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Original Research

Severe Intrahepatic Cholestasis of Pregnancy: Longitudinal Evaluation of the Immuno-Nutritional Hemoglobin, Albumin, Lymphocyte, and Platelet Score for Discriminating Disease Severity—A Retrospective Cohort Study

Erkan Mavigök[1,*], Güven Arslan[2]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Kahramanmaraş Sütçü İmam University, 46100 Kahramanmaraş, Türkiye
[2]Obstetrics and Gynecology Clinic, Necip Fazıl City Hospital, 46050 Kahramanmaraş, Türkiye
*Correspondence: rknmvgk@gmail.com (Erkan Mavigök)

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Abstract

Background: Intrahepatic cholestasis of pregnancy (ICP) poses significant risks to maternal and fetal health. This study aimed to investigate whether trimester-specific changes in the hemoglobin, albumin, lymphocyte, and platelet (HALP) scores are associated with the presence and severity of ICP. **Methods:** This retrospective cohort study included 312 pregnant women (120 healthy controls and 192 patients with ICP). Patients were categorized into mild (n = 96), moderate (n = 60), and severe (n = 36) ICP groups based on peak serum bile acid levels (severe, ≥100 µmol/L). HALP scores were calculated for each trimester, and severity was classified according to the peak value. The primary outcome measure was the inter-trimester change in HALP score (ΔT3–T2) and its discriminatory accuracy. **Results:** Third-trimester HALP scores peaked in the severe ICP group (58.3 ± 15.8), which was significantly higher than in controls (45.6 ± 10.3; $p < 0.001$). The ΔT3–T2 showed a mean increase of 24.7 ± 12.3 units in severe ICP. Receiver operating characteristic (ROC) curve analysis yielded an area under the ROC curve (AUC) of 0.901 for the ΔT3–T2 in severe ICP. A cutoff value of 12.0 provided 83.3% sensitivity and 87.3% specificity. ΔT3–T2 values also correlated with peak total serum bile acid concentrations (r = 0.612, $p < 0.001$). **Conclusions:** A longitudinal change in the HALP score (ΔT3–T2) was associated with severe ICP and may help to identify higher-risk pregnancies. As this study was retrospective in nature, prospective external validation is needed before this measure is used for risk stratification or triage.

Keywords: bile acids; prognosis; serum albumin levels; maternal biomarkers

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease specific to gestation. ICP affects approximately 2.9% of the population worldwide [1]. This rate varies significantly between geographic regions, reaching up to 4.7% in Southeast Asia and 1.6% in the Eastern Mediterranean region [1]. The level of economic development is also an important factor affecting the incidence of ICP; the incidence is 3.5% in low- and middle-income countries and 2.1% in high-income countries [1].

Bile acids play a central role in the pathogenesis of the disease. High bile acid levels in pro-inflammatory hepatocytes trigger the production of mediators and lead to oxidative stress and mitochondrial damage [2]. The passage of bile acids from the placenta to the fetus's circulation causes arrhythmias and can lead to serious complications, such as hypoxia [3]. ICP can also lead to serious morbidities for both maternal and fetal health. Among maternal complications, the risk of preeclampsia is 2.39 times higher, the risk of cesarean delivery is 1.28 times higher, the risk of premature birth is 2.71 times higher, and the risk of maternal infection is 3.22 times higher [4]. Granese et al. [5] showed that the rates of gestational diabetes, gestational hypertension, and thrombophilia were significantly higher in pregnant women with ICP than in the control group. Regarding fetal outcomes, the incidence of meconium-stained amniotic fluid reached 46.5% in the ICP group and only 2.4% in the control group [5]. Chen et al. [6] reported that the risk of gestational age being shorter than 259 days was 4.57 times higher in ICP pregnancies. The risk of fetal death is significantly increased, especially in cases with total serum bile acid levels ≥40 µmol/L [2].

