RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

Harran Üniversitesi Tıp Fakültesi Dergisi (Journal of Harran University Medical Faculty) 2026;23(1):123-131.
DOI: 10.35440/hutfd.1845800

Evaluation of Maternal and Fetal Outcomes and Biochemical Indices in Intrahepatic Cholestasis of Pregnancy

Gebeliğin İntrahepatik Kolestazının Maternal ve Fetal Sonuçları ile Biyomkimyasal İndekslerinin İncelenmesi

Hüseyin Kayaalp[1], Sertaç Ayçiçek[2]

[1]University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Department of Obstetrics and Gynecology, Perinatology Unit, Ankara, TÜRKİYE
[2]University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital, Department of Obstetrics and Gynecology, Diyarbakır, TÜRKİYE

Abstract

Background: Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder associated with an increased risk of adverse perinatal outcomes. The aim of this study is to investigate biochemical indices as potential predictors of ICP and adverse outcomes.

Materials and Methods: This retrospective case-control study was conducted at a tertiary care center.A total of 134 pregnant women who delivered between June 2022 and December 2024 were included. Of these, 58 were diagnosed with ICP (study, Group 1) and 76 had no diagnosis of cholestasis (control, Group 2). Clinical and laboratory findings, as well as biochemical indices, were compared between the groups.

Results: In the study group, significant differences were observed in first-trimester albumin (p<0.001), alanine aminotransferase (ALT) (p=0.018), aspartate aminotransferase (AST) (p=0.007), third-trimester ALT and AST (p<0.001), first-trimester Albumin/Creatinine ratio (ALCIR), AST/Creatinine ratio (ACRI) (p<0.05), and AST/ALT ratio (De Ritis) (p<0.001), as well as third-trimester De Ritis and ACRI (p<0.001) and ALCIR (p=0.013). Receiver operating characteristic(ROC) analysis performed for the prediction of cholestasis in all patients demonstrated that first and third- trimester ACRI, De Ritis, and ALCIR were statistically significant (p<0.05). In the study group, ROC analysis for predicting composite adverse perinatal outcomes (CAPO) and neonatal intensive care ünit (NICU) revealed that third- trimester ACRI and De Ritis were significant predictors (p<0.05).

Conclusions: In this study for all patients first and third-trimester ACRI, De Ritis, and ALCIR were significant predictors of cholestasis, while third-trimester ACRI and De Ritis predicted NICU and CAPO in the study group. Due to their low cost and clinical applicability, these indices may provide valuable contributions to the literature.

Keywords: Intrahepatic cholestasis of pregnancy, Aspartate aminotranferase, Albumin, Creatinine, Neonatal intensive care units

Öz

Amaç: Gebeliğin intrahepatik kolestazı (GİK), olumsuz perinatal sonuç riskinin arttığı gebeliğe özgü bir karaciğer hastalığıdır. Bu çalışmanın amacı biyokimyasal indekslerin, GİK ve olumsuz sonuçların öngörüsünde potansiyel belirteçler olarak araştırmaktır.

Materyal ve metod: Bu retrospektif vaka-kontrol çalışması, tersiyer basamak bir merkezde gerçekleştirildi. Çalışmaya haziran 2022, aralık 2024 tarihleri arasında kolestaz tanılı olan 58 ve kolestaz tanılı olmayan 76 gebe hasta dahil edildi. Hastalar çalışma (grup 1) ve kontrol (grup 2) şeklinde 2 gruba ayrıldı. Çalışma ve kontrol gruplarının sonuçları karşılaştırıldı.

Bulgular: Çalışma grubunda 1. trimester albümin (p<0,001), alanin aminotransferaz (ALT) (p=0,018), aspartat aminotransferaz (AST) (p=0,007), 3. trimester ALT, AST (p<0,001) 1. trimester Albumin/Kreatinin oranı (ALCIR), AST/Kreatinin oranı (ACRİ) (p<0,05), AST/ALT oranı (De Ritis) (p<0,001) ve 3. trimester De Ritis, ACRİ (p<0,001) ve ALCIR (p=0,013) açısından anlamlı farklılıklar izlendi. Tüm hastalarda kolestaz tahmini için yapılan alıcı işletim karakteristiği (ROC) analizinde 1. trimester ve 3. trimester ACRİ, DeRitis, ALCIR (p<0,05) anlamlı olarak görülmüştür. Çalışma grubunda birleşik olumsuz gebelik sonuçları (CAPO) ve yeni doğan yoğunbakım ünitesine (NICU) yatış öngörüsü için yapılan ROC analizinde 3. trimester ACRİ ve De Ritis (p<0,05) anlamlı olarak izlenmiştir.

