Obstetrics; *Maternal Fetal Medicine and Perinatology*

Diagnostic Value of GGT/PLT, AST/ALT, and AST/PLT Ratios in Intrahepatic Cholestasis of Pregnancy: A Retrospective Analysis

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ABSTRACT

OBJECTIVES: This study evaluated the diagnostic performance of gamma-glutamyltransferase-to-platelet (GGT/PLT), aspartate aminotransferase-to-alanine aminotransferase (AST/ALT), and aspartate aminotransferase-to-platelet (AST/PLT) ratios in intrahepatic cholestasis of pregnancy (ICP), and their association with composite adverse perinatal outcomes (CAPO).

STUDY DESIGN: A retrospective cohort analysis was conducted of 329 pregnant women (156 with ICP, 173 controls) who delivered at a tertiary center between November 2022 and November 2024. ICP was diagnosed in the presence of pruritus and fasting serum bile acid levels ≥10 μmol/L. Maternal demographics, liver enzymes, platelet counts, and perinatal outcomes were retrieved from hospital records. Ratios were calculated from second-trimester laboratory results. Diagnostic performance was evaluated using receiver operating characteristic (ROC) analysis. CAPO was defined as at least one of the following: preterm birth, fetal growth restriction, oligohydramnios/polyhydramnios, premature rupture of membranes, or intrapartum fetal distress.

RESULTS: Compared with controls, the ICP group had higher GGT/PLT (0.05 [0.07] vs. 0.04 [0.07], p<0.001) and AST/PLT ratios (0.19 [0.30] vs. 0.07 [0.04], p<0.001), and a lower AST/ALT ratio (0.76 [0.55] vs. 1.09 [0.91], p<0.001). Among the ratios, AST/PLT provided the highest diagnostic accuracy for distinguishing ICP (AUC=0.840; cut-off >0.083; sensitivity 77.3%; specificity 74.8%), followed by AST/ALT (AUC=0.788; cut-off <1.060; sensitivity 75.6%; specificity 75.0%), with GGT/PLT showing the lowest diagnostic value (AUC=0.668; cut-off >0.044; sensitivity 67.5%; specificity 64.1%). The ICP group had increased rates of preterm birth (33.3% vs. 10.8%, p<0.001), NICU admission (22.4% vs. 10.4%, p=0.003), and CAPO (50.0% vs. 13.9%, p<0.001), but none of the assessed ratios were significantly associated with CAPO in ICP cases.

CONCLUSIONS: Among the indices evaluated, AST/ALT and AST/PLT ratios showed moderate-to-good accuracy in diagnosing ICP, while the GGT/PLT ratio exhibited moderate accuracy. These indices can be useful, cost-effective, and accessible adjunctive tools for ICP diagnosis, particularly in settings where bile acid testing is unavailable. However, their ability to predict perinatal outcomes is limited.

Keywords: Cholestasis; Complications; Biomarkers; Intrahepatic; Liver; Pregnancy

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most prevalent hepatic disorder in pregnancy, typically arising in the third trimester (1,2). Prevalence varies globally, with an average between 2.5% and 3.3% (3). ICP results from impaired intrahepatic bile flow, causing accumulation of bile

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acids in maternal blood due to deficient biliary excretion. The precise cause remains unknown, but it likely involves hormonal, genetic, immunologic, and environmental influences (4-6). Maternal symptoms are usually mild and resolve quickly postpartum (1,2). However, ICP is linked with substantial adverse perinatal outcomes, such as preterm birth, respiratory distress, and intrauterine fetal demise (2,4). Elevated maternal bile acids appear to cross the placenta and contribute to fetal complications. Pruritus, particularly on the palms and soles, is the hallmark of ICP. Additionally, fasting serum bile acid levels above 10 μmol/L confirm diagnosis (2,4). However, bile acid testing is costly and not always accessible, underscoring demand for alternative, affordable biomarkers.