Although the serum total bile acid level is considered the most sensitive biochemical marker for the diagnosis of ICP, it has been emphasized that this parameter alone is insufficient in terms of specificity [7]. Recent studies have shown that routine laboratory parameters, such as hemoglobin, albumin, lymphocytes, and platelets (HALP), have predictive value in the diagnosis and estimation of ICP's severity [7,8]. The HALP score (hemoglobin × albumin × lymphocyte / platelet) is used as a prognostic marker in various malignancies and inflammatory conditions. However, its predictive value in ICP has not yet been investigated. Most current studies are based on measure-

ments at a single time point, and the clinical significance of dynamic changes between trimesters has not been sufficiently investigated. Furthermore, previous research generally does not consider how corticosteroid treatment and infections affect the components that comprise the HALP score. A further gap is that the biological link between the HALP score and cholestatic disease has not been clearly established, and it is still unclear which inflammatory and nutritional pathways might connect its individual components to the course of ICP.

In addition, the bile acid thresholds used to grade ICP's severity vary between guidelines, with severe disease defined from 40 µmol/L upward in some. We classified severity from the peak total serum bile acid level using a three-tier scheme. In this scheme, a value of ≥100 µmol/L indicated severe disease, since the risk of stillbirth is not appreciably raised below this level but increases markedly at and above it [9]. The rationale for this choice is given in the Methods. In this study, we examined how the HALP score and its changes across trimesters were associated with the diagnosis and severity of ICP. Moreover, we evaluated the relationship between this score and bile acid levels.

2. Materials and Methods

2.1 Study Design, Population, and Sample

This study was conducted at Kahramanmaraş Sütçü İmam University (Kahramanmaraş, Türkiye) between November 2024 and November 2025. The research was approved by the Kahramanmaraş Sütçü İmam University Medical Research Ethics Committee, utilizing a retrospective observational and group comparison model. All data were obtained anonymously through the Hospital Information Management System (HIMS). The sample size was calculated using G*Power Version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). At least 64 participants per group were sufficient for a 95% confidence level, 80% power and a 0.5 effect size. The sample size was expanded to increase the power of the subgroup analyses. Nonetheless, the severe ICP subgroup remained small (n = 36), which limited the statistical power of the severe disease analyses and is acknowledged as a limitation.

Patient records in the HIMS were screened using International Classification of Diseases (ICD)-10 codes. After applying inclusion–exclusion criteria, the study was structured to include 312 pregnant women, comprising 192 ICP patients and 120 healthy control subjects. Exclusion criteria included missing trimester data (n = 45), multiple pregnancies (n = 12), chronic liver disease (n = 8), the presence of preeclampsia/HELLP (hemolysis elevated liver enzymes low platelet count) syndrome with normotension (blood pressure [BP] <140/90 mmHg) and the absence of hemolysis at diagnosis (n = 6), signs of infection (defined as C-reactive protein [CRP] >10 mg/L or a positive urine culture; n = 23), and other comorbidities such as hematological disease or malignancy (n = 6). The detailed selection process and group distributions are summarized in the study flow diagram (Fig. 1).

The case group consisted of patients diagnosed with ICP who had complete hemoglobin (HGB), albumin (ALB), lymphocyte (LYM), and platelet (PLT) values in all three trimesters. The control group was selected from healthy, uncomplicated, and term pregnancies and matched to the case group regarding age, gestational age, body mass index, and the week in which third-trimester blood sampling was performed. Third-trimester blood samples were taken at similar gestational weeks in all groups (control: 35.2 ± 2.1, mild ICP: 35.0 ± 2.3, moderate ICP: 34.6 ± 2.4, severe ICP: 34.2 ± 2.5 weeks, $p = 0.082$). Thus, comparability between groups was ensured [10].