Sonuç: Bu çalışmada tüm hastalar değerlendirildiğinde 1. ve 3. trimester ACRİ, De Ritis ve ALCIR kolestaz öngörüsünde, çalışma grubu değerlendirildiğinde ise 3. trimester ACRİ ve De Ritis NICU ve CAPO öngörüsünde anlamlı olarak izlendi. Bu indekslerin kullanımı kolay ucuz ve klinik pratikte uygulanabilir olması sebebiyle kullanılabileceğini ve bu sebeple çalışmanın literatüre katkı sunacağını düşünmekteyiz.

Anahtar Kelimeler: Gebeliğin intrahepatik kolestazı, Aspartat aminotransferaz, Albümin, Kreatinin, Yeni doğan yoğun bakım

Corresponding Author: Hüseyin Kayaalp, University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Department of Obstetrics and Gynecology, Perinatology Unit, Ankara, TÜRKİYE

E-mail: huseyinkayaalp.2121@gmail.com / **ORCID ID:** 0009-0001-8372-0518

Received: 20.12.2025 / **Accepted:** 05.03.2026

Cite this article as: Kayaalp H, Ayçiçek S. Evaluation of Maternal and Fetal Outcomes and Biochemical Indices in Intrahepatic Cholestasis of Pregnancy. Harran Üniversitesi Tıp Fakültesi Dergisi (Journal of Harran University Medical Faculty) 2026;23(1):123-131. DOI: 10.35440/hutfd.1845800.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-specific liver disorder and, when diagnosis and treatment are delayed, it may lead to significant maternal and fetal complications (1). The diagnosis of ICP is primarily based on elevated serum bile acid levels (2). Clinically, the most prominent symptom is intense pruritus, particularly beginning in the second or third trimester, which typically resolves spontaneously after delivery (3).

Elevated bile acids in the maternal circulation resulting from impaired bile flow due to various causes or hepatocellular oxidative stress, inflammation, and injury may cross the placenta and have been shown to contribute to adverse perinatal outcomes such as preterm birth, fetal distress, meconium-stained amniotic fluid, sudden intrauterine fetal demise, and increased need for neonatal intensive care (2-5). Previous studies have demonstrated that hepatocellular injury in ICP leads to increases in serum Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and other biochemical markers (6-9). Considering the adverse outcomes associated with ICP, early diagnosis and careful interpretation of laboratory parameters are essential.

In recent years, several biochemical indices have been increasingly utilized for this purpose. In the present study, we aimed to compare maternal and fetal outcomes between patients diagnosed with ICP and healthy pregnant controls, and to evaluate the predictive value of indices such as the AST/Creatinine ratio (ACRI), Albumin/Creatinine ratio (ALCIR), and AST/ALT ratio (De Ritis) in identifying ICP and forecasting adverse outcomes.

Materials and Methods

Study Population

This study was designed as a retrospective, single-center, case-control study. Written informed consent was obtained from all patients included in the study. Pregnant women aged 18–45 years who were diagnosed with intrahepatic cholestasis of pregnancy at a tertiary care hospital between June 2022 and December 2024 were included in the study. The exclusion criteria of the study were defined as the presence of major fetal anomalies, pregnancies with fetuses known to have genetic defects, multiple pregnancies, those with comorbid diseases, and pregnancies with preterm premature rupture of membranes (PPROM).

In this study, patients with fasting plasma bile acid levels ≥10 µmol/L were considered to have cholestasis, in accordance with previously established diagnostic criteria. In accordance with established diagnostic criteria, patients with fasting serum bile acid levels ≥10 µmol/L were diagnosed with ICP. Among these, patients with bile acid levels between 10–39 µmol/L were classified as having mild cholestasis, whereas those with levels ≥40 µmol/L were defined as having severe cholestasis. (8). Patients were categorized as the study group (Group 1) and the control group (Group 2). The study group consisted of patients diagnosed with cholestasis, while the control group included pregnant women selected from a low-risk population without systemic diseases (such as neurological, cardiac, thoracic, gastrointestinal, genitourinary, endocrine, or gastrointestinal disorders) or obstetric pathologies (such as preeclampsia, gestational diabetes mellitus (GDM), or PPROM). Homogeneity was ensured between the study and control groups regarding the evaluation periods of blood parameters: the first trimester(0–14 weeks) and the third trimester(28–36 weeks). All stages of the study were conducted in accordance with the Declaration of Helsinki. This study was approved by the Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (approval no: 544, date: July 11, 2025).

