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Original Article

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Alanine aminotransferase to platelet ratio as a diagnostic tool for mild intrahepatic cholestasis of pregnancy

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Abstract

Objective: This study investigated the potential of readily available laboratory parameters, specifically the alanine aminotransferase to platelet ratio (ALT/PLT) and other novel hematological ratios, as diagnostic predictors of mild intrahepatic cholestasis of pregnancy (ICP), particularly in settings where bile acid testing poses a financial or logistical barrier.

Methods: A retrospective analysis was conducted on data from 83 pregnant women with pruritus at a single center in Türkiye. They were categorized into two groups: 40 diagnosed with mild ICP and 43 with non-pathological pruritus as a control group. The laboratory parameters on admission and the perinatal outcomes of the patients in the two groups were compared. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic accuracy of the ratios.

Results: The ICP group showed significantly higher levels of ALT/PLT, aspartate aminotransferase (AST) to platelet ratio, and ALT to total bile acid (TBA) ratio compared to the control group, while PLT/TBA was significantly lower. ALT/PLT demonstrated promising results with 82.5% sensitivity and 88.37% specificity for diagnosing mild ICP. Additionally, PLT/TBA ratio exhibited exceptional performance, achieving 97.5% sensitivity and 97.67% specificity.

Conclusion: This study suggests that the ALT/PLT ratio may serve as valuable and cost-effective tool for diagnosing mild ICP, especially in resource-limited settings where traditional total bile acid testing is challenging. The integration of AST/PLT, ALT/PLT, and PLT/TBA ratios into diagnostic algorithms contributes to the more accessible and cost-effective identification of mild ICP in pregnant women with pruritus.

Keywords: Intrahepatic cholestasis of pregnancy, pruritus gravidarum, ALT/PLT ratio, PLT/TBA ratio

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific hepatobiliary disorder characterized by pruritus and elevated serum bile acid levels, occurring primarily during the latter trimesters.[1] Its global incidence has been steadily rising, reaching 0.58% in 2005 from 0.32% in 1997.[2] Notably, prevalence exhibits significant ethnic variations, ranging from 0.7% in multi-ethnic regions like the UK to 1.5% among Pakistani-Asian populations.[3,4]

Accurate diagnosis of ICP is crucial for managing both maternal and fetal well-being, with serum total bile acid (TBA) measurement playing a pivotal role. However, discrepancies exist between professional societies regarding the specific TBA cutoff for diagnosis. The Society for Maternal-Fetal Medicine (SMFM) recommends a threshold of >10 µmol/L, while the Royal College of Obstetricians and Gynaecologists (RCOG) suggests 19 µmol/L based on non-fasting ranges to account for potential racial disparities.[1,5] While TBA levels are considered the most reliable method for the diagnosis of ICP, the accessibility of this test is still restricted, particularly in areas with limited infrastructure.[6] Furthermore, the expense of the test may pose a financial hardship for disadvantaged segments of the population.[7]

The presence of ICP significantly increases the risk of adverse perinatal outcomes, including preterm birth, meconium-stained amniotic fluid, fetal distress, and stillbirth.[8,9] Additionally, pregnant women with ICP are

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more susceptible to premature rupture of membranes, hypertension, gestational diabetes, and postpartum hemorrhage.[10]

Differentiation of ICP from other causes of pruritus in pregnancy is critical, as pruritus itself is a relatively common occurrence affecting approximately 20% of pregnancies, often attributed to physiological skin dryness .[1,11,12] However, when pruritus manifests within the context of ICP, it potentially foreshadows detrimental consequences for both mother and fetus.[11] Furthermore, TBA levels, apart from being challenging to access and costly, may require several days to be determined[13] and might potentially hinder the timely implementation of treatment and induce anxiety in pregnant women whom are experiencing pruritus.[14]

This study aims to investigate the potential of complete blood count (CBC) and liver function tests (LFTs) as predictors of ICP in pregnant women presenting with pruritus, particularly in settings where bile acid testing poses a cost barrier.

