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Diagnostic and prognostic value of transaminase complex-platelet ratio in intrahepatic cholestasis of pregnancy: A novel composite index based on routine blood tests

Gebeliğin intrahepatik kolestazında transaminaz kompleksi-trombosit oranının tanısal ve prognostik değeri: Rutin kan testlerine dayalı yeni bir bileşik endeks

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Abstract

Objective: The study aims to evaluate the transaminase complex-platelet ratio (TACPR), a novel composite biomarker derived from routine laboratory parameters, in its ability to serve as a predictor of intrahepatic cholestasis of pregnancy (ICP) and related adverse perinatal outcomes.

Materials and Methods: This retrospective study included 98 pregnant women diagnosed with ICP and 100 matched healthy controls at a tertiary referral center between January 2024 and March 2025. TACPR was calculated as (alanine aminotransferase x aspartate aminotransferase)/platelet count. Groups were compared in terms of clinical characteristics, TACPR values (first trimester and diagnosis), and perinatal outcomes. Receiver operating characteristic analysis and multivariate logistic regression were used to assess predictive performance and independent risk factors for ICP and composite adverse perinatal outcomes (CAPO).

Results: TACPR values were significantly higher in the ICP group at both time points ($p<0.001$). In the first trimester, a TACPR >1.35 predicted ICP [area under curve (AUC)=0.806], while a TACPR >1.81 predicted CAPO (AUC=0.759). At diagnosis, a TACPR >27.7 predicted severe ICP and a TACPR >7.15 predicted CAPO. TACPR >1 in the first trimester was independently associated with ICP [odds ratio (OR)=5.49, $p<0.001$], and TACPR >50 at diagnosis was independently associated with CAPO (OR=4.38, $p=0.009$). A weak yet statistically significant correlation was identified between first trimester TACPR and peak serum bile acid levels ($r=0.325$, $p=0.001$).

Conclusion: TACPR is a novel, cost-effective biomarker for early identification and risk stratification of ICP and associated perinatal complications. Its integration into routine prenatal screening may enhance timely diagnosis and intervention, particularly in resource-limited settings.

Keywords: Composite biomarker, intrahepatic cholestasis of pregnancy, liver enzymes, perinatal outcomes, TACPR

Öz

Amaç: Bu çalışmanın amacı rutin laboratuvar parametrelerinden elde edilen yeni bir bileşik biyomarker olan transaminaz kompleksi-trombosit oranının (TAKPO), gebeliğin intrahepatik kolestazı (GİHK) ve ilgili perinatal advers sonuçları öngörmede tanısal ve prognostik değerini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, Ocak 2024 ile Mart 2025 tarihleri arasında bir üçüncü basamak sevk merkezinde GİHK tanısı alan 98 hamile kadın ve 100 eşleştirilmiş sağlıklı kontrol dahil edildi. TAKPO, (alanin aminotransferaz x aspartat aminotransferaz)/platelet sayısı olarak hesaplandı. Gruplar klinik özellikler, TAKPO değerleri (ilk trimester ve tanı) ve perinatal sonuçlar açısından karşılaştırıldı. Alıcı işletim karakteristiği analizi ve çok

PRECIS: Transaminase complex-platelet ratio, a novel biomarker derived from routine blood tests, effectively predicts the onset, severity, and adverse perinatal outcomes of intrahepatic cholestasis of pregnancy.

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değişkenli lojistik regresyon, GİHK ve kompozit perinatal olumsuz sonuçlar (KAPO) için prediktif performansı ve bağımsız risk faktörlerini değerlendirmek için kullanıldı.

Bulgular: TAKPO değerleri her iki zaman noktasında da GİHK grubunda anlamlı olarak daha yüksekti (p<0,001). İlk trimesterde TAKPO >1,35 GİHK'yi [eğri altındaki alan (AUC)=0,806], >1,81 ise KAPO'yu (AUC=0,759) öngördü. Tanı anında, TAKPO >27,7 şiddetli GİHK'yi, >7,15 ise KAPO'yu öngörmüştür. İlk trimesterde TAKPO >1, GİHK ile bağımsız olarak ilişkiliydi [risk oranı (OR)=5,49, p<0,001] ve tanı anında TAKPO >50, KAPO ile bağımsız olarak ilişkiliydi (OR=4,38, p=0,009). İlk trimester TAKPO ile pik serum safra asidi düzeyleri arasında zayıf ancak anlamlı bir korelasyon gözlendi (r=0,325, p=0,001).

Sonuç: TAKPO, GİHK ve ilişkili perinatal komplikasyonların erken tanısı ve risk sınıflandırması için yeni ve maliyet-etkin bir biyomarkerdir. Rutin prenatal taramaya dahil edilmesi, özellikle kaynakların sınırlı olduğu ortamlarda, zamanında tanı ve müdahaleyi artırabilir.