Data Collection

The clinico-demographic characteristics and obstetric histories of the included patients were recorded. First-trimester and third-trimester blood values (albumin, ALT, AST, creatinine, ACRI, De Ritis, and ALCIR) were examined and documented. Delivery mode, gestational week at delivery, and birth weight were also recorded. Neonatal outcomes including 1- and 5-minute APGAR scores, neonatal intensive care unit (NICU) admission, NICU admission was defined as hospitalization due to any clinical indication, including respiratory distress, neonatal hypoglycemia, hyperbilirubinemia requiring treatment, and prematurity. Composite adverse perinatal outcome (CAPO) components (NICU admission, 5-minute APGAR<7, cord pH < 7.1) were also collected. ALT, AST, creatinine and albumin levels were analyzed using the Architect C8000 system (Abbott, USA); All tests were performed in our clinical laboratory in accordance with ISO 15189 standards.ACRI was calculated as AST (U/L) divided by serum creatinine (mg/dL) (AST/creatinine). The De Ritis ratio was defined as AST (U/L) divided by ALT (U/L). ALCIR was calculated as serum albumin (g/dL) divided by serum creatinine (mg/dL). No normalization to the upper limit of

normal AST was performed.These calculations were performed using the SPSS 25.0 statistical software program (SPSS Inc., Chicago, IL, USA).

Statistical Analysis

Statistical analysis were performed us ing SP SS version 25.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess normality of data distribution. The Mann-Whitney U test was used for variables that did not show a normal distribution. Descriptive statistics for non-normally distributed data were expressed as median and interquartile range. Categorical variables were compared using the chi-square test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive ability for cholestasis, NICU and CAPO. An a priori power analysis was performed assuming an alpha level of 0.05 and a desired statistical power of 80% for the primary comparison between the ICP and control groups. The final sample size was considered sufficient to achieve adequate statistical power. A p-value <0.05 was considered statistically significant.

Results

A total of 134 patients were included in the study, consisting of 58 patients in the ICP group and 76 patients in the control group.

There were significant differences between the groups in terms of gestational age at delivery (p<0.001), birth weight (p=0.001), 1-minute APGAR score (p=0.004), 5-minute APGAR score (p<0.001), and cord pH (p=0.05) (Table 1). No significant differences were observed regarding maternal age, gravidity, parity, body mass index (BMI), mode of delivery, week of blood sampling (p>0.05) (Table 1). 81% of the patients had a mild form of the disease, while 19% had a severe form; 22.4% of them used Ursofalk (Table 1).

Significant differences were found between the groups for preterm birth (p<0.001), NICU admission (p=0.005), and CAPO (p<0.001) (Table 1).

Table 1. Comparison of the clinico-demographic characteristics of the groups

		(Group 1) Cholestasis (n:58)	(Group 2) Control (n:76)	p value
Age (years) median (IQR)		28.5 (7.0)	30.0 (7.0)	0.302
Gravidity, median (IQR)		2.0 (2.0)	2.0 (2.0)	0.771
Parity, median (IQR)		1.0 (1.0)	1.0 (1.0)	0.130
BMI(kg/m^2), median (IQR)		26.2 (9.5)	25.0 (10.3)	0.686
Week of blood sampling, medyan (IQR)	1st trimester	10.2 (2.05)	10.3 (2.15)	0.745
	3rd trimester	32.0 (4.32)	31.5 (4.05)	0.801
Weeks of birth, median (IQR)		37.0 (2.0)	39.2 (1.9)	<0.001
Fetal weight, median (IQR)		2902 (497.5)	3230 (532.5)	<0.001
1-.minute APGAR, median (IQR)		7.0 (1.0)	8.0 (1.0)	0.004
5- minute APGAR, median (IQR)		9.0 (1.0)	9.0 (0.0)	<0.001
Umb cord pH, median (IQR)		7.28 (0.15)	7.36 (0.07)	0.050
Umb cord BE, median (IQR)		-4.4 (3.3)	-2.2 (5.3)	0.187
FBA (µmol/L), Cholestasis type, (n/%)	10 -39 Mild	47.0 (81.0)		
	≥40 Severe	11.0 (19.0)		
Number of patients using Ursofalk, (n/%)	Yes	13 (22.4)		
	No	45 (77.6)		

Table 1. Continued				
Mode of delivery, (n/%)	VD	20.0 (34.5)		
	CS	38.0 (65.5)		
PTB, (n/%)		19.0 (32.7)	2.0 (2.6)	<0.001
NICU, (n/%)		11.0 (19.0)	3.0 (3.9)	0.005
NICU indications,(n/%)	Respiratory failure	6.0 (54.5)	2.0 (66.6)	0.005
	Hypoglycemia	1.0 (9.1)	0.0 (0.0)	
	Hyperbilirubinemia	2.0 (18.2)	0.0 (0.0)	
	Prematurity	2.0 (18.2)	1.0 (33.4)	
CAPO, (n/%)		14.0 (24.1)	3.0 (3.9)	0.001
NICU: Neonatal intensive care unit, CAPO: Composite adverse perinatal outcome, PTB: Preterm birth, BMI: Body mass index, statistical test Mann-Whitney U, IQR: Interquartile range, VD: Vagınal delivery, CS: Cesarean section delivery, FBA: Fasting bile acid, Significant value p<0.05				

There were no significant differences in first- or third-trimester creatinine levels (p>0.05), whereas significant differences were observed for first-trimester albumin (p<0.001), ALT (p=0.018), AST (p=0.007), and third-trimester albumin (p=0.003), ALT (p<0.001), and AST (p<0.001) (Table 2).