2.2 Variable Definitions, ICP Classification, and Timing of Measurements

The main variable of the study, the HALP score, is an index that comprehensively reflects immune–nutritional status. It was calculated using the formula: HALP = (hemoglobin × albumin × lymphocyte) / platelet. Before calculating the HALP score, hemoglobin and albumin values were mathematically converted from g/dL to g/L. All laboratory values were evaluated in International System of Units (SI) [11,12]. Complete blood count parameters, including hemoglobin concentration, lymphocyte count, and platelet count, were measured with an automated hematology analyzer (XN-1000; Sysmex Corporation, Kobe, Japan). Serum albumin (bromocresol green method), total serum bile acids (enzymatic cycling method), and CRP (immunoturbidimetry) were measured with an automated clinical chemistry analyzer (cobas c 702 module, cobas 8000 series; Roche Diagnostics GmbH, Mannheim, Germany). ICP patients were divided into three groups according to their highest total serum bile acid (TSBA) levels: mild (10–39 µmol/L; n = 96), moderate (40–99 µmol/L; n = 60), and severe (≥100 µmol/L; n = 36) [13,14]. This three-tier scheme is consistent with recent clinical literature, in which peak bile acids of 40–99 µmol/L and ≥100 µmol/L define moderate and severe ICP, respectively [15]. The ≥100 µmol/L threshold for severe disease was used because the risk of stillbirth and adverse perinatal outcomes increases substantially at and above this level, as illustrated by a large population-based cohort study [9] and reflected in societies' recommendations to offer delivery at 36 weeks once bile acids reach this value [16]. Therefore, the ≥100 µmol/L definition was retained to keep the present grouping comparable with these reference standards.

Trimesters were defined as the first trimester (T1) before 14 weeks, the second trimester (T2) between 14 and 28 weeks, and the third trimester (T3) after 28 weeks. Clinical records confirmed this classification [17]. To avoid the confounding effects of medical interventions, third-trimester blood samples were collected from patients receiving corticosteroid treatments before steroid injections at an average gestational period of 34–35 weeks (range: 30–38 weeks).