Methods

This retrospective cross-sectional study was conducted at the Perinatology Clinic of Mersin University Faculty of Medicine, Türkiye, from January 1, 2016, to October 31, 2023. Data were obtained from pregnant women aged 18–45 who received prenatal care and were delivered at the clinic by scanning the hospital database. Ethical approval was granted by the Mersin University Ethics Committee (Decision No. 2023/773). Due to the retrospective and anonymized nature of the study, informed consent was waived.

A total of 83 pregnant women presenting with pruritus who fulfilled the inclusion and exclusion criteria were included in the study, categorized into two groups: 40 women diagnosed with mild ICP (TBA level between 10 and 40µmol/L) and 43 women diagnosed with non-pathological pruritus gravidarum without cholestasis. Inclusion criteria encompassed presenting with pruritus, undergoing serum bile acid and blood tests, and delivering at the participating hospital. Exclusion criteria included maternal comorbidities like infective or inflammatory conditions, gestational diabetes, hepatobiliary diseases, and hypertensive disorders of pregnancy, as well as known fetal anomalies and multiple pregnancies.

ICP diagnosis followed established criteria: pruritus in the absence of rash, elevated fasting serum bile acid levels (>10 µmol/L), and/or elevated aminotransferases.[1] The ICP group consisted of mild ICP patients with TBA between 10 and 40 µmol/L. Pruritus gravidarum without cholestasis was diagnosed by a dermatologist after excluding alternative causes (allergies, infections, medical conditions) and confirming itching without rash based on physiological changes starting in the second trimester.[11,15]

Demographic characteristics, obstetric history, body mass index (BMI: weight (kg)/height² (m²)), admission laboratory results (including CBC, LFTs, and fasting serum bile acid levels), and specific maternal and fetal outcomes were extracted from the hospital database for analysis. To determine total bile acid (TBA) levels, blood samples were collected from the antecubital vein following a ten-hour fast. (DNI) Delta Neutrophil Index is a measure that calculates the percentage of immature granulocytes in relation to the total number of neutrophils. This index is a standard component of CBC results in our hospital. Using CBC and LFTs parameters, we calculated the following inflammatory indices: Neutrophil to lymphocyte ratio (NLR) = neutrophil count/lymphocyte count, platelet to lymphocyte ratio (PLR) = platelet count/lymphocyte count, Systemic inflammatory index (SII) = neutrophil count × PLR, Systemic inflammation response index (SIRI) = neutrophil count × monocyte count/lymphocyte count, Pan-Immune-Inflammation Value (PIV): neutrophil count × platelet count × monocyte count /lymphocyte count [16] APRI : ([AST/ULN[a]]/platelet count.[×10⁹/L]) × 100 [17] (ULN: upper limits of normal).[18] [a]The upper limit of normal AST value was 40 IU/L in this study. RPR = Red Cell Distribution Width (RDW) / platelet count.[19] Derived neutrophil to lymphocyte ratio (dNLR) = neutrophil count /(white blood cell count – neutrophil count).[20]

Data analysis was performed using the SPSS 18.0 software package. Descriptive statistics were presented as follows: categorical variables were reported as frequencies and percentages (n, %), while continuous variables were presented as mean ± standard deviation (SD) and median (interquartile range, IQR). For comparing categorical data, the Pearson chi-square test was used, with the Fisher exact test employed when applicable. The Shapiro-Wilk test assessed normality of continuous variables. Normally distributed continuous variables were compared between the two groups using the independent samples t-test, while the Mann-Whitney U test was used for non-normally distributed data. Spearman's rank correlation analysis explored relationships between non-normally distributed continuous variables. Correlation strengths were interpreted as follows: 0.05-0.30, low; 0.30-0.40, low-moderate; 0.40-0.60, moderate; 0.60-0.70, good; 0.70-0.75, very good; 0.75-1.00, excellent. The diagnostic performance of each parameter in predicting cholestasis was evaluated using receiver operating characteristic (ROC) curve

analysis. A significance level of $p < 0.05$ was considered statistically significant for all tests.