Anahtar Kelimeler: Bileşik biyomarker, gebeliğin intrahepatik kolestazı, karaciğer enzimleri, perinatal sonuçlar, TAKPO

Introduction

The most prevalent prenatal liver disease is known as intrahepatic cholestasis of pregnancy (ICP)[1]. The incidence of ICP varies by geographical region, ethnic origin of the population, and accepted diagnostic criteria. It ranges from 0.3% to 5.6%[2], with an approximate rate of 0.9% in our country[3]. This disease manifests clinically in the second trimester and later stages of pregnancy, and is characterized by elevated serum bile acid (SBA) concentrations (>10 μmol/L) or abnormal liver function tests. It is frequently accompanied by pruritus, particularly on the palms or soles, without cutaneous rash. These symptoms and clinical findings usually resolve rapidly after birth[2,4].

The ICP is related to poor perinatal outcomes such as preterm birth, low birth weight (LBW), meconium-stained amniotic fluid, fetal asphyxia, and intrauterine death[2,5]. Although uncertainties remain regarding its pathogenesis, multifactorial processes (genetic predisposition, hormonal and environmental factors) are thought to play a role. An increase in bile acid concentrations in amniotic fluid, which is associated with altered expression of hepatobiliary transport proteins due to increased estrogen and progesterone levels during pregnancy, may be one of the underlying mechanisms of these complications[2,6-8].

The biomarkers of hepatocellular injury, aspartate transaminase (AST) and alanine transaminase (ALT), catalyze the transfer of amino groups from aspartic acid or alanine to ketoglutaric acid. This process is involved in gluconeogenesis, resulting in the formation of oxaloacetic acid and pyruvic acid. AST, which is found in the cytosol and mitochondria of cells, is present in the liver as well as in heart muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and red blood cells. Consequently, as compared to ALT, AST is less sensitive and specific for evaluating hepatic function. An increase in AST may also be due to non-hepatic causes[9]. ALT, a cytosolic enzyme found in high levels in the liver, is more likely than AST to increase in the blood in most liver diseases associated with hepatocyte cytosol pathology (e.g., acute viral hepatitis). Even in cases of hepatocellular damage without cell death, these enzymes tend to be released into the circulation[9,10].

The ICP is frequently diagnosed in the latter stages of pregnancy. Additionally, SBA level measurement, a valuable diagnostic tool, is costly and not readily accessible. These factors have precipitated the necessity for more accessible and cost-effective techniques, such as routine blood tests, to predict this disease in the early weeks of pregnancy. In line with these objectives, the APRI score obtained by dividing the AST by platelet (PLT) count[11]; has been associated with many pathologies previously linked to liver damage[10,12,13] has recently been introduced as a valuable and easy-to-use routine blood test index for the early prediction of ICP and adverse perinatal outcomes[4,14]. In this study, considering that ALT is a highly sensitive biomarker for liver diseases, we present the transaminase complex-platelet ratio (TACPR), obtained by adding the multiplying value of ALT to the APRI score, as a novel and more robust predictor index in ICP and its outcomes.

Materials and Methods

This retrospective study was carried out at the Perinatology Clinic of Ankara Bilkent City Hospital between January 2024 and March 2025. The study was reviewed by the Ethics Committee of the Republic of Türkiye Ministry of Health, Ankara Bilkent City Hospital, and approved by the Institutional Review Board (approval number: TABED 2-25-1116, date: 30.04.2025). Every part of the study followed the rules of the Declaration of Helsinki.

Women aged 18-45 were included in the study. The case group consisted of 98 pregnant women who were hospitalized due to ICP during the study period and gave birth in the maternity ward of our hospital. A control group of 100 healthy, low-risk pregnant women was included and matched with the case group based on demographic characteristics and median gestational weeks at blood sampling (Figure 1). The diagnosis of ICP was based on the presence of pruritus and maternal SBA concentrations >10 μmol/L following exclusion of other hepatobiliary causes[15]. Multiple gestations, pregnancies with known multisystemic diseases (malignancies, hepatobiliary, rheumatological, or cardiovascular diseases), obstetric pathologies other than ICP (gestational diabetes, hypertensive disorders of pregnancy, placental abruption), active viral or bacterial infections, and congenital anomalies were excluded from the study. No medications or medical/surgical interventions were administered to any pregnant women in the study population prior to blood sampling.