Recently, non-invasive biochemical indices have gained attention as diagnostic tools. The GGT/PLT, AST/ALT, and AST/PLT ratios are straightforward, easily measured parameters reflecting liver injury and fibrosis (7-9). The GGT/PLT ratio, in particular, is noteworthy. It aids in predicting prognosis in various liver diseases, including chronic hepatitis B and cystic fibrosis (7,10). Moreover, the GGT/PLT ratio can surpass conventional liver enzymes, such as ALT, AST, and GGT, in identifying hepatic inflammation among chronic hepatitis B patients with normal or mildly elevated ALT levels (11).

Although ICP typically does not result in permanent maternal liver damage, it is strongly associated with adverse perinatal outcomes. It is accompanied by hepatocellular membrane injury, which can lead to elevations in ALT, AST, and GGT levels. The primary objective of the present study was to evaluate the diagnostic performance of these ratios in patients with ICP. The secondary objective was to investigate whether these biochemical indices were associated with composite adverse perinatal outcomes.

Material and Method

The study was a retrospective cohort analysis of pregnant women aged 18 to 40 years who registered and delivered at the perinatology clinic of Etlik City Hospital from November 2022 to November 2024. The study protocol received approval from the local ethics committee (AEŞH-BADEK2-2025-007) and was executed in compliance with the Declaration of Helsinki.

The diagnosis of ICP was made in patients with pruritic symptoms and fasting bile acid levels above 10 μmol/L (1). Patients with multiple pregnancies, maternal systemic diseases (pre-eclampsia, diabetes, collagen tissue diseases, etc.), maternal thrombocytosis-causing diseases, diseases that could cause maternal liver fibrosis (hepatitis, cirrhosis, etc.), fetal congenital diseases or incomplete or insufficient data were excluded from the study. The control group consisted of pregnant women with comparable maternal, gestational, and obstetric features who were not diagnosed with cholestasis. The study included 329 patients (156 in the ICP group and 173 in the control group).

We collected data on maternal age, gestational age, parity, and BMI (kg/m²) at diagnosis. We also recorded platelet count (10^9/L), AST, ALT, GGT, serum bile acids, gestational age at delivery, birth weight, mode of delivery, complications, neonatal intensive care, and CAPO. CAPO meant at least one of the following: spontaneous preterm birth, fetal growth restriction (FGR), oligohydramnios or polyhydramnios, preterm rupture of membranes, or fetal compromise (defined as category III fetal heart rate by ACOG guidelines (12)). We calculated study parameters from fasting bile acid tests taken at diagnosis. We compared outcomes between the ICP and control groups. In the ICP group, we also compared those with and without CAPO. We compared GGT/PLT, AST/ALT, and AST/PLT ratios between these groups.

Statistical analysis

IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA), was used for statistical analyses. Categorical variables were expressed as numbers and percentages, whereas continuous variables were presented as medians with interquartile ranges (IQRs; 25th–75th percentiles). The Kolmogorov-Smirnov test was used to assess the assumption of normality for continuous variables. Since most variables were not normally distributed, non-parametric tests were applied. Accordingly, the Mann–Whitney U test was used to compare continuous variables between two independent groups. Pearson's chi-square test or Fisher's exact test was used for categorical variables, as appropriate. The diagnostic performance of the GGT/PLT, AST/ALT, and AST/PLT ratios was evaluated using receiver operating characteristic (ROC) curve analysis, and optimal cut-off values were determined using the Youden index. A p-value of less than 0.05 was considered statistically significant.

Sample Size and Power Analysis: Sample size calculation was performed prior to the study using the G*Power 3.1 software. Based on a two-tailed independent samples t-test with an effect size of Cohen's d=0.607 (derived from Hu et al. (7)), a significance level of α=0.05 and a target power of 95%, the minimum required sample size was calculated as 72 participants per group (total n=144), resulting in an achieved statistical power of 95.18%.