Results

Out of 83 enrolled pregnant women, 48.2% (n=40) were diagnosed with intrahepatic cholestasis of pregnancy (ICP group), while the remaining 51.8% (n=43) had non-pathological pruritus without cholestasis (Control group). Table 1 presents a comparison of their baseline demographic and clinical characteristics. The groups showed no statistically significant differences in age, BMI, gravida, parity, and number of previous miscarriages (p>0.05).

Table 1. Comparison of Demographic and Clinical Characteristics of Populations

Variables	Control group (n=43)	ICP group (n=40)	p value
Age (years)	30.00 (27.00-35.00)	30.00 (25.50-33.75)	0.562*
BMI (kg/m²)	26.00 (24.00-29.00)	27.0 (26.00-28.00)	0.329*
Gravidity	3.00 (2.00-4.00)	2.00 (1.00-3.00)	0.053*
Parity	1.00 (0.00-2.00)	1.00 (0.00-2.00)	0.097*
Miscarriage	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.069*

*: Mann Whitney U Test

In Table 2, the distribution of laboratory parameters within the control and ICP populations is presented. Significantly elevated levels of TBA, ALT, AST, and GGT were observed in the ICP group ($p < 0.001$). Upon analyzing the indicators derived from laboratory evaluations, no statistically significant difference was found between the groups in terms of DNI, ALT/TBA, NLR, PLR, SII, SIRI, PIV, RPR, and DNLR. APRI (p<0.001), AST/PLT (p<0.001), ALT/PLT (p<0.001), ALT/TBA (p=0.003) were significantly higher in the ICP group than in the control group. In the ICP group, PLT/TBA was significantly lower (p<0.001).

Table 3. Distribution of Obstetrical and Fetal Outcomes in Control and ICP Populations

Variables	Control group (n=43)	ICP group (n=40)	p value
Gestational age at birth	38.20 (37.50-39.10)	36.80 (34.12-38.17)	<0.001**
APGAR 1 min	8.00 (8.00-9.00)	8.00 (6.25-9.00)	0.023**
APGAR 5 min	10.00 (9.00-10.00)	9.00 (8.00-10.00)	0.007**
Birth weight (grams)	3214 (3000-3595)	3160 (2625-3559)	0.305**
Umblical artery cord blood pH	7.34 (7.31-7.40)	7.31 (7.29-7.35)	0.004**
Nonreassuring fetal status, n (%)	7 (16.3)	20 (50.0)	0.001*
MSA, n (%)	1 (2.3)	6 (15.0)	0.052***
NICU admission	7 (16.3)	21 (52.5)	<0.001*

MSA: Meconium Stained Amniotic Fluid. NICU: Neonatal Intensive Care Unit.
*: Pearson Chi-square Test. **: Mann Whitney U Test. ***: Fisher Exact Test.

Table 2. Distribution of Laboratory Characteristics in Control and ICP Populations

Variables	Control group (n=43)	ICP group (n=40)	p value
TBA	5.10 (4.36-6.1)	26.56 (21.70-29.77)	<0.001*
AST (U/L)	17.00 (15.00-20.10)	76.0 (39.08-173.50)	<0.001*
ALT (U/L)	13.50 (10.30-20.00)	159.90 (56.60-274.07)	<0.001*
DNI (%)	0.60 (030-1.00)	0.50 (0.30-1.15)	0.982*
APRI	0.19 (0.15-0.27)	0.77 (0.31-1.88)	<0.001*
AST/PLT	0.07 (0.06-0.10)	0.31 (0.12-0.75)	<0.001*
ALT/PLT	0.06 (0.04-0.08)	0.57 (0.22-1.17)	<0.001*
AST/TBA	3.40 (2.73-4.73)	3.30 (1.49-3.16)	0.597*
ALT/TBA	2.60 (1.95-4.00)	5.55 (2.65-10.81)	0.003*
PLT/TBA	39.11 (34.11-58.85)	9.89 (6.68-12.51)	<0.001*
NLR	3.53 (2.68-4.46)	3.55 (2.46-4.78)	0.827*
PLR	122.96 (104.48-154.06)	141.84 (118.78-175.81)	0.073*
SII	769.69 (671.06-1192.18)	813.09 (665.53-1289.52)	0.695*
SIRI	2.38 (1.47-3.25)	2.14 (1.32-3.47)	0.855*
PIV	515.92 (352.12-751.56)	533.77 (370.57-882.44)	0.715*
RPR	0.06 (0.04-0.06)	0.05 (0.04-0.07)	0.152*
DNLR	2.46 (1.85-3.14)	2.53 (1.77-2.98)	0.433*