Table 2. Comparison of maternal laboratory results and indices between the groups				
	(Group 1) (n:58) median (IQR)	**(Group 2) (n:76) median (IQR)**	**p value**	
Albumin (g/L)	1st trimester	40.5(5.0)	45.0(2.0)	<0.001
	3rd trimester	36.0(3.)	37.0(3.0)	0.003
Creatinine(mgdL)	1st trimester	0.53(0.13)	0.52(0.13)	0.811
	3rd trimester	0.48(.0.09)	0.47(0.11)	0.201
ALCIR	1st trimester	76.4(15.4)	85.2(18.6)	0.005
	3rd trimester	73.1(12.3)	78.2(18.2)	0.013
FBA (µmol/L)	1st trimester	10.5(5.0)		
	3rd trimester	27.5(22.2)		
ALT(U/L)	1st trimester	23.5(24.0)	18.5(9.75)	0.018
	3rd trimester	30.0(33.0)	12.0(6.0)	<0.001
AST(U/L)	1st trimester	20.5(18.0)	17.0(6.75)	0.007
	3rd trimester	25.0(23.0)	16.0(8.0)	<0.001
De Ritis	1st trimester	0.69(0.39)	0.88(0.37)	<0.001
	3rd trimester	0.91(0.32)	1.2(0.65)	<0.001
ACRI	1st trimester	40.8(42.8)	32.0(15.3)	0.018
	3rd trimester	52.1(45.5)	34.4(18.8)	<0.001
FBA: Fasting bile acid, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ACRI : AST/cratinine ratio, ALCIR: Albumin /creatinine ratio, De Ritis: AST/ALT ratio, Statistical test Mann-withney U, IQR: Interquartile range, Significant value p<0.05, 1st: First, 3rd: Third				

The groups differed significantly in terms of first- trimester ALCIR (p=0.005), ACRI (p=0.018), and De Ritis ratio (p<0.001), as well as third- trimester ALCIR (p=0.013), De Ritis ratio (p<0.001), and ACRI (p<0.001) (Table 2).

In ROC analysis for predicting cholestasis, the following results were obtained: first- trimester ACRI (AUC=0.624; p=0.016; cutoff 33.0; sensitivity 61.1%; specificity 55.3%) with values above the cut-off associated with an increased likelihood of ICP, De Ritis ratio (AUC=0.618; p=0.022; cut-off 0.775; sensitivity 63.0%; specificity 61.1%) with values below the cut-off indicating a higher probability of ICP, ALCIR (AUC=0.641; p=0.006; cutoff 79.0; sensitivity 59.3%; specificity 57.9%) with lower values associated with ICP.

For the third-trimester ACRI (AUC=0.817; p<0.001; cutoff 43.3; sensitivity 77.8%; specificity 76.3%) with values above the cut-off linked to cholestasis, De Ritis ratio (AUC=0.731; p<0.001; cutoff 1.02; sensitivity 72.2%; specificity 60.5%) with values below the cut-off associated with ICP, ALCIR (AUC=0.618; p=0.022; cutoff 75.2; sensitivity 59.3%; specificity 57.8%) with lower values indicating cholestasis demonstrated predictive performance.

These results are shown in Table 3, and the ROC curves are presented in Figures 1 and 2.

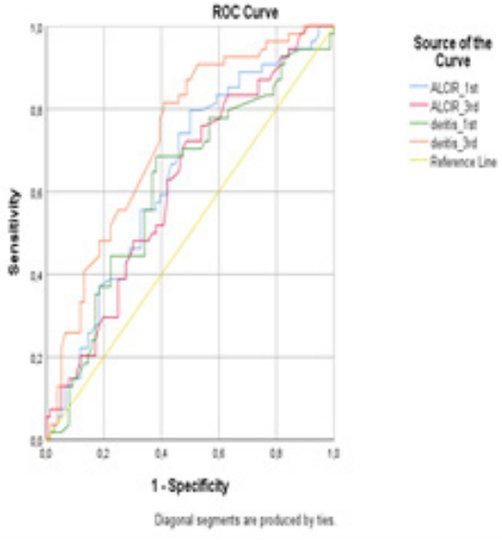

Figure 1. ROC curve analysis of first- and third-trimester ALCIR and De Ritis indices for predicting cholestasis