The researchers obtained the medical records of the study groups from the hospital database retrospectively. The recorded data included maternal age, body mass index (BMI) (calculated by dividing weight in kilograms by the square of height in

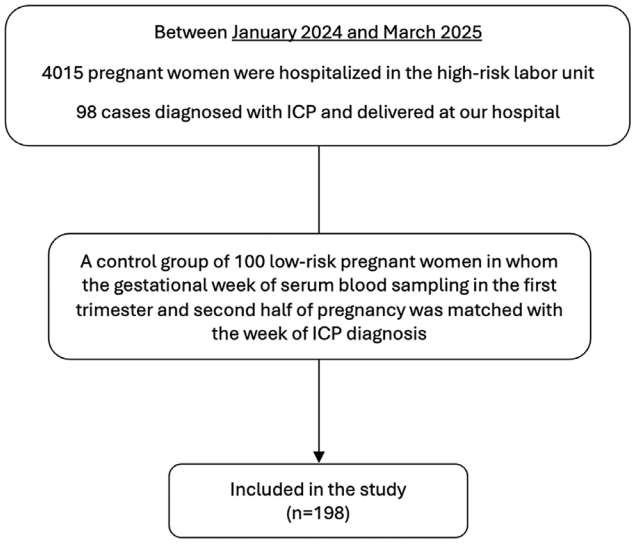

Figure 1. Flowchart of the study population

ICP: Intrahepatic cholestasis of pregnancy

meters), gravidity, parity, C-section rate, gestational age at ICP diagnosis, highest SBA concentration (μmol/L) in the case group, and first trimester and diagnosis-time AST, ALT, PLT, and TACPR values, as well as perinatal outcomes. Information on birth week and weight, 1- and 5-minute APGAR scores, preterm birth and LBW rates, presence of meconium-stained amniotic fluid, neonatal intensive care unit (NICU) admission, and stillbirth were recorded as perinatal outcomes. TACPR was calculated by dividing the product of AST and ALT values by PLT [TACPR=AST (IU/L) x ALT (IU/L)/PLT (10/L)]. While births occurring before the 37th week of pregnancy are considered preterm[16], births weighing less than 2500 grams are considered LBW[17]. Composite adverse perinatal outcomes (CAPO) are defined as stillbirth alone or the presence of at least two of the following: preterm birth, LBW, APGAR score of less than seven at 1 minute and 5 minutes, meconium-stained amniotic fluid, and admission to the NICU. The ICP and control groups were compared in terms of clinical and demographic characteristics, first trimester and diagnosis week, TACPR indices, perinatal outcomes, and CAPO.

The ICP cases were divided into two groups according to SBA levels at diagnosis: mild ICP (SBA: 10-40 μmol/L) and severe ICP (SBA >40 μmol/L)[18]. These groups, classified according to clinical severity, were compared in terms of parameters measured between the ICP and control groups, as well as the highest SBA concentrations, the number of patients receiving ursodeoxycholic acid (UDCA) treatment, and the average UDCA dose (mg/day).

Statistical Analysis

The required sample size was calculated using the G*Power software (version 3.1; Heinrich-Heine-Universität, Düsseldorf, Germany). Assuming a medium effect size (f^2=0.15), a significance level of 0.05, and 80% statistical power, the minimum sample needed was 76 participants per group. All statistical procedures were carried out with the Statistical Package for Social Sciences (SPSS, version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation if normally distributed, or as median with interquartile range or with minimum-maximum values when not normally distributed. Categorical variables were summarized as frequencies and percentages. Normality of the data was tested using the Kolmogorov-Smirnov test. For group comparisons, normally distributed continuous data were analyzed with the Independent Samples t-test, while non-normally distributed data were compared using the Mann-Whitney U test. Associations between categorical variables were assessed using the Pearson chi-square test or Fisher's exact test where appropriate.

In the ICP group, correlations between TACPR values (measured during the first trimester and at diagnosis) and peak SBA levels were examined using Pearson's correlation analysis, and the correlation coefficient (r) was reported. Receiver operating characteristic (ROC) curve analysis was applied to determine cut-off points of TACPR indices for predicting ICP development and severity, as well as CAPO occurrence, with the Youden index used to optimize sensitivity and specificity.

Multivariable logistic regression was performed to identify independent predictors of ICP and CAPO. Candidate variables with $p<0.10$ in univariate analysis were included in the multivariable model using the enter (forced entry) method. The model's calibration and goodness of fit were evaluated with the Hosmer–Lemeshow test. Results are presented as odds ratios (OR) with 95% confidence intervals CIs. A two-sided $p<0.05$ was considered statistically significant for all analyses.

Results

During the study period, a total of 4015 pregnant women were hospitalized in the high-risk labor unit, and the incidence of ICP was 2.44%. The median diagnosis week in the ICP group was at 33, and higher C-section rates were observed in this group (p=0.007). The TACPR value during the first trimester and at the diagnosis week was significantly higher in cases of ICP ($p<0.001$, all). Preterm birth, LBW, meconium-stained amniotic fluid, and NICU admission rates were significantly higher in the ICP group ($p<0.05$, all). Although stillbirth rates were higher in the ICP group, the difference was not statistically significant (p=0.244). When these adverse perinatal outcomes were evaluated, the CAPO rate was 30.6% in cases of ICP and was found to be statistically significant ($p<0.001$). Detailed data on the comparison of clinical and demographic characteristics, TACPR, and perinatal outcomes between the study groups are presented in Table 1.