TBA: Total Bile Acid Concentration
*: Independent Samples T Test **: Mann Whitney U Test

The distribution of obstetrical and fetal outcomes in the control and ICP patient groups is summarized in Table 3. ICP patients underwent delivery at a mean gestational age of 36.80 weeks (range 34.12–38.17), which was significantly lower than the control group's mean gestational age of 38.20 weeks (range 37.50–39.10) ($p < 0.001$). Neonates born to mothers with ICP exhibited lower 1-minute ($p = 0.023$) and 5-minute ($p = 0.007$) Apgar scores, along with a decreased umbilical cord pH ($p = 0.004$), in comparison to neonates born to mothers in the control group. Delivery prompted by non-reassuring fetal status occurred significantly more frequently in the ICP group (50%) than in the control group (16.3%) ($p < 0.001$). The necessity for neonatal intensive care unit (NICU) admission was markedly higher in the ICP group (52.5% vs. 16.3%, $p < 0.001$), and the presence of meconium-stained amniotic fluid (MSA) was also significantly elevated in the ICP group (15% vs. 2.3%, $p = 0.052$).

Receiver operating characteristic (ROC) curve analysis was conducted to identify optimal cut-off points for AST/PLT, ALT/PLT, ALT/TBA, and PLT/TBA ratios in predicting cholestasis diagnosis (Table 4).

Table 4. ROC Analysis of AST/PLT, ALT/PLT, ALT/TBA and PLT/TBA Parameters for ICP Diagnosis

	AST/PLT	ALT/PLT	ALT/TBA	PLT/TBA
Cut-off	≥0.119	≥0.125	≥3.123	≤20.538
AUC (%95 CI)	0.885 (0.811-0.960)	0.913 0.840-0.985)	0.686 (0.566-0.807)	0.978 (0.945-1.000)
Sensitivity (%95 CI)	82.50 (67.22-92.66)	90.00 (76.34-97.21)	82.50 (67.22-92.66)	97.50 (86.84-9.94)
Specificity (%95 CI)	88.37 (74.92-96.11)	90.70 (77.86-97.41)	88.37 (74.92-96.11)	97.67 (87.71-99.94)
PPV (%95 CI)	86.84 (74.09-93.84)	90.00 (77.87-95.84)	86.84 (74.09-93.84)	97.50 (84.89-99.63)
NPV (%95 CI)	84.44 (73.30-91.48)	90.70 (79.29-96.13)	84.44 (73.30-97.48)	97.67 (85.84-99.66)
Accurary (%95 CI)	85.54 (76.11-92.30)	90.36 (91.89-95.75)	85.54 (76.11-92.30)	97.59 (91.57-99.71)
p value	<0.001	<0.001	0.003	<0.001

CI: Confidence Interval, AUC: Area Under the Curve, PPV: Positive Predictive Value, NPV: Negative Predictive Value

Values of 0.119 and higher for the AST/PLT parameter result in the diagnosis of ICP with 82.50% sensitivity and 88.37% specificity. ALT/PLT values of 0.125 and above are associated with a diagnosis of ICP with 90.00% sensitivity and 90.70% specificity. Similarly, for the ALT/TBA parameter, values of 3.123 and greater predict ICP diagnosis with 82.50% sensitivity and 88.37% specificity. Regarding the PLT/TBA value, values of 20.538 and lower predict ICP diagnosis with 97.50% sensitivity and 97.67% specificity (p<0.05) (Figure 1 and 2).