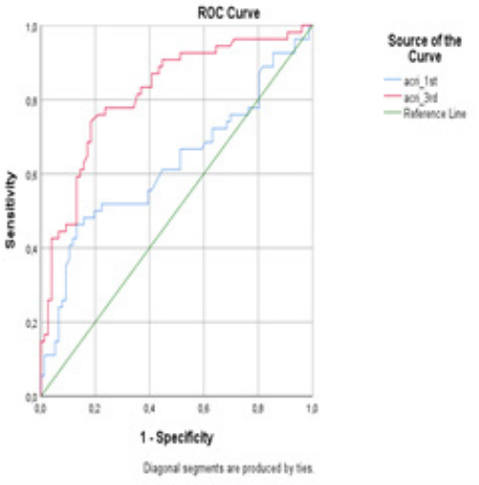

Figure 2. ROC curve analysis of first- and third-trimester ACRI for predicting cholestasis

For predicting CAPO in the ICP group, third- trimester ACRI (AUC=0.676; p=0.038; cutoff 63.3; sensitivity 70.6%; specificity 69.2%) with values above the cut-off associated with increased risk, and the De Ritis ratio (AUC=0.677; p=0.036; cutoff 0.911; sensitivity 64.7%; specificity 59.0%) with values below the cut-off indicating higher risk, were significant predictors. These findings are shown in table 4, and the ROC curves are illustrated in Figure 3.

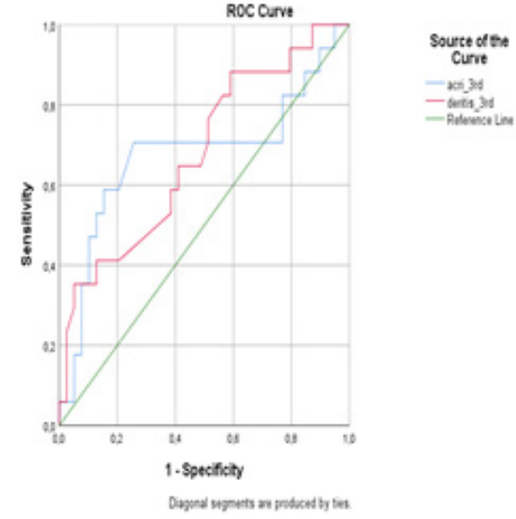

Figure 3. ROC curve analysis of third-trimester ACRI and De Ritis for predicting CAPO

Table 3. ROC analysis results of first- and third-trimester blood parameters for predicting cholestasis

	Area	Standard deviation	p value	AUC 95% ALT	AUC 95% ÜST	Cut-off value	Sensitivity	Specificity
1st trimester ACRI	0.624	0.052	0.016	0.522	0.727	33.0	61.1	55.3
3rd trimester ACRI	0.817	0.038	<0.001	0.742	0.893	43.3	77.8	76.3
1st trimester De Ritis	0.618	0.050	0.022	0.519	0.717	0.775	63.0	61.1
3rd trimester De Ritis	0.731	0.044	<0.001	0.644	0.817	1.02	72.2	60.5
1st trimester ALCIR	0.641	0.049	0.006	0.545	0.736	79.0	59.3	57.9
3rd trimester ALCIR	0.618	0.049	0.022	0.522	0.715	75.2	59.3	57.8

1st trimester, De Ritis: First trimester, AST/ALT ratio 1st trimester, ACRI : First trimester, AST/creatinine ratio, 1st trimester, ALCIR: First trimester Albumin/Creatinine ratio, 3rd trimester De Ritis: Third trimester AST/ALT ratio, 3rd trimester ACRI: Third trimester AST/ creatinine ratio, 3rd trimester ALCIR: Third trimester Albumin/Creatinine ratio, Significant value p<0.05, 1st: First, 3rd: Third

For predicting NICU in the ICP group, third- trimester ACRI (AUC=0.666; p=0.050; cutoff 60.4; sensitivity 64.7%; specificity 64.1%) with values above the cut-off associated with increased NICU risk, and the De Ritis ratio (AUC=0.676; p=0.037; cutoff 0.925; sensitivity 64.7%; specificity 64.1%) with values below the cut-off indicating a higher likelihood of NICU admission, were significant predictors. These results are presented in Table 4, with ROC curves shown in Figure 4. Since NICU admission was included as a component of CAPO, the analyses are partially overlapping.