No statistically significant disparity was not identified between mild and severe ICP with regard to demographic characteristics, C-section rates, and median gestational weeks at diagnosis

Table 1. Comparison of clinical and demographic data, TACPR, and perinatal outcomes between study groups

	ICP group (n=98)	Controls (n=100)	p-value*
Age	28.62±5.14	29.28±5.30	0.377[a]
BMI (kg/m^2)	27.76±2.72	27.05±2.47	0.059[a]
Gravidity	2 (1)	2 (2)	**0.017**[b]
Parity	0 (1)	1 (1)	**0.042**[b]
GA at diagnosis (weeks)	33 (5)	33 (4)[#]	0.925[b]
C-section rates	44 (44.9%)	26 (26%)	**0.007**[c]
First trimester blood parameters			
AST (IU/L)	22 (11)	16.35±5.60	**<0.001**[b]
ALT (IU/L)	27.5 (19.5)	14.85±5.67	**<0.001**[b]
PLT (10^9/L)	260.21±58.96	244.27±64.74	0.072[a]
TACPR	2.41 (3.05)	0.86 (0.95)	**<0.001**[b]
Blood parameters at the diagnosis week[#]			
AST (IU/L)	55 (64)	17.90±5.30	**<0.001**[b]
ALT (IU/L)	85.5 (112.5)	17.17±6.41	**<0.001**[b]
PLT (10^9/L)	255 (94)	243.88±64.35	**0.039**[b]
TACPR	20.67 (47.38)	1.24 (1.01)	**<0.001**[b]
Perinatal outcomes			
GA at delivery (week)	37 (1)	38 (2)	**<0.001**[b]
Preterm birth	32 (32.7%)	5 (5%)	**<0.001**[c]
Low birth weight (<2500 g)	15 (15.3%)	-	**<0.001**[c]
Birth weight (g)	2969.5±504.3	3327.45±382.27	**<0.001**[a]
APGAR score (1st min.)	7 (1)	7 (1)	0.972[b]
APGAR score (5th min.)	9 (1)	9 (0)	0.277[b]
Meconium-stained amniotic fluid	10 (10.2%)	2 (2%)	**0.018**[c]
NICU admission	25 (25.5%)	3 (3%)	**<0.001**[c]
Stillbirth	2 (2.04%)	-	0.244[c]
CAPO	30 (30.6%)	2 (2%)	**<0.001**[c]

ALT: Alanine transaminase, AST: Aspartate transaminase, BMI: Body mass index, CAPO: Composite adverse perinatal outcomes, GA: Gestational age, ICP: Intrahepatic cholestasis of pregnancy, NICU: Neonatal intensive care unit, PLT: Platelet, TACPR: Transaminase complex-to-platelet ratio

Data Presentation: Continuous variables are expressed as **mean ± standard deviation** or **median with interquartile range**, depending on distribution. Categorical data are shown as **frequency and percentage**.

[#]**Control Group Note:** The median GA at the time of sample collection in the control group was aligned with the diagnostic week of ICP in the case group.

*Significance testing was performed using:

[a]: Independent samples *t*-test

[b]: Mann-Whitney *U* test

[c]: Fisher's exact test

A *p*-value below 0.05 was regarded as statistically significant. Outcomes meeting this threshold are **emphasized in bold.**

(p>0.05, all). Although there was no significant difference in the TACPR value between the mild and severe ICP groups for the first trimester (p=0.204), the TACPR value at diagnosis was significantly higher for severe ICP cases (p<0.001). The highest SBA concentration, the percentage of patients receiving UDCA treatment, and the daily UDCA dose were significantly higher in severe ICP cases (p<0.05, all). The CAPO rate (38.5%) was also found to be significantly higher in severe ICP due to higher rates of preterm delivery, meconium-stained amniotic fluid, and admission to the NICU (p<0.05, all). Detailed data on the comparison of clinical and demographic characteristics, TACPR, and perinatal outcomes according to groups based on the clinical severity of ICP are presented in Table 2.

Table 2. Comparison of clinical and demographic characteristics, TACPR, and perinatal outcomes in groups based on the clinical severity of ICP