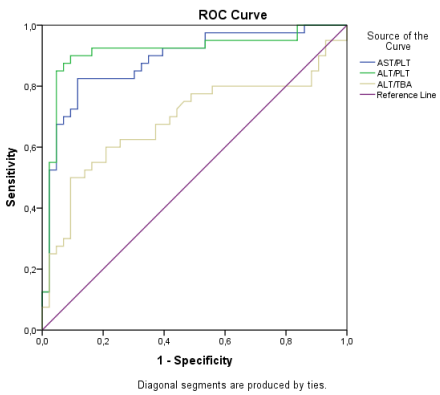

Fig 1. ROC curve for AST/PLT, ALT/PLT, and ALT/TBA parameters in the diagnosis of mild ICP ROC : receiver operating characteristic.

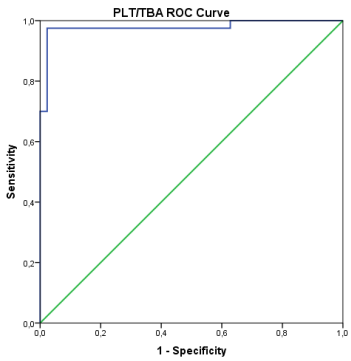

Fig 2. ROC Curve for PLT/TBA parameter for mild ICP diagnosis

Discussion

In pregnant women experiencing pruritus, two established methods for differentiating ICP from non-pathological causes are liver function tests and TBA measurements. However, bile acid analysis often necessitates morning fasting samples, incurs processing delays, and can be financially prohibitive. Recognizing this limitation, the present study sought to identify simple indicators for ICP diagnosis in scenarios where bile acid analysis is impractical or unattainable. Our investigation revealed that AST/PLT and ALT/PLT ratios demonstrate promising accuracy in predicting ICP in this population, exhibiting noteworthy sensitivity (82.50% and 90.00%, respectively) and specificity (88.37% and 90.70%, respectively). Additionally, we explored the PLT/TBA ratio as a secondary outcome, demonstrating its potential as a diagnostic tool with 97.50% sensitivity and 97.67% specificity for ICP when values fall below 20.538 (p < 0.05). In this context, we aimed to contribute to our ICP diagnostic power with PLT/TBA ratio. To our knowledge, PLT/TBA ratio has not been studied in the literature before.

Our study population included patients diagnosed with mild ICP and exhibiting total bile acid (TBA) levels below 40 µmol/L. The mean maternal age in this group was 30 years. This finding aligns with reports by Mashburn et al. who observed a similar mean maternal age (30 years) in their ICP population with TBA < 40 µmol/L.[21] Notably, Herrera et al. also investigated the association between maternal age and TBA levels, reporting a mean age of 28.0 years for mild ICP (TBA 10-39 µmol/L), 28.1 years for moderate ICP (TBA 40-99 µmol/L), and 29.7 years for severe ICP (TBA 9100 µmol/L), with no statistically significant differences.[22]

The use of inflammatory markers derived from maternal CBC for predicting ICP is gaining traction due to its simplicity and cost-effectiveness. While Eroğlu et al. observed elevated DNI in ICP patients compared to healthy pregnant women[23], our study did not replicate this finding. This discrepancy might be attributed to our

selection of pregnant women with pruritus as the control group and mild ICP cases for the study group. There is a lack of research on the involvement of DNI in predicting ICP, and our study is the second one to explore this topic.

A previous Chinese study investigating a population with a higher ICP prevalence (2.3%–6%) reported significantly elevated NLR and PLR values in ICP patients. [24] However, their diagnostic sensitivity remained limited (44.41% for NLR and 61.84% for PLR). Notably, our study focused on the Turkish population with a lower ICP incidence (0.86%).[25] This potentially explains the absence of an increase in NLR and PLR values we observed, particularly among individuals with mild ICP.

