0.651	0.530

ICP: Intrahepatic cholestasis of pregnancy, PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio, AUC: Area under the curve, CI: Confidence interval

Adverse neonatal outcomes: NICU (Neonatal intensive care unit) admission, TTN (Transient tachypnea of the newborn), Need for CPAP (Continuous positive airway pressure), Need for phototherapy, Neonatal sepsis

Table 3 shows the ROC analysis evaluating the association of fasting bile acid, PALBI score, ALBI score, APRI score, and FAR values with adverse neonatal outcomes in ICP patients. Fasting bile acid, PALBI score, ALBI score, APRI score, and FAR values were not associated with adverse neonatal outcomes in ICP patients.

Table 4. Receiver Operating Characteristic (ROC) Analysis to Evaluate PALBI Score, ALBI Score, APRI Score, and FAR in Predicting Adverse Neonatal Outcomes in All Patients

	Cut-off	Sensivity	Specificity	AUC	CI	P value
PALBI score	>-2.13	25%	59%	0.512	0.437-0.587	0.831
ALBI score	>-2.29	36%	85%	0.519	0.443-0.594	0.751
APRI score	>0.1	94%	19%	0.539	0.463-0.613	0.460
FAR	>16.59	36%	80%	0.555	0.479-0.629	0.313

PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio, AUC: Area under the curve, CI: Confidence interval

Adverse neonatal outcomes: NICU (Neonatal intensive care unit) admission, TTN (Transient tachypnea of the newborn), Need for CPAP (Continuous positive airway pressure), Need for phototherapy, Neonatal sepsis

Table 4 shows the ROC analysis evaluating the association between PALBI score, ALBI score, APRI score and FAR values with adverse neonatal outcomes in all patients. When all patients enrolled in the study are evaluated, the PALBI, ALBI, APRI scores and FAR values cannot predict adverse neonatal outcomes.

Table 5. Spearman's Correlation Between Fasting Bile Acid Concentration and Maternal-Perinatal Characteristics

	r	p
APGAR Score at 1st minute	-0.023	0.832
APGAR Score at 5th minute	0.007	0.947
PALBI score	0.348	**0.001**
ALBI score	0.312	**0.003**
APRI score	0.041	0.705
FAR	0.216	**0.041**

PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio

Table 5 shows the Spearman's correlation between fasting bile acid and maternal-perinatal characteristics. Fasting bile acid was associated with PALBI score (r = 0.348, p = 0.001), ALBI score (r = 0.312, p = 0.003), and FAR (r = 0.216, p = 0.041).

DISCUSSION

In this study, we found that the PALBI score, ALBI score, APRI score and FAR value were significantly higher in ICP patients and could be predictive in differentiating ICP patients. When the cut-off values and AUCs are compared with the ROC analysis, the APRI score is higher than the ALBI score, the PALBI score and FAR. PALBI score, ALBI score, APRI score, and FAR values were not associated with adverse neonatal outcomes in ICP patients.

ICP is associated with adverse neonatal outcomes such as fetal distress, preterm birth, meconium in the amniotic fluid and intrauterine fetal loss. Diagnosis and treatment of ICP is extremely important to avoid these adverse outcomes. Despite being implicated in the development of fetal illness, bile acids are the most reliable and specific biochemical indicator employed for the diagnosis and monitoring of ICP.[7,16] However, the exact cause of ICP is not completely understood, several researches have focused on establishing a relationship between maternal serum biochemistry and fetal outcomes. Some markers have been scrutinized for their ability to predict ICP patients, however bile acid is commonly employed for diagnosis.[17] The study conducted by Chen et al. found that irisin levels in maternal serum and cord blood were high in patients diagnosed with ICP and that irisin levels correlated with disease severity.[18] In the study conducted by Agaoglu et al., maternal calprotectin levels were found to be higher in ICP patients than in control patients and it was shown that this marker could be a diagnostic marker for ICP patients.[19] In the study conducted by Kırbas et al., higher IL-17 levels were found in ICP patients compared to control patients.[20] Similarly, Biberoğlu et al. investigated a marker that may be effective in the diagnosis and pathology of ICP patients, and IL-6 was detected at higher levels in ICP patients than in the control group.[21]the most common liver disease in pregnancy, is characterized by elevated serum total bile acid and/or transaminase concentration, and pruritus. Interleukin-6 (IL-6 Desteli et al. demonstrated that pregnancy-associated plasma protein-A (PAPP-A), a component of the first trimester screening test, can serve as an indicator for intrahepatic cholestasis of pregnancy (ICP). They found that a reduction in PAPP-A levels is related with an elevated chance of developing ICP.[22] None of these markers, which have been shown to be involved in the pathogenesis of ICP and predict its diagnosis, can be measured in routine laboratory tests. This situation brings new investigations.