	Mild ICP (n=72)	Severe ICP (n=26)	p-value*
Age	28.34±5.44	28.92±5.10	0.763[a]
BMI (kg/m^2)	27.73±2.91	28.15±2.08	0.275[a]
Gravidity	2 (2)	2 (3)	0.292[b]
Parity	0 (1)	0 (2)	0.320[b]
GA at diagnosis (weeks)	33 (4)	33 (6)	0.238[b]
C-section rates	29 (40.3%)	15 (57.7%)	0.168[c]
First trimester blood parameters			
AST (IU/L)	22.08±7.83	31.12±17.24	**0.020**[a]
ALT (IU/L)	28.5 (20.5)	29 (38)	0.275[b]
PLT (10^9/L)	254.96±59.98	271.48±58.05	0.275[a]
TACPR	2.26 (2.95)	3.11 (7.7)	0.204[b]
Blood parameters at the diagnosis week			
AST (IU/L)	53.5 (58)	96 (104.5)	**<0.001**[b]
ALT (IU/L)	88 (84.25)	230.84 (227.5)	**<0.001**[b]
PLT (10^9/L)	255 (74)	265.36±76.82	0.971[b]
TACPR	17.39 (32.1)	59.1 (201.27)	<0.001[b]
Clinical characteristics			
Highest SBA concentration (µmol/L)	19.68±7.08	80.70±31.67	**<0.001**[a]
Cases treated with UDCA	56 (77.8%)	25 (96.2%)	**0.037**[c]
Dose of UDCA (mg/day)	750 (187.5)	750 (250)	**0.002**[b]
Perinatal outcomes			
GA at delivery (week)	37 (1)	36 (2)	**0.016**[b]
Preterm birth	17 (23.6%)	15 (57.7%)	**0.003**[c]
Low birth weight (<2500 g)	11 (15.3%)	4 (15.4%)	1.000[c]
Birth weight (g)	2952.5±506.42	2879.8±461	0.430[a]
APGAR score (1st min.)	7 (1)	7 (1)	**0.049**[b]
APGAR score (5th min.)	9 (1)	9 (1)	0.245[b]
Meconium-stained amniotic fluid	3 (4.2%)	7 (26.9%)	**0.003**[c]
NICU admission	10 (13.9%)	15 (57.7%)	**<0.001**[c]
Stillbirth	1 (1.4%)	1 (3.8%)	0.462[c]
CAPO	14 (19.4%)	16 (38.5%)	**<0.001**[c]

ALT: Alanine transaminase, AST: Aspartate transaminase, BMI: Body mass index, CAPO: Composite adverse perinatal outcomes, GA: Gestational age, ICP: Intrahepatic cholestasis of pregnancy, NICU: Neonatal intensive care unit, PLT: Platelet, SBA: Serum bile acid, TACPR: Transaminase complex-to-platelet ratio, UDCA: Ursodeoxycholic acid

Data Presentation: Values are expressed as mean ± standard deviation for normally distributed continuous variables, median with interquartile range for non-normally distributed data, or count (percentage) for categorical variables.

*Significance levels were assessed using the following tests:

[a]: Independent sample *t*-test,

[b]: Mann-Whitney *U* test,

[c]: Fisher's exact test.

A *p*-value below 0.05 was regarded as statistically significant. Outcomes meeting this threshold are **emphasized in bold.**

In cases of ICP, a weak positive correlation was observed between TACPR in the first trimester and the highest SBA concentration (r=0.325, p=0.001), while also no significant correlation between TACPR at the time of diagnosis and the highest SBA concentration (p=0.060). In the study population, ROC analyses were performed to calculate the optimal cut-off values of first trimester TACPR for predicting ICP and CAPO, and these values were determined as 1.35 [68.4% sensitivity, 68% specificity, (AUC) 0.806, p<0.001] and 1.81 [65.6% sensitivity, 65.7% specificity, (AUC) 0.759, p<0.001], respectively. The ROC curves for these analyses are shown in Figure 2A, 2B. In cases of ICP, the optimal cut-off value of TACPR at diagnosis for predicting severe ICP was determined to be 27.7 [69.2% sensitivity, 70.8% specificity, (AUC) 0.774, p<0.001]. In the study population, the optimal cut-off value of TACPR at diagnosis for predicting CAPO was determined to be 7.15 [75% sensitivity, 74.1% specificity, (AUC) 0.807, p<0.001]. The ROC curves for these analyses are shown in Figure 3A, 3B. A summary of ROC analyses showing the cut-off values of the first trimester and the diagnosis week TACPR indices in predicting clinical outcomes associated with ICP and CAPO is presented in Table 3.

Multivariate logistic regression analysis was conducted to identify independent predictors of ICP in the study population (n=198). The model demonstrated a good fit (Nagelkerke R^2=0.426; Hosmer and Lemeshow test, χ^2=8.606, df=8, p=0.377). Three variables exhibited statistical significance as independent predictors of ICP development. First trimester ALT levels were positively associated with the development of ICP (OR=1.16, 95% CI: 1.09-1.24, p<0.001), indicating that for each unit increase in ALT, the odds of developing ICP increased by 16%. In contrast, first trimester AST levels were inversely associated with ICP risk (OR=0.84, 95% CI: 0.78-0.90, p<0.001). Furthermore, patients with a TACPR greater than 1 in the first trimester had significantly higher odds of developing ICP (OR=5.49, 95% CI: 2.48-12.18, p<0.001) (Table 4).