Although the calculation initially assumed equal group sizes, several patients in the ICP group were excluded after data screening due to predefined exclusion criteria and incomplete records, resulting in a final ICP sample size of 156. The control group size was intentionally not reduced in order to avoid unnecessary loss of statistical power and to preserve the robustness of the statistical analyses.

Results

Maternal age, number of pregnancies, number of births, BMI, and platelet count did not differ significantly between the ICP and control groups (all p > 0.05). Nonetheless, notable variations were observed in liver enzyme levels and the derived ratios. Compared with controls, the ICP group's median GGT/PLT ratio was considerably higher (0.05 [0.07] vs. 0.04 [0.07], p<0.001). Similarly, the AST/ALT ratio was lower in the ICP group than in the control group (0.76 [0.55] vs. 1.09 [0.91], p<0.001). Additionally, the ICP group had a substantially higher AST/PLT ratio (0.19 [0.30] vs. 0.07 [0.04], p<0.001). The median fasting serum bile acid level in the ICP group was 19.3 µmol/L (Table I).

The diagnostic effectiveness of biochemical ratios in identifying ICP was evaluated using receiver operating characteristic (ROC) curve analysis. The GGT/PLT ratio showed a cut-off value of >0.044 with a sensitivity of 67.5% and a specificity of 64.1% (AUC=0.668, 95% CI: 0.602–0.735, p<0.001). The AST/ALT ratio had a cut-off value of <1.060, yielding a sensitivity of 75.6% and a specificity of 75.0% (AUC=0.788, 95% CI: 0.737–0.839, p<0.001). The AST/PLT ratio had the strongest predictive value, with a cut-off of >0.083, 77.3% sensitivity, and 74.8% specificity (AUC=0.840, 95% CI: 0.791–0.888, p<0.001). Table II presents these findings, and Figures 1 and 2 show the ROC curves for these analyses.

Pregnancy outcomes in the ICP and control groups differed significantly, as shown in Table III. Compared with the controls, the ICP group had a lower median gestational age at birth (37.0 [1.1] vs. 38.0 [1.0] weeks, p<0.001). Additionally, the ICP group had a considerably lower mean birth weight (2905 g [623.2] vs. 3230 g [496.0], p<0.001). The mode of delivery also differed, with a higher proportion of primary cesarean sections in the ICP group (32.5% vs. 19.1%, p<0.001). Both the 1-minute and 5-