Prior studies have documented the association between rising APRI scores in the third trimester and liver damage in the context of ICP.[18, 26-28] Our study observed elevated scores for APRI, ALT/PLT, and AST/PLT in patients with ICP. Notably, the areas under the curve (AUC) for AST/PLT and ALT/PLT were 0.885 and 0.913, respectively, demonstrating strong discriminatory power. Additionally, these ratios exhibited high sensitivity (82.5% and 90%, respectively) and specificity (88.37% and 90.7%, respectively) for diagnosing mild ICP. These findings contribute to the existing literature by highlighting the superior sensitivity and specificity of AST/PLT and ALT/PLT ratios in detecting mild ICP.

A recent study by Ipek et al. identified a novel marker, SIRI, which was significantly lower in both severe and mild ICP patients at delivery.[29] Notably, their subgroup analysis of patients with mild ICP revealed no statistically significant differences in SIRI values at diagnosis, a finding consistent with our own investigation.

While several biomarkers like PIV, SII, DNLR, and RPR have been explored for their predictive potential in preeclampsia [16,20], their utility in identifying ICP remains unevaluated. Similarly, RPR has shown promise in predicting acute pancreatitis during pregnancy[30], but its application in ICP has not been studied. This study also aimed to address this gap by assessing these markers in ICP patients. However, we found no significant differences in PIV, SII, RPR, or DNLR levels compared to controls, suggesting their limited suitability for ICP prediction.

Our investigation further explored the potential of combining platelet count (PLT) and LFTs with TBA to enhance the diagnosis of mild ICP. Notably, ALT/TBA and PLT/TBA ratios exhibited significant differences between the ICP group and the control group ($p = 0.003$ and $p< 0.001$, respectively), highlighting their potential diagnostic utility. ROC analysis revealed impressive performance for both ratios, with sensitivities of 82.5% and 97.5% and specificities of 88.37% and 97.67% for ALT/TBA and PLT/TBA, respectively. These findings suggest that these ratios could be particularly valuable in diverse ethnic populations where intermediate TBA values can complicate the diagnosis of mild ICP. We believe that incorporating these ratios into diagnostic algorithms, particularly in such scenarios, has the potential to significantly improve diagnostic accuracy.

A key strength of this study lies in its exploration of alternative, hematological ratios for diagnosing ICP. This approach offers a potentially more accessible and cost-effective solution, especially in resource-limited settings where traditional bile acid testing may be unavailable or expensive. The investigation of novel markers such as AST/PLT, ALT/PLT, and PLT/TBA contributes valuable insights to the current understanding of ICP diagnostics. Their promising results in terms of sensitivity and specificity suggest that these ratios could become valuable additions to the diagnostic toolbox.

Our study acknowledges several limitations that could affect the generalizability of its findings. The retrospective, single-center design may introduce inherent biases and limit the external validity of the results. Additionally, although the sample size was sufficient for the study's purposes, it may not be adequate to ensure generalizability to other populations. Additionally, it is important to note that the exclusion of certain comorbidities and the specific bile acid thresholds chosen may limit the applicability of the findings to wider cohorts of individuals. Lastly, the study highlights the necessity for external validation in independent cohorts to confirm the diagnostic accuracy and reliability of the proposed ratios. Despite these limitations, the study provides valuable insights into the diagnostic landscape of ICP, offering a foundation for further research and potential improvements in clinical practice.

Conclusion

In conclusion, this study sheds light on the diagnostic potential of ALT/PLT and AST/PLT ratios in the context of ICP, particularly in settings where traditional bile acid testing faces practical and financial constraints. The findings underscore the importance of exploring alternative diagnostic markers to facilitate timely and cost-effective identification of ICP in pregnant women presenting with pruritus. Specifically, the study introduces novel ratios such as AST/PLT, ALT/PLT, and PLT/TBA, demonstrating their promising accuracy in predicting ICP. These ratios exhibit notable sensitivity and specificity, offering a valuable contribution to the field and emphasizing their potential integration into diagnostic algorithms. As a result, this research lays the groundwork for further investigations into the clinical utility of these ratios, potentially offering a more accessible and efficient diagnostic approach for ICP in low-resource healthcare settings.

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