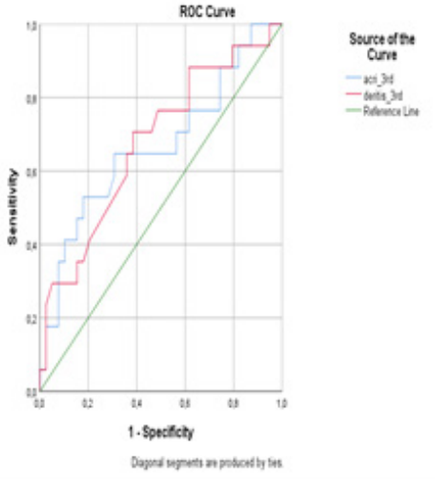

Figure 4. ROC curve analysis of third-trimester ACRI and De Ritis for predicting NICU

Table 4. ROC analysis results of third-trimester blood parameters for predicting NICU and CAPO in the cholestasis group

		Area	Standard deviation	p value	AUC 95% ALT	AUC 95% AST	Cut-off value	Sensitivity	Specificity
CAPO	3rd trimester ACRI	0.676	0.090	0.038	0.499	0.853	63.3	70.6	69.2
	3rd trimester DeRitis	0.677	0.079	0.036	0.522	0.832	0.911	64.7	59.0
NICU	3rd trimester ACRI	0.666	0.084	0.050	0.521	0.831	60.4	64.7	64.1
	3rd trimester DeRitis	0.676	0.080	0.037	0.521	0.832	0.925	64.7	64.1

3rd tr ACRI: Third trimester AST/ creatinine ratio, 3rd tr DeRitis: Third trimester AST/ ALT ratio, CAPO: Composite adverse perinatal outcome, NICU: Neonatal ıntensive care unit, Significant value p<0.05 3rd: Third

Discussion

The aim of this study was to compare the maternal and fetal outcomes of patients diagnosed with ICP with those of healthy controls, and to evaluate the predictive role of the studied indices for cholestasis, NICU, and CAPO. In this study, the ICP group demonstrated lower maternal age, gestational age at delivery, birth weight, 1- and 5-minute APGAR scores, and cord pH, whereas PTB, NICU admission, and CAPO were significantly higher. First- and third- trimester ACRI values were significantly higher in the ICP group, while De Ritis and ALCIR values were significantly lower. ROC analysis performed in all patients showed that first- and third- trimester ACRI, De Ritis, and ALCIR were significant predictors of cholestasis. Furthermore, in the ICP group, third- trimester ACRI and De Ritis were significant predictors of CAPO and NICU.

ICP is the most common pregnancy-specific liver disorder, and delayed diagnosis or treatment may lead to significant maternal and fetal complications (1). Elevated bile acids resulting from impaired bile flow, oxidative stress, inflammation, or hepatocellular injury can cross the placenta and have been shown to cause adverse perinatal outcomes such as preterm birth, fetal distress, meconium-stained amniotic fluid, sudden intrauterine demise, and increased NICU (4,5). Numerous studies have supported these findings. In a meta-analysis by Ovadia et al., increasing disease severity was associated with a higher risk of adverse outcomes (9). Similarly, Sarker et al. reported increased rates of PTB in their recent study (2). Garcia et al. and Geenes et al. found that PTB, NICU admission, low Apgar scores, fetal asphyxia, and other adverse outcomes were significantly more frequent in ICP patients than in controls (10,11). Consistent with the literature, our study also demonstrated lower Apgar scores, lower cord pH, and higher rates of PTB and NICU in the ICP group.

Due to cholestasis or hepatocellular injury, disturbances occur in the synthesis, degradation, and clearance of serum biochemical parameters, resulting in elevated ALT and AST levels (6,7). Additionally, hepatic dysfunction may reduce albumin synthesis, whereas renal alterations may impair creatinine clearance, resulting in higher creatinine and lower albumin levels. Studies have reported increased ALT, AST and decreased albumin levels in ICP patients (1,12,13). However, creatinine findings have varied across studies, with some showing decreased, normal, or increased levels (14,15). In our study, albumin was significantly lower and ALT, AST significantly higher in accordance with the literature, while creatinine levels were comparable between the groups. These discrepancies may be related to disease severity and comorbid conditions.

The De Ritis ratio, traditionally known as the De Ritis ratio, has been used to differentiate various hepatic disorders (16–18). Studies by Dinçgez and Kale in ICP patients showed significantly lower De Ritis ratios compared with healthy controls, with suggested cutoffs of ≤1.3 and <1.07, respectively (19,20). Yılmaz et al. similarly reported significantly reduced De Ritis ratios, identifying an optimal cutoff of 1.09 and demonstrating a strong negative correlation with APRI (21). In the present study, the De Ritis ratio was also significantly lower in the ICP group. Although most studies have focused on its diagnostic value for cholestasis rather than adverse outcomes, one study investigating severe fever with thrombocytopenia syndrome (SFTS) found increased creatinine, ALT, AST, and De Ritis ratios in non-survivors (22). Yılmaz et al. also reported that the De Ritis ratio was negatively associated with birthweight and gestational age in ICP; however, they did not report its association with NICU (21). In our study, the De Ritis ratio was lower in ICP patients than controls in the third trimester, but higher in both groups compared with the first trimester. Additionally, in the advanced stage of cholestasis, third- trimester De Ritis was associated with adverse outcomes, similar to the findings of Wang et al. (22). ROC analysis also demonstrated that De Ritis significantly predicted CAPO and NICU.