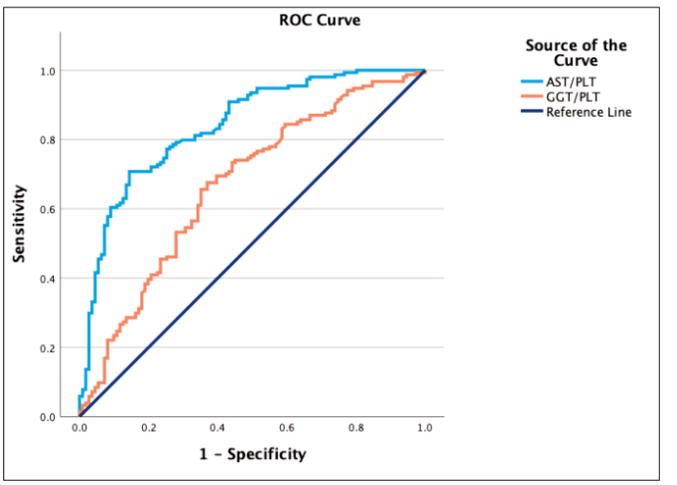

Figure 1: *ROC curves of AST/PLT and GGT/PLT scores in predicting ICP.*

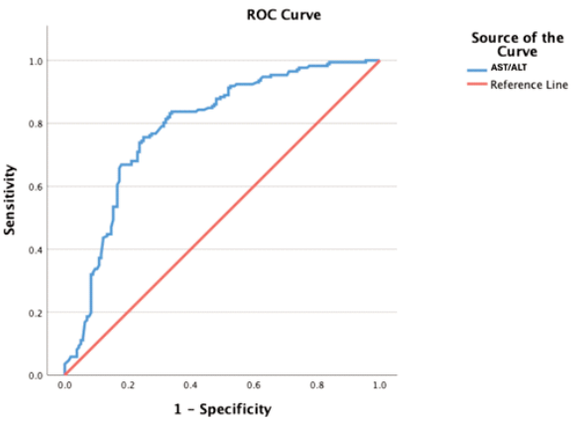

Figure 2: *ROC curve of the AST/ALT score in predicting ICP.*

Table I: *Comparison of demographic and clinical characteristics and laboratory scores of the case and control groups.*

	ICP group n=156	Control group n=173	p
Maternal age (year)	28.0 (6)	28.5 (8)	0.366[a]
Gravidity	2 (2)	2 (2)	0.628[b]
Parity	0 (1)	1 (1)	0.484[b]
BMI (kg/m^2)	28.64 (5.71)	29.4 (4.48)	0.078[a]
Gestational age at blood sampling (weeks)	33.6 (3.5)	33 (3)	0.694[a]
Second trimester platelet count (10^9/L)	250.0 (94.0)	237.0 (102.0)	0.658[a]
GGT (IU/L)	14.0 (15.5)	11.5 (24.3)	**<0.001**[a]
AST (IU/L)	47.0 (73.5)	18.0 (10.5)	**<0.001**[a]
ALT (IU/L)	69.0 (112.0)	15.0 (23.3)	**<0.001**[a]
GGT/PLT score	0.05 (0.07)	0.04 (0.07)	**<0.001**[a]
AST/ALT score	0.76 (0.55)	1.09 (0.91)	**<0.001**[a]
AST/PLT score	0.19 (0.30)	0.07 (0.04)	**<0.001**[a]
Serum fasting bile acid levels (µmol/L)	19.3 (20.9)	-	-

Data are presented as median (interquartile range) or n (%), as appropriate. a: Mann-Whitney U test, b: Pearson's chi-square test. A p-value < 0.05 was considered statistically significant, and statistically significant p-values are shown in bold. Since the continuous variables were not normally distributed, non-parametric tests were applied. ICP: Intrahepatic cholestasis of pregnancy, BMI: Body mass index, GGT: Gamma-glutamyl transferase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PLT: Platelet count

Table II: *ROC analysis for the determination of optimal cutoff values for GGT/PLT, AST/ALT, and AST/PLT scores in the prediction of ICP*

	Cut-off*	Sensitivity	Specificity	AUC	%95 CI	p
GGT/PLT score	>0.044	67.5%	64.1%	0.668	0.602-0.735	**<0.001**
AST/ALT score	<1.060	75.6%	75.0%	0.788	0.737-0.839	**<0.001**
AST/PLT score	>0.083	77.3%	74.8%	0.840	0.791-0.888	**<0.001**

Cut-off values were determined using receiver operating characteristic (ROC) curve analysis and the Youden index. Sensitivity, specificity, area under the curve (AUC), and 95% confidence intervals (95% CI) are reported.
A p-value <0.05 was considered statistically significant, and statistically significant values are shown in bold. ICP: Intrahepatic cholestasis of pregnancy, GGT: Gamma-glutamyl transferase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PLT: Platelet count, AUC: Area under the curve, CI: Confidence interval

Table III: *Comparison of pregnancy outcomes between the case and control groups*