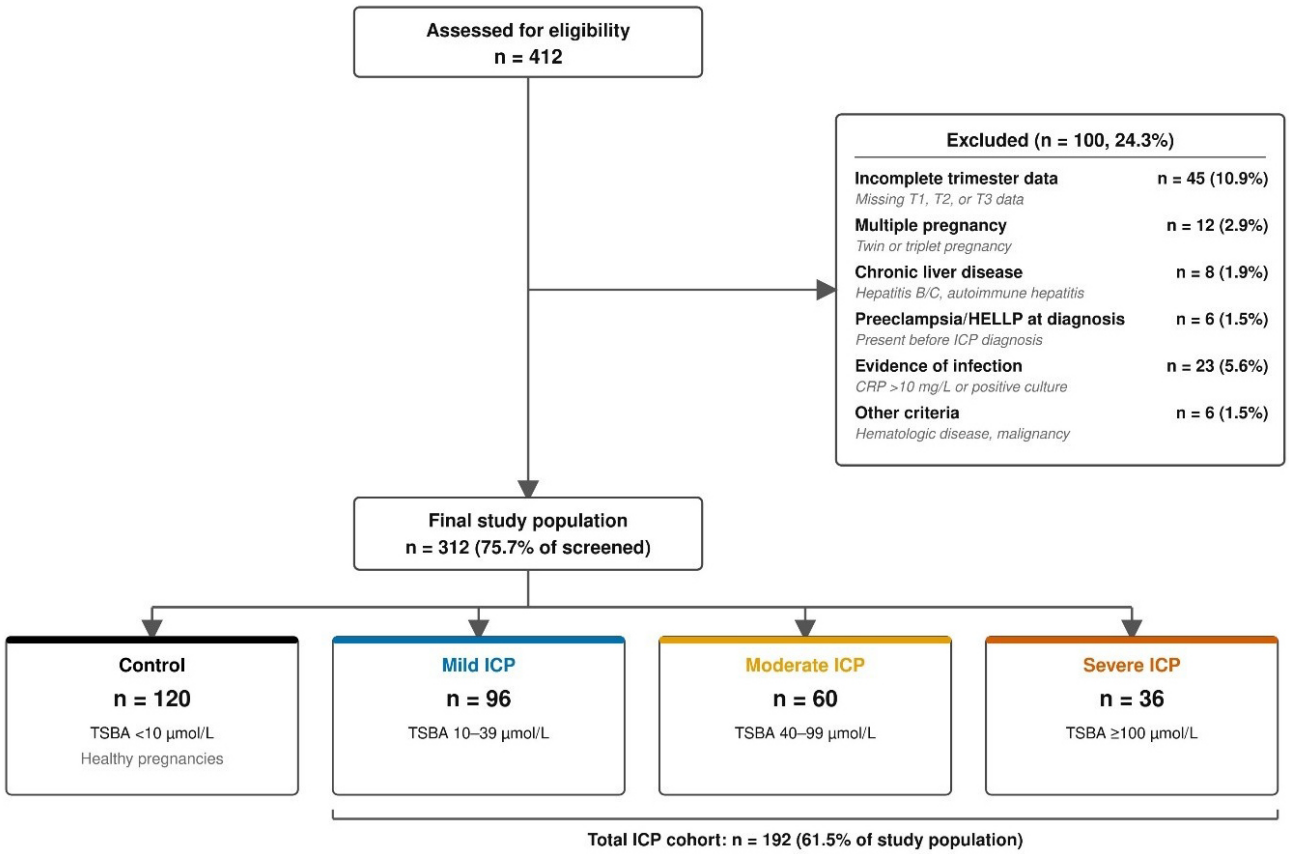

Fig. 1. Study flow and participant selection. Of the 412 pregnancies assessed for eligibility, 100 (24.3%) were excluded for the reasons indicated above, leaving 312 (75.7%) in the final cohort, classified by peak total serum bile acids into control (n = 120), mild (n = 96), moderate (n = 60), and severe (n = 36) groups. The three ICP groups formed the total ICP cohort (n = 192). Preeclampsia and HELLP syndrome were exclusion criteria only when present at diagnosis. ICP, intrahepatic cholestasis of pregnancy; TSBA, total serum bile acids; CRP, C-reactive protein; HELLP, hemolysis, elevated liver enzymes, low platelets; T1/T2/T3, first/second/third trimester.

Regarding the temporal sequence of measurements, HALP scores were obtained from samples drawn at routine antenatal visits in each trimester before any treatment for cholestasis. ICP was diagnosed, the peak TSBA value was reached in the third trimester, and the disease's severity was classified retrospectively from the peak TSBA. Because the HALP measurements and the bile acid peak fell within overlapping time windows, the analyses in this study describe the cross-sectional discrimination of the disease's severity rather than true prospective prediction. The longitudinal HALP change is interpreted as a marker that tracks worsening disease, not as an early warning test applied before diagnosis.

Among the inter-trimester changes, ΔT3–T2 was prespecified as the primary longitudinal parameter because the most pronounced haematological and biochemical changes in ICP occur in the third trimester. Thus, the second-to-third-trimester change was expected to capture the disease-related shift most directly. ΔT2–T1 and ΔT3–T1 were treated as secondary parameters.

2.3 Definition and Evaluation of Clinical Outcomes

The study evaluated adverse obstetric and neonatal outcomes, including preterm births occurring before the 37th week of gestation and fetal complications such as intrauterine growth restriction (IUGR), fetal distress, admission to the neonatal intensive care unit (NICU), and neonatal death. These clinical outcomes were obtained by retrospectively reviewing medical records. After excluding all files containing missing or inaccurate information, the research team evaluated these parameters across the ICP and control groups. Preeclampsia and HELLP syndrome were recorded only as follow-up outcomes. Women in whom either condition was present at the time of ICP diagnosis had already been excluded (see exclusion criteria), so these conditions were never both an exclusion and an outcome in the same patient.