To our knowledge, no previous study has evaluated ACRI in pregnancy. Prior research has primarily focused on APRI in predicting cholestasis and adverse outcomes. Therefore, we considered this an important gap in the literature. In our study, first- trimester ACRI was significantly higher in the ICP group, and ROC analysis demonstrated significant predictive value for cholestasis (AUC=0.624; p=0.016; cutoff 33.0; sensitivity 61.1%; specificity 55.3%). This suggests that ACRI may be a useful, practical biomarker when used alongside other indices. Although pregnancy-related data on ACRI are limited, studies in other medical conditions have shown meaningful associations: Wu et al. reported that elevated ACRI was associated with mortality in non-alcoholic steatohepatitis (NASH), and Feng et al. also found higher ACRI in patients at increased risk for Metabolic dysfunction–associated steatohepatitis MASH (14,23). In our study, third-tr ACRI was significantly higher in ICP patients and showed borderline significance for predicting NICU admission. This index may be promising in more severe cases involving both hepatic and renal dysfunction.

ALCIR has been evaluated predominantly in studies of urinary albumin/creatinine ratios, generally in non-pregnant populations. The only pregnancy-related study we identified was in preeclampsia, where Nisell et al. (24) reported an AUC of 0.985 and high predictive accuracy for 24-hour urinary protein

excretion. Outside obstetrics, serum albumin/creatinine ratio has recently emerged as a marker of systemic inflammation, metabolic stress, and organ dysfunction. In a large cohort of 2,625 heart failure patients, low serum ALCIR was associated with significantly increased mortality and was proposed as an independent predictor of cardiometabolic risk (25). Similarly, in septic patients, higher ALCIR was associated with better outcomes, suggesting it may reflect systemic inflammatory burden and metabolic reserve (26). In our study, third- trimester ALCIR was significantly different between groups and ROC analysis showed significant predictive value for cholestasis in both trimesters; however, it did not significantly predict CAPO or NICU outcomes.

The strengths of this study include its design as a tertiary-center case-control study examining novel indices in high-risk pregnancy. Limitations include its retrospective nature, single-center design, and limited sample size.

Conclusion

This study demonstrated that ACRI, De Ritis, and ALCIR differed significantly between ICP patients and healthy controls. ROC analysis showed that first- and third- trimester ACRI, De Ritis, and ALCIR significantly predicted cholestasis. Third- trimester ACRI and De Ritis also showed borderline significance in predicting NICU and CAPO. These indices may be useful, inexpensive, and practical tools for clinical practice. We believe that their predictive value for adverse outcomes will be further clarified through larger studies involving more severe cases and combined index analyses. This study contributes to the literature by evaluating underexplored indices in high-risk pregnancies, comparing them with healthy pregnancies, and assessing their predictive performance for cholestasis and adverse outcomes within the same research framework.

Ethical Approval: *This study was approved by the Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (approval no: 544, date: July 11, 2025).*

Author Contributions:

Concept: H.K., S.A.
Literature Review: H.K., S.A.
Design: H.K., S.A.
Data acquisition: H.K., S.A.
Analysis and interpretation: H.K., S.A.
Writing manuscript: H.K., S.A.
Critical revision of manuscript: H.K., S.A.