Among patients diagnosed with ICP (n=98), multivariate logistic regression was performed additionally to evaluate predictors of CAPO. The model fit was robust (Nagelkerke R^2=0.477; Hosmer and Lemeshow test, χ^2=1.632, df=4, p=0.803). TACPR remained a consistent risk indicator in this subgroup analysis. A TACPR value >5 in the first trimester was associated with a threefold increase in the odds of CAPO (OR=3.06, 95% CI: 1.06-8.83, p=0.038), while a TACPR >50 at the time of ICP diagnosis was associated with a greater than fourfold increased risk (OR=4.38, 95% CI: 1.44-13.30, p=0.009). Additionally, severe ICP was independently associated with a significantly elevated risk of CAPO (OR=4.08, 95% CI: 1.39-11.93, p=0.010) (Table 5).

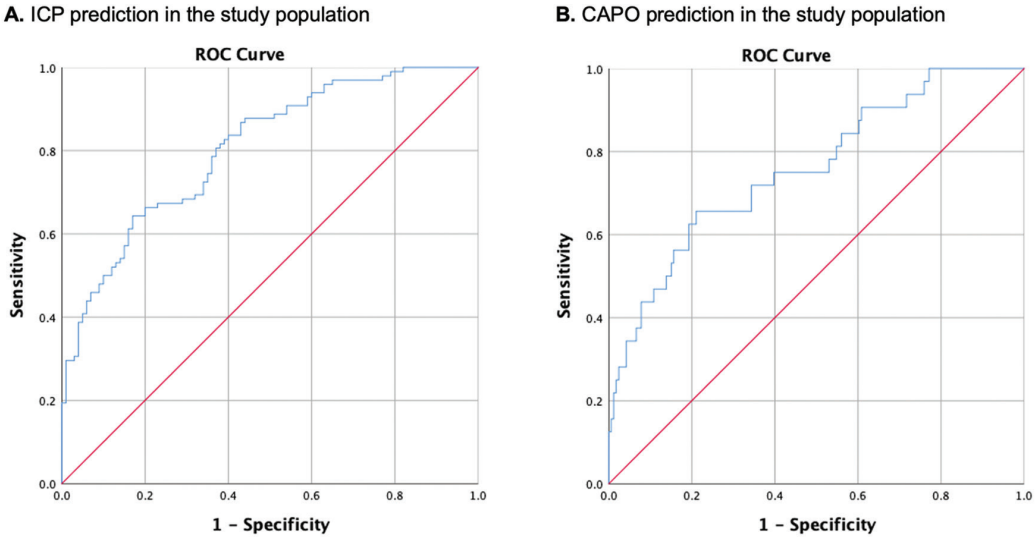

Figure 2. Receiver operating characteristic curves of first trimester TACPR in predicting ICP (A) and CAPO (B) in the study population

ROC: Receiver operating characteristic, CAPO: Composite adverse perinatal outcomes, ICP: Intrahepatic cholestasis of pregnancy, TACPR: Transaminase complex-platelet ratio

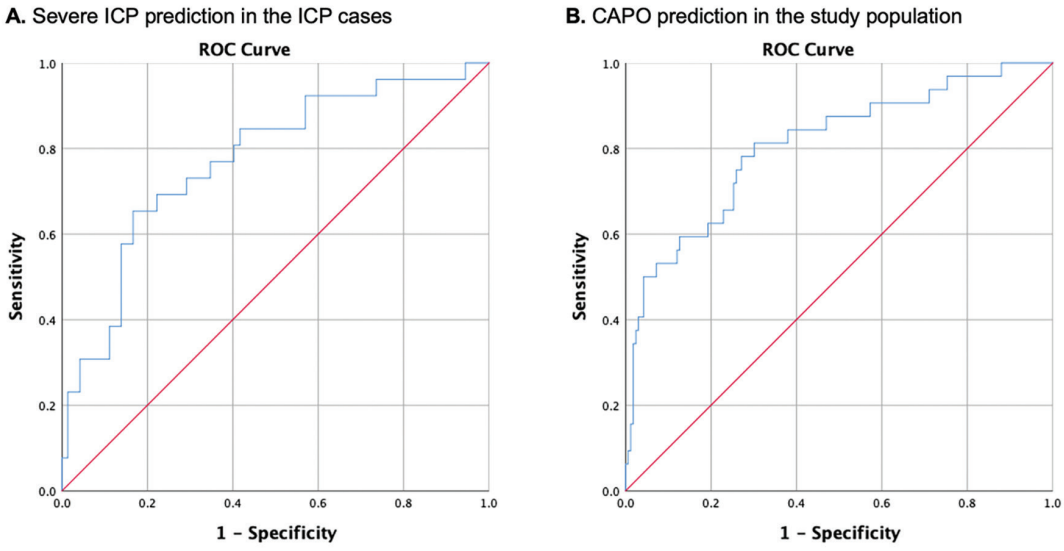

Figure 3. Receiver operating characteristic curves of TACPR at diagnosis week in predicting severe ICP in the case group (A) and CAPO in the study population (B)

ROC: Receiver operating characteristic, CAPO: Composite adverse perinatal outcomes, ICP: Intrahepatic cholestasis of pregnancy, TACPR: Transaminase complex-platelet ratio.