	ICP group n=156	Control group n=173	p
Gestational week at birth	37.0 (1.1)	38.0 (1.0)	**<0.001**[a]
Birth weight, grams	2905.0 (623.2)	3230.0 (496.0)	**<0.001**[a]
Mode of delivery			
Vaginal delivery			
Primary cesarean section			
Repeat cesarean section			**<0.001**[b]
Mode of delivery			
Vaginal delivery			
Primary cesarean section			
Repeat cesarean section	71 (45.5)	105 (60.7)	**<0.001**[b]
Mode of delivery			
Vaginal delivery			
Primary cesarean section			
Repeat cesarean section	51 (32.7)	33 (19.1)	**<0.001**[b]
Mode of delivery			
Vaginal delivery			
Primary cesarean section			
Repeat cesarean section	34 (21.8)	35 (20.2)	**<0.001**[b]
1-min APGAR score	9 (1)	9 (1)	**0.020**[a]
5-min APGAR score	10 (1)	10 (1)	**0.021**[a]
Fetal Compromise, n (%)	16 (10.3)	17 (9.8)	0.619[b]
Fetal growth restriction, n (%)	11 (7.1)	6 (3.5)	0.143[b]
Preterm labor, n (%)	52 (33.3)	18 (10.8)	**<0.001**[b]
Oligohydramnios, n (%)	5 (3.2)	2 (1.2)	0.262[b]
Polyhydramnios, n (%)	5 (3.2)	6 (3.5)	0.903[b]
NICU admission, n (%)	35 (22.4)	18 (10.4)	**0.003**[b]
Composite adverse outcomes, n (%)	78 (50.0)	24 (13.9)	**<0.001**[b]

Data are presented as median (interquartile range) or n (%), as appropriate. a: Mann-Whitney U test, b: Pearson's chi-square test. Since the continuous variables were not normally distributed, nonparametric tests were used. A p-value <0.05 was considered statistically significant, and statistically significant values are shown in bold. ICP: Intrahepatic cholestasis of pregnancy, NICU: Neonatal intensive care unit

minute Apgar scores were lower in the ICP group (p=0.020 and p=0.021, respectively). Preterm labor was more common in ICP pregnancies (33.3% vs. 10.8%, p<0.001), and admission to the NICU was also significantly more common (22.4% vs. 10.4%, p=0.003). Furthermore, 50.0% of the ICP group experienced composite poor perinatal outcomes, compared with 13.9% in the control group (p<0.001). Other comparisons, including fetal compromise, fetal growth restriction, oligohydramnios, and polyhydramnios, showed no statistically significant changes between groups.

Biochemical ratios did not differ significantly between ICP patients with and without composite adverse perinatal outcomes (Table IV). The median GGT/PLT ratio was 0.05 (0.08) in patients with CAPO and 0.06 (0.07) in those without (p=0.781). The AST/ALT ratio (0.70 [0.49] vs. 0.84 [0.64], p=0.086) and the AST/PLT ratio (0.18 [0.27] vs. 0.20 [0.31], p=0.763) also did not differ significantly between the groups.

Discussion

In this study, we were able to demonstrate that the ratios based on liver enzymes and platelet count- GGT/PLT, AST/ALT, and AST/PLT- were significantly altered in patients diagnosed with ICP compared to the healthy control group. In the ROC analysis, we showed that the AST/ALT and

Table IV: *Comparison of GGT/PLT, AST/ALT, and AST/PLT scores between the ICP groups with and without composite adverse outcomes.*

	Composite adverse outcome (n=78)	No composite adverse outcome (n=78)	p
GGT/PLT score	0.05 (0.08)	0.06 (0.07)	0.781[a]
AST/ALT score	0.70 (0.49)	0.84 (0.64)	0.086[a]
AST/PLT score	0.18 (0.27)	0.20 (0.31)	0.763[a]

Data are presented as median (interquartile range). a: Mann-Whitney U test. Since the data were not normally distributed, non-parametric testing was applied. A p-value <0.05 was considered statistically significant. ICP: Intrahepatic cholestasis of pregnancy, GGT: Gamma-glutamyl transferase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PLT: Platelet count

AST/PLT ratios had higher AUC and specificity/sensitivity compared to the GGT/PLT ratio, indicating moderate-to-good diagnostic performance. These results highlight the potential utility of inexpensive, rapid biochemical markers for diagnosing ICP, especially in centers where fasting bile acid tests are not readily available, and results are time-consuming to obtain. Although these ratios were informative for diagnosing ICP, they were not informative for predicting CAPO, which is common in the ICP group. This situation suggests that these indices may be helpful in diagnosis but have limited utility in predicting fetal complications.