Recent studies have evaluated liver-based scores for diagnosing ICP. Tolunay et al. showed that the APRI score, calculated in the first trimester, predicted ICP in the third trimester.[23] The APRI score was developed by Wai et al. in 2003.[24]most models for predicting liver fibrosis are complicated and separate formulas are needed to predict significant fibrosis and cirrhosis. The aim of our study was to construct one simple model consisting of routine laboratory data to predict both significant fibrosis and cirrhosis among patients with CHC. Consecutive treatment-naive CHC patients who underwent liver biopsy over a 25-month period were divided into 2 sequential cohorts: training set (n = 192 This score enables the assessment of liver fibrosis without invasive procedures.[24,25]most models for predicting liver fibrosis are complicated and separate formulas are needed to predict significant fibrosis and cirrhosis. The aim of our study was to construct one simple model consisting of routine laboratory data to predict both significant fibrosis and cirrhosis among patients with CHC. Consecutive treatment-naive CHC patients who underwent liver biopsy over a 25-month period were divided into 2 sequential cohorts: training set (n = 192 Obut et al. demonstrated the utility of APRI and ALBI scores in predicting ICP [26]. The ALBI score, developed by Johnson et al., was initially used to assess liver function in hepatocellular carcinoma patients.[9]the severity of which is currently assessed by the Child-Pugh (C-P Xu et al. later confirmed its relevance for non-malignant liver diseases.[27] The PALBI score was developed based on the consideration that the ALBI score is not an objective determinant of liver disease and by adding the platelet count to this score.[28]which are recently reported to be simple and objective measurements for liver reserve in HCC. Methods Between 2002 and 2014, consecutive 3182 HCC patients were enrolled to follow up their survival. The area under receiver-operator-characteristic curve (AUC A study conducted in patients with hepatocellular carcinoma

has shown that the PALBI score is a decisive factor for the occurrence of liver dysfunction after resection.[29] Albumin and fibrinogen are secreted in the liver. The FAR, the ratio of these two parameters, is considered an important parameter for predicting the prognosis of cancer patients.[30] In our study, PALBI score, ALBI score, APRI score and FAR values, which are indicators of liver damage, predicted ICP. The laboratory values used to calculate these scores and ratios can be easily checked in any hospital.

Glantz et al. found no increased fetal risk in ICP patients with bile acid levels <40 µmol/L but noted a 1-2% increase in fetal risk for each µmol/L of bile acid above this threshold.[31] Lee et al. reported an 18% incidence of meconium-stained amniotic fluid in severe ICP patients, with a 19.7% increased risk for each 10 µmol/L increase in bile acid levels.[32] A meta-analysis by Ovadia et al. showed that the risk of stillbirth was significantly increased in ICP patients with a serum bile acid level of >100 µmol/L[33]but the association with the concentration of specific biochemical markers is unclear. We aimed to quantify the adverse perinatal effects of intrahepatic cholestasis of pregnancy in women with increased serum bile acid concentrations and determine whether elevated bile acid concentrations were associated with the risk of stillbirth and preterm birth.\n\nMethods\nWe did a systematic review by searching PubMed, Web of Science, and Embase databases for studies published from database inception to June 1, 2018, reporting perinatal outcomes for women with intrahepatic cholestasis of pregnancy when serum bile acid concentrations were available. Inclusion criteria were studies defining intrahepatic cholestasis of pregnancy based upon pruritus and elevated serum bile acid concentrations, with or without raised liver aminotransferase concentrations. Eligible studies were case-control, cohort, and population-based studies, and randomised controlled trials, with at least 30 participants, and that reported bile acid concentrations and perinatal outcomes. Studies at potential higher risk of reporter bias were excluded, including case reports, studies not comprising cohorts, or successive cases seen in a unit; we also excluded studies with high risk of bias from groups selected (eg, a subgroup of babies with poor outcomes were explicitly excluded. In our study, we found no significant correlation between fasting bile acid levels and adverse neonatal outcomes, with a cut-off value of >67.1 µmol/L, sensitivity of 18%, and specificity of 97%. Similarly, liver damage markers did not correlate with adverse neonatal outcomes.

Our study had some limitations. Due to an inadequate number of ICP patients, it was not possible to categorize them based on severity. As a result, we were unable to describe the individual prediction abilities of these scores for mild and severe cases. Nevertheless, the study's main advantage is that ICP can be anticipated by utilizing scores obtained from standard maternal blood tests. These tests are available in any clinical setting. Moreover, this is the first study which evaluates the PALBI score and FAR values in ICP patients.

CONCLUSION

In conclusion, the PALBI score, ALBI score, APRI score, and FAR value can be used to diagnose ICP. In facilities where it is not possible to test fasting bile acid levels, these scores provide an alternative approach to evaluate individuals with intrahepatic cholestasis of pregnancy (ICP). Future studies with larger patient cohorts are necessary to enhance the reliability of these parameters.

Conflict of Interest

The authors declare that they have no conflict of interest.

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