Table 3. Receiver operating characteristics analysis table showing cut-off values of first trimester and diagnosis week TACPR indices in predicting clinical outcomes associated with ICP and CAPO

Variable	Group	Outcome	AUC	Std. error	Sensitivity	Specificity	Asymp. Sig*	95% CI		Cut-off value
								Lower	Upper	
First trimester TACPR	All	ICP	0.806	0.030	68.4%	68%	<0.001	0.747	0.864	1.35
First trimester TACPR	All	CAPO	0.759	0.048	65.6%	65.7%	<0.001	0.665	0.853	1.81
TACPR at diagnosis week	ICP	Severe ICP	0.774	0.055	69.2%	70.8%	<0.001	0.666	0.881	27.7
TACPR at diagnosis week	All	CAPO	0.807	0.045	75%	74.1%	<0.001	0.719	0.896	7.15

AUC: Area under the curve, CI: Confidence interval, ICP: Intrahepatic cholestasis of pregnancy, TACPR: Transaminase complex-platelet ratio, CAPO: Composite adverse perinatal outcomes
*Significance threshold: p<0.05

Table 4. Multivariate logistic regression analysis table showing independent risk factors associated with ICP development in the study population

Outcome: ICP (group: all, n=198)			
Independent risk factors	OR	95% CI	p-value*
First trimester AST (IU/L)	0.84	0.78-0.90	<0.001
First trimester ALT (IU/L)	1.16	1.09-1.24	<0.001
TACPR >1 at first trimester	5.49	2.48-12.18	<0.001

ALT: Alanine transaminase, AST: Aspartate transaminase, CI: Confidence interval, ICP: Intrahepatic cholestasis of pregnancy, OR: Odds ratio, TACPR: Transaminase complex-to-platelet ratio. Nagelkerke R^2=0.426; Hosmer and Lemeshow test: $\chi 2$=8.606; df=8; p=0.377.
*Significance threshold: p<0.05

Table 5. Multivariate logistic regression analysis table showing independent risk factors associated with the occurrence of CAPO in cases of ICP

Outcome: CAPO (group: ICP, n=98)			
Independent risk factors	OR	95% CI	p-value*
TACPR >5 at first trimester	3.06	1.06-8.83	0.038
TACPR >50 at diagnosis week	4.38	1.44-13.30	0.009
Severe ICP	4.08	1.39-11.93	0.010

CAPO: Composite adverse perinatal outcomes, CI: Confidence interval, ICP: Intrahepatic cholestasis of pregnancy, OR: Odds ratio, TACPR: Transaminase complex–platelet ratio. Nagelkerke R^2=0.477; Hosmer and Lemeshow test: $\chi 2$=1.632; df=4; p=0.803.
*Significance threshold: p<0.05

Discussion

This study evaluated the clinical utility of the TACPR as a novel, composite biomarker for the early prediction and severity assessment of ICP and related adverse perinatal outcomes. The results support TACPR as a significantly elevated marker in ICP cases both in the first trimester and at the time of diagnosis, with notable correlations to disease severity and poor perinatal outcomes. To the best of our knowledge, this study is the first to propose and clinically validate TACPR as a meaningful predictor of ICP based on the combination of existing biomarkers, including APRI and ALT.

The observed incidence of ICP in our study population (2.44%) falls within the previously reported global range of 0.3% to 5.6%[2], confirming its clinical relevance in high-risk pregnancy cohorts. However, this incidence rate is higher than expected in our country[3]; which may be due to the hospital being a referral center and only high-risk pregnancies monitored in the maternity ward. In line with prior research, ICP was associated with an increased risk of preterm birth, LBW, NICU admission, and meconium-stained amniotic fluid, consistent with documented outcomes[19-21]. Although stillbirth rates were also elevated in the ICP group, the lack of statistical significance may be due to limited sample size or timely intervention in delivery planning. In addition, the CAPO rate in severe ICP (38.5%) was double that of mild cases (19.4%), further emphasizing the clinical relevance of risk stratification at diagnosis.

The ROC curve analysis confirmed TACPR's robust predictive ability for both ICP (AUC: 0.806) and CAPO (AUC: 0.759-0.807). Notably, a first-trimester TACPR >1.35 was significantly predictive of ICP, while a cut-off >1.81 was associated with CAPO. At diagnosis, a TACPR >7.15 predicted CAPO, and a value >27.7 predicted severe ICP. These findings align with previous studies emphasizing the prognostic value of early liver function tests in ICP[4,22,23]. However, our study goes further by offering a composite score that could be integrated into routine screening.