ICP is a pregnancy disorder that leads to poor perinatal outcomes (13). Bile acids accumulated in maternal blood have been shown to pass across the placenta and accumulate in the fetus and fetal tissues, leading to toxicity (14). Bile acids have been reported to accumulate in the placenta and in the smooth muscle of blood vessels, causing vasoconstriction that can lead to hypoxia, malnutrition, fetal impairment, and intrauterine fetal death (14,15). There is also evidence that bile acids accumulate in the myometrium, increase contractility, and cause preterm birth (14,16). Piechota et al. demonstrated that ICP patients had a heightened risk of preterm delivery, fetal compromise, and intrauterine fetal demise in comparison to the control group (4). In addition to these risks, studies emphasize that the babies of ICP patients also have an increased need for NICU care (14,17). In our study, we demonstrated increased preterm birth, need for NICU care, and CAPO in the ICP group, consistent with the literature. No differences were seen between the two groups regarding fetal compromise or fetal growth restriction; nevertheless, fetal weight was significantly diminished in the ICP group relative to the control group.

ICP is a disease that typically occurs in the third trimester of pregnancy. In addition to pruritus, bile acid levels are also used for diagnosis (7). However, the high cost and limited availability of bile acid measurements make diagnosis difficult. Therefore, there is a need for inexpensive and easily accessible rapid diagnostic methods. This has opened up the area of serum parameters. Ratios derived from biochemical and complete blood count data have gained popularity in this regard. It is known that accumulation of maternal bile acids in the ICP leads to hepatocyte damage, resulting in increased ALT and AST levels. GGT also increases due to cell damage in the bile ducts and impaired bile flow (18). In addition, increased hepatic oxidative stress in ICP can also lead to elevated GGT levels (19). Luo et al. showed that, in addition to ALT, AST, and GGT, inflammatory parameters were also significantly elevated in ICP patients. They used neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, white blood cell count, and neutrophil count as inflammatory markers (20). In our study, we included the ratios GGT/PLT, AST/ALT, and AST/PLT, which are biomarkers of liver fibrosis and also indicate the inflammatory state in ICP. Compared to the control group, we found that these parameters were noticeably higher in the ICP group. The GGT/PLT ratio demonstrated intermediate diagnostic performance (AUC=0.668) in the ROC analysis, whereas the AUCs for the AST/ALT and AST/PLT ratios were 0.788 and 0.840, respectively, indicating moderate-to-good diagnostic performance. Similar to our investigation, Saadi et al. discovered that ICP patients had a considerably higher AST/PLT ratio; however, their sensitivity and specificity were lower (65.3% and 73.2%, respectively) than ours (21). Kale et al. showed that AST/PLT and AST/ALT ratios were significantly elevated in ICP patients. However, the diagnostic value remained moderate (AUC = 0.681) (22). In our study, AST/PLT and AST/ALT ratios showed higher sensitivity and specificity (77.3%-74.8% and 75.6%-75.0%, respectively).

Various studies have shown that the GGT/PLT ratio increases in HELLP syndrome during pregnancy and in liver diseases (23,24). Lemoine et al. reported that the GGT/PLT ratio increased significantly in liver diseases, especially in chronic hepatitis B and liver fibrosis, and correlated with the severity of the disease (24). In their retrospective study, Chen et al. demonstrated that an increase in the GGT/PLT ratio in the late stages of pregnancy is predictive of unfavorable pregnancy outcomes such as HELLP syndrome and preterm labor (23). However, no previous studies have reported the GGT/PLT ratio in ICP. To our knowledge, this study is the first to investigate the diagnostic utility of GGT/PLT in ICP. In our investigation, ICP patients had a considerably greater GGT/PLT ratio than the control group ($p<0.001$). However, in further analyses, the sensitivity and specificity of the GGT/PLT ratio (67.5% and 64.1%) were lower than those of the AST/ALT and AST/PLT ratios. This suggests that AST/PLT and AST/ALT provide better diagnostic performance for ICP.