2.4 Infection Screening and Corticosteroid Administration

For infection screening, CRP, a complete urinalysis, and urine cultures were evaluated. Pregnant women showing signs of infection (CRP >10 mg/L, leukocyte posi-

tivity on urinalysis, or a positive urine culture) were excluded from the study (n = 23). In patients with an indication of corticosteroids (betamethasone sodium phosphate/acetate; Celestone® Soluspan®, Organon LLC, Jersey City, NJ, USA) for fetal lung maturation due to the risk of preterm birth (n = 51; 5 patients with mild ICP, 18 with moderate ICP, and 28 with severe ICP), blood parameters obtained before steroid administration were used from archival records for third-trimester assessments. This approach was employed to exclude the possible confounding effects of corticosteroids on hematological parameters. Because the study was retrospective and relied on archival records spanning several years and many patients, the batch (lot) numbers of the laboratory reagents and of the corticosteroid could not be retrieved from the records. Consequently, the manufacturer, model, and location of the instruments and of the drug were reported instead, while individual lot numbers were not.

2.5 Statistical Analysis

All collected data were statistically analyzed using SPSS Version 26.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed for normality using the Kolmogorov–Smirnov or Shapiro–Wilk tests. For comparisons among the four groups, normally distributed continuous variables were analysed with one-way analysis of variance. Non-normally distributed variables—including inter-trimester HALP changes, which were right-skewed (Shapiro–Wilk $p < 0.05$)—were analysed with the Kruskal–Wallis test followed by Dunn post-hoc correction. Categorical variables were analysed using the chi-square test.

For longitudinal analysis, repeated measures Analysis of Variance (ANOVA) or mixed-effects models were applied to examine trends in HALP scores across trimesters. Delta HALP values were calculated as inter-trimester differences (ΔT2–T1, ΔT3–T2, ΔT3–T1), with ΔT3–T2 used as the primary parameter, as defined above. Relationships between continuous variables, such as TSBA and HALP scores, were examined using Pearson or Spearman correlation analyses, depending on data distribution.

The discrimination of any ICP and severe ICP by HALP-based parameters and by the third-trimester platelet count was evaluated using receiver operating characteristic (ROC) analysis. Optimal cutoff values were determined by maximizing the Youden index, and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The areas under the curve for ΔT3–T2 and the platelet count were compared using the DeLong test. Given the few severe cases, the areas under the ROC curve (AUCs) were internally validated by bootstrapping (1000 resamples), and optimism-corrected values were reported alongside the apparent estimates.

For severe ICP, multivariable logistic regression was performed using a single HALP-derived predictor (ΔT3–T2) adjusted for maternal age and parity. To avoid mathematical overlap, the components of the HALP score (albumin and platelet count) and other HALP-derived terms were not entered into the same model. Multicollinearity was assessed with variance inflation factors, and all values were below 5. In a separate nested model, ΔT3–T2 and the third-trimester platelet count were entered together to test whether the longitudinal change carried information beyond the static platelet level. Infection status and corticosteroid use were addressed through exclusion and sampling timing, respectively, and were not included as covariates. In addition, univariable linear regression analyses were performed to examine the association of HALP parameters with peak TSBA. Because the HALP score and its components are mathematically interrelated, each parameter was examined in a separate univariable model rather than combined in a single multivariable model. Beta coefficients (β), standard errors (SE), t-statistics, and coefficient of determination (R^2) values are presented. Data are reported as mean ± standard deviation, median (interquartile range [IQR]), or n (%). An independent biostatistician reviewed the statistical analysis. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 General Characteristics of the Study Population

The mean age of the participants was 27.2 ± 5.4 years. The control group consisted of 120 healthy pregnant women, while the 192 women diagnosed with ICP were divided into three subgroups: mild (n = 96), moderate (n = 60), and severe (n = 36). Of the 412 pregnancies screened, 100 (24.3%) were excluded—45 (10.9%) for incomplete trimester data, 23 (5.6%) for signs of infection, 12 (2.9%) for multiple pregnancies, eight (1.9%) for chronic liver disease, six (1.5%) for preeclampsia or HELLP syndrome already present at diagnosis, and six (1.5%) for other reasons—leaving 312 women for analysis (Fig. 1). There were no significant differences between the groups in age, nulliparity, body mass index (BMI), or the gestational week of third-trimester sampling (all $p > 0.05$; Table 1).