Multivariate analysis further solidified ALT and TACPR as independent predictors of ICP, echoing similar findings in non-pregnant liver disease models[11,24]. TACPR retained its predictive power even when adjusted for gestational age and BMI. Specifically, TACPR >5 in the first trimester tripled the risk of CAPO, and TACPR >50 at diagnosis increased this risk more than fourfold. These associations may reflect worsening hepatic inflammation and impaired placental function, which are hallmarks of more severe disease forms[25].

From a pathophysiological standpoint, the hepatocellular disruption seen in ICP is influenced by hormonal, genetic, and environmental factors, many of which modulate bile acid metabolism and hepatobiliary transport[20]. Previous work has shown that ALT and AST levels increase in liver disease due to hepatocyte membrane damage, even in the absence of overt necrosis[24]. ALT, being more liver-specific, showed a stronger correlation with ICP in our multivariate model, while AST, due to its broader tissue distribution and lower specificity, showed an inverse correlation in the results of the study.

No significant differences were observed in demographic or baseline clinical characteristics, such as mother's age, BMI, gravida, or parity, when comparing mild with severe ICP. This aligns with earlier studies suggesting that biochemical markers, rather than maternal characteristics, are the primary differentiators in disease severity[25]. However, in the first trimester, patients who later developed severe ICP already exhibited significantly elevated AST levels (p=0.020), hinting at an underlying subclinical hepatocellular injury early in pregnancy.

At the time of diagnosis, severe ICP cases displayed a significantly more deranged liver profile; ALT and AST values were nearly 2-3 times higher than those in the mild group, consistent with the concept that progressive cholestasis exacerbates hepatocellular stress[24]. Notably, the TACPR value at diagnosis was over threefold higher in severe ICP (median 59.1 vs. 17.39; p<0.001), reinforcing its value as a severity marker. Interestingly, while UDCA treatment was more commonly administered in severe ICP cases, and at a higher dose, this did not appear sufficient to equalize outcomes between groups. This suggests that early detection using biomarkers like TACPR may be necessary to initiate treatment before severe liver dysfunction manifests, rather than as a response to elevated SBA.

The study revealed a weak yet statistically significant positive correlation between first trimester TACPR and the highest recorded SBA concentration during pregnancy (r=0.325, p=0.001). This finding suggests that hepatic stress or dysfunction may begin well before clinical manifestations of

ICP or SBA elevation become apparent. The absence of a similar correlation at the time of diagnosis (p=0.060) could reflect confounding influences such as disease-modifying treatments (e.g., UDCA), physiological compensations, or non-linear dynamics of bile acid accumulation. These findings highlight the potential of TACPR as an early biomarker: not necessarily for directly quantifying bile acid burden, but for flagging hepatocellular vulnerability in early pregnancy. This allows clinicians to identify at-risk pregnancies before cholestasis fully manifests. This early predictive utility aligns with the increasing demand for cost-effective, non-invasive tools to optimize timing of surveillance and intervention in obstetric hepatology.

Study Limitations

Despite promising results, this study has some limitations. The retrospective, single-center design may limit generalizability, and external validation is necessary to confirm TACPR thresholds in different populations. Furthermore, while TACPR appears promising, clinical implementation would require harmonization of lab measurement units and prospective studies assessing real-world effectiveness.

Conclusion

This study demonstrated that the TACPR is a valuable, novel biomarker for the early prediction and severity assessment of ICP. First-trimester elevated TACPR values were significantly associated with subsequent ICP development and adverse perinatal consequences, such as preterm birth, NICU admission, and meconium-stained amniotic fluid. Furthermore, TACPR values at diagnosis were markedly higher in severe ICP cases and independently predicted poor perinatal outcomes.

Importantly, TACPR showed a weak but significant correlation with the highest SBA concentrations when measured in early pregnancy, suggesting its utility as an early indicator of subclinical hepatocellular stress before cholestasis becomes clinically apparent. As a simple, cost-effective index derived from routine laboratory parameters, TACPR represents a promising alternative or adjunct to SBA testing, particularly in low-resource settings where SBA assays may not be readily accessible.

Incorporating TACPR into standard prenatal screening protocols could improve the timely identification of at-risk pregnancies, allowing for closer monitoring, earlier interventions, and potentially better maternal and fetal outcomes. The necessity of future prospective studies is indicated to validate its predictive thresholds and evaluate its integration into broader clinical workflows.

Ethics

Ethics Committee Approval: This retrospective study was carried out at the Perinatology Clinic of Ankara Bilkent City Hospital between January 2024 and March 2025. The study was reviewed by the Ethics Committee of the Republic of Turkey Ministry of Health, Ankara Bilkent City Hospital, and approved by the Institutional Review Board (approval number: TABED 2-25-1116, date: 30.04.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.O., Concept: D.Ş., Design: D.Ş., Data Collection or Processing: G.O., Analysis or Interpretation: D.Ş., Literature Search: G.O., D.Ş., Writing: G.O., D.Ş.

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