The association between AST/PLT and AST/ALT ratios and unfavorable perinatal outcomes has been the subject of numerous studies. Peker et al. demonstrated that the AST/PLT ratio is associated with CAPO. However, this relationship remained of low prognostic value in a further analysis (AUC 0.590-0.600) (25). An increase in the ALT/AST ratio was also associated with unfavorable outcomes in a study by Fan et al. (26) investigating the association between the ALT/AST ratio and unfavorable perinatal outcomes in ICP patients. In our study, we grouped ICP patients according to whether they developed CAPO, and our statistical analysis revealed no significant association between changes in these ratios and CAPO. Although previous studies have suggested that AST/PLT or ALT/AST ratios may be associated with unfavorable outcomes, our results did not confirm such an association in ICP patients. This situation emphasizes the need for larger cohorts to clarify whether these indices have prognostic significance beyond diagnosis.

Strengths and Limitations: The comparatively high cohort size, the inclusion of a clearly defined control group, and the thorough assessment of both maternal biochemical markers and perinatal outcomes are among the strengths of our study. Furthermore, to the best of our knowledge, this study adds new data to the literature and is the first to examine the diagnostic use of the GGT/PLT ratio in intrahepatic cholestasis during pregnancy.

Despite these strengths, several important limitations should be acknowledged. First, the retrospective and single-center design may limit the generalizability of the findings to broader populations. Second, although our sample size was sufficient for the main analyses, the number of intrauterine fetal deaths (one case in each group) was too small to allow a meaningful statistical comparison, precluding a reliable evaluation of this rare but clinically important outcome. Third, the severity of intrahepatic cholestasis of pregnancy could not be stratified into mild, moderate, and severe subgroups, as such classification was not uniformly available in the dataset. Since disease severity is closely associated with perinatal risk, the lack of a severity-based subgroup analysis may have limited the ability to assess the prognostic utility of the investigated ratios. Therefore, future prospective multicenter studies incorporating standardized severity classification and larger sample sizes are warranted to confirm and refine the diagnostic and prognostic value of these biochemical indices.

Conclusions

In conclusion, our study shows that GGT/PLT, AST/ALT, and AST/PLT ratios were significantly altered in patients with ICP compared to healthy controls. Among these, AST/ALT and AST/PLT showed the best diagnostic performance, suggesting that they could be used as a rapid, inexpensive tool for diagnosing ICP, especially when a bile acid test is not readily available. However, these indices were not associated with composite perinatal adverse outcomes, suggesting that their value may be limited to diagnosis rather than prognosis. To confirm these results and explore the possible clinical uses of these biochemical markers in standard obstetric practice, large-scale prospective studies are required.

Declarations

Ethics approval and consent to participate: Approval was obtained from the Institutional Review Board of Ankara Etlik City Hospital (decision number: AEŞH-BADEK2-2025-007, dated 15/04/25). Due to this study's retrospective nature, informed consent was waived with the Ethics Committee of Ankara Etlik City Hospital's approval. All data were anonymized, and participant confidentiality was strictly maintained.

Consent for publication: With the approval of the Ankara Etlik City Hospital Ethics Committee, informed consent was waived due to the study's retrospective design.

Availability of data and materials: If requested, the corresponding author can share the data with patient names anonymized.

Competing interests: The authors declare no conflicts of interest.

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Author contributions: MAO; conception, design, materials, data collection and processing, analysis and interpretation, literature review, writing, critical review, RD; materials, analysis and interpretation, literature review, GK; design, data collection and processing, analysis and interpretation, NVT: conception, design, data collection and processing, DDB: materials, analysis and interpretation, literature review, ZS; design, data collection and processing, analysis and interpretation, FA: materials, data collection and processing, analysis and interpretation, ATC: conception, design, supervision.

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