All participants underwent infection screening, and CRP values were similar across the groups (control median 3.2 mg/L vs. severe ICP 4.1 mg/L; $p = 0.186$). Since 23 women with signs of infection had already been excluded, none of the participants in the final analysis had elevated CRP or positive cultures (Table 1).

3.2 Evaluation of HALP Scores Across Trimesters

No significant difference in HALP scores was observed between the groups in the first trimester (control 38.5 ± 8.2 vs. severe ICP 35.2 ± 9.1; $p = 0.214$). A difference appeared in the second trimester, where the score was 42.3 ± 9.1 in the controls but lower, at 33.6 ± 10.2, in the severe ICP group ($p = 0.018$). In the third trimester, the score rose in the severe ICP group to 58.3 ± 15.8, significantly higher than in the controls (45.6 ± 10.3; $p < 0.001$; Table 2; Fig. 2A).

Table 1. Demographic characteristics, HALP score components, infection screening, and corticosteroid status.

Parameter	Control (n = 120)	Mild ICP (n = 96)	Moderate ICP (n = 60)	Severe ICP (n = 36)	*p* value
Demographic characteristics					
Age, years	27.4 ± 5.2	27.1 ± 5.5	27.0 ± 5.6	27.8 ± 5.3	0.842
Nulliparity, n (%)	52 (43.3)	44 (45.8)	28 (46.7)	17 (47.2)	0.924
Body mass index, kg/m^2	25.4 ± 4.2	25.8 ± 4.5	26.1 ± 4.3	26.4 ± 4.6	0.524
Timing of blood sampling					
Third-trimester sampling, weeks	35.2 ± 2.1	35.0 ± 2.3	34.6 ± 2.4	34.2 ± 2.5	0.082
Hemoglobin, g/dL					
T1	12.8 ± 1.1	12.5 ± 1.2	12.3 ± 1.1	12.1 ± 1.2	0.024
T2	11.9 ± 1.0	11.6 ± 1.1	11.5 ± 1.0	11.3 ± 1.1	0.038
T3	11.4 ± 1.1	11.2 ± 1.2	11.0 ± 1.1	10.8 ± 1.3	0.042
ΔT3–T2, %	−4.2	−3.4	−4.3	−4.4	–
Albumin, g/dL					
T1	4.1 ± 0.3	4.0 ± 0.3	3.9 ± 0.3	3.8 ± 0.3	0.018
T2	3.8 ± 0.3	3.7 ± 0.3	3.6 ± 0.3	3.5 ± 0.3	0.022
T3	3.6 ± 0.3	3.5 ± 0.3	3.4 ± 0.4	3.2 ± 0.4	0.001
ΔT3–T2, %	−5.3	−5.4	−5.6	−8.6	–
Lymphocytes, ×10^3/μL					
T1	2.0 ± 0.5	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.5	0.682
T2	1.9 ± 0.4	2.0 ± 0.4	2.0 ± 0.4	2.0 ± 0.4	0.574
T3	2.0 ± 0.5	2.1 ± 0.5	2.1 ± 0.5	2.2 ± 0.6	0.287
ΔT3–T2, %	+5.3	+5.0	+5.0	+10.0	–
Platelets, ×10^3/μL					
T1	248 ± 45	246 ± 44	244 ± 43	245 ± 42	0.892
T2	235 ± 40	230 ± 39	225 ± 38	218 ± 38	0.124
T3	225 ± 38	218 ± 36	195 ± 40	142 ± 35	<0.001
ΔT3–T2, %	−4.3	−5.2	−13.3	−34.9	–
HALP score					
T1	38.5 ± 8.2	37.8 ± 7.9	36.9 ± 8.5	35.2 ± 9.1	0.214
T2	42.3 ± 9.1	40.7 ± 8.8	38.4 ± 9.3	33.6 ± 10.2*	0.018
T3	45.6 ± 10.3	44.2 ± 10.1	46.8 ± 11.7	58.3 ± 15.8***	<0.001
ΔT3–T2, %	+7.8	+8.6	+21.9	+73.5	–
Infection screening					
CRP, mg/L, median (IQR)	3.2 (1.8–5.1)	3.5 (2.0–5.4)	3.8 (2.2–5.8)	4.1 (2.4–6.2)	0.186
CRP >10 mg/L, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Urinalysis leukocytes (+), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Positive urine culture, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Corticosteroid administration					
Betamethasone use, n (%)	0 (0.0)	5 (5.2)	18 (30.0)	28 (77.8)***	<0.001
Risk of delivery <34 weeks, n (%)	0 (0.0)	5 (5.2)	18 (30.0)	28 (77.8)	<0.001
T3 sample before steroid, n (%)	–	5 (100)	18 (100)	28 (100)	–