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

Financial Disclosure: *Authors declared no financial support.*

References

1. Allen K, Jaeschke H, Copple BL. Bile acids induce inflammatory genes in hepatocytes: a novel mechanism of inflammation during obstructive cholestasis. Am J Pathol. 2011;178(1):175-86.
2. 2.Sarker M, Ramirez Zamudio A, DeBolt C, Ferrara L. Beyond stillbirth: intrahepatic cholestasis of pregnancy severity and associations with adverse neonatal outcomes. Am J Obstet Gynecol. 2022;227(3):517.e1-517.e7.
3. 3.Roediger R, Fleckenstein J. Intrahepatic cholestasis of pregnancy. Clin Liver Dis (Hoboken). 2024;23(1):e0119.
4. 4.Zorić L, Štritof PG, Čičak H, Zekan P, Pavasović MG, Blagaić V, et al. Validation of a bile acid determination method and establishment of reference intervals for biochemical and hematological parameters in pregnant women in the third trimester. Clin Chem Lab Med. 2024;62(10):2048-61.
5. 5.Zhou Q, Yuan Y, Wang Y, He Z, Liang Y, Qiu S, et al. The severity of intrahepatic cholestasis of pregnancy increases the risk of adverse outcomes beyond stillbirth: evidence from 15,826 pregnancies. BMC Pregnancy and Childbirth. 2024;24(1):476.
6. Wood AM, Livingston EG, Hughes BL, Kuller JA. Intrahepatic cholestasis of pregnancy: a review of diagnosis and management. Obstet Gynecol Surv. 2018;73:103-9.
7. Terrault NA, Williamson C. Liver diseases associated with pregnancy. Gastroenterology. 2022;163(1):97-117.e1.
8. Lagon EP, Soffer MD, James KE, Mecklai K, Li DK, Schaefer EA, et al. Gestational age trends at delivery and adoption of societal guidelines for intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol MFM. 2022;4:100709.
9. Ovadia C, Seed PT, Sklavounos A, Geenes V, Di Illio C, Chambers J, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: A meta-analysis of individual patient data. Lancet. 2019;393(10174):899-909.
10. Garcia-Flores J, Canamares M, Cruceyra M, Garicano A, Espada M, Lopez A, et al. Clinical value of maternal bile acid quantification as a predictor of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy. Gynecol Obstet Invest. 2015;79:222-8.
11. Geenes V, Chappell LC, Seed PT, Philip J Steer , Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population based case control study. Hepatology. 2014;59:1482-91.
12. Cemortan M, Iliadi-Tulbure C, Sagaidac I, Cernetchi O. Evaluation of aspartate aminotransferase/platelet ratio index and fibrosis-4 index score in women with intrahepatic cholestasis of pregnancy. AJOG Glob Rep. 2024;4(2):100337.
13. Yang J, Chen C, Liu M, Zhang S. No increased risk of adverse perinatal outcomes in women successfully treated for severe intrahepatic cholestasis of pregnancy. Medicine (Baltimore) 2019;98(27):e16214.
14. Wu XX, Zheng KI, Boursier J, Chan WK, Yılmaz Y, Romero-Gómez M, et al.

acNASH index to diagnose non-alcoholic steatohepatitis: a prospective derivation and global validation study. EClinicalMedicine. 2021;41:101145.
15. Liu H, Zhang J, Yu J, Li D, Jia Y, Cheng Y, et al. Prognostic value of serum albumin–creatinine ratio in patients with acute myocardial infarction: Findings from a retrospective acute chest pain study. Medicine (Baltimore). 2020;99(35):e22049.
16. De Ritis F, Coltorti M, Giusti G. An enzymatic test for the diagnosis of viral hepatitis: serum transaminase activities. Clin Chim Acta. 1957;2(1):70-4.
17. Botros M, Sikaris KA. The De Ritis ratio: the test of time. Clin Biochem Rev. 2013;34(3):117-30.
18. Wroblewski F. The clinical significance of alterations in transaminase activity of serum and other body fluids. Adv Clin Chem. 1958;1(2):313-51.
19. Dincgez B, Ozgen G, Ozgen L. Comparison of the predictive role of first trimester APRI score and De Ritis ratio in intrahepatic cholestasis of pregnancy. J Contemp Med. 2024;14(5):222-7.
20. Kale I. Predictive value of aspartate aminotransferase to platelet ratio index and aspartate aminotransferase to alanine aminotransferase ratio in early diagnosis of intrahepatic cholestasis of pregnancy. Med Sci Discov. 2021;8(11):650-4.
21. Yılmaz EBS, Sağlam E, Yalçın S, Özler MR. Diagnostic and prognostic value of APRI and De Ritis ratio in intrahepatic cholestasis of pregnancy. BMC Pregnancy Childbirth. 2025;25:892.
22. Wang L, Xu Y, Zhang S, Bibi A, Xu Y, Li T. AST/ALT ratio (De Ritis ratio) represents an unfavorable prognosis in early-stage SFTS patients: an observational cohort study. Front Cell Infect Microbiol. 2022;12:725642.
23. Feng G, Mózes FE, Dongji D, Wong VWS, Pavlides M, Zheng MH, et al. acFibroMASH index for diagnosis of fibrotic MASH and prediction of liver-related events: an international multicenter study. Hepatology. 2025;23(5):785-96.
24. Nisell H, Trygg M, Sirt R. Urinary albumin/creatinine ratio in the evaluation of albuminuria in pregnancy hypertension. Acta Obstet Gynecol Scand. 2006;85(11):1327-30.
25. Li S, Xie X, Zeng X, Wang S, Lan J. Association between serum albumin/serum creatinine ratio and mortality risk in patients with heart failure. Clin Transl Sci. 2023;16(11):2345-55.
26. Hu Z, Song C, Zhang J. High serum albumin-creatinine ratio as a protective factor on clinical outcomes in critically septic patients: a retrospective study. Front Med. 2024;11:1436533.