Data are mean ± SD, except for C-reactive protein (median, IQR) and categorical variables (n, %). Groups were compared using one-way Analysis of Variance (ANOVA) for normally distributed variables, the Kruskal–Wallis test for non-normally distributed variables, and the chi-square test for categorical variables. Normality was checked with the Shapiro–Wilk test. Maternal age, nulliparity, body mass index, and the week of third-trimester sampling were similar across the groups (all $p > 0.05$). Only maternal age and nulliparity were entered as covariates in the regression analysis. *$p < 0.05$, ***$p < 0.001$ versus the control. HALP, hemoglobin, albumin, lymphocyte, and platelet; T1–T3, first–third trimester; IQR, interquartile range; Δ, inter-trimester change; SD, standard deviation.

3.3 Analysis of HALP Changes Between Trimesters (Delta Analysis)

From the first to the second trimester (ΔT2–T1), the control group showed a mean increase of 3.8 units (95% CI: 3.0 to 4.6), whereas the severe ICP group depicted a mean decrease of 1.6 units (95% CI: −3.2 to 0.0). A positive change occurred in 78.3% of the controls but only 33.3% of the severe cases. From the second to the third trimester (ΔT3–T2), the severity of the change increased, reaching a mean of 24.7 units (95% CI: 20.7 to 28.7) in se-

Table 2. Distribution of HALP scores across trimesters.

HALP score	Control (n = 120)	Mild ICP (n = 96)	Moderate ICP (n = 60)	Severe ICP (n = 36)	*p* value
First trimester (T1)					
Mean ± SD	38.5 ± 8.2	37.8 ± 7.9	36.9 ± 8.5	35.2 ± 9.1	0.214
Median (IQR)	37.8 (32.4–44.1)	37.2 (31.8–43.5)	36.5 (30.9–42.8)	34.8 (29.3–41.2)	–
Second trimester (T2)					
Mean ± SD	42.3 ± 9.1	40.7 ± 8.8	38.4 ± 9.3	33.6 ± 10.2*	0.018
Median (IQR)	41.6 (35.8–48.2)	40.1 (34.2–46.9)	37.9 (31.6–44.8)	32.5 (26.8–39.7)	–
Third trimester (T3)					
Mean ± SD	45.6 ± 10.3	44.2 ± 10.1	46.8 ± 11.7	58.3 ± 15.8***	<0.001
Median (IQR)	44.9 (38.1–52.4)	43.5 (36.8–51.2)	45.3 (37.2–55.6)	56.7 (46.2–68.9)	–

Values are presented as mean ± standard deviation and median (interquartile range). Between-group differences were assessed using the Kruskal-Wallis test with Dunn post-hoc correction. *$p < 0.05$ and ***$p < 0.001$ versus the control group. T1, first trimester; T2, second trimester; T3, third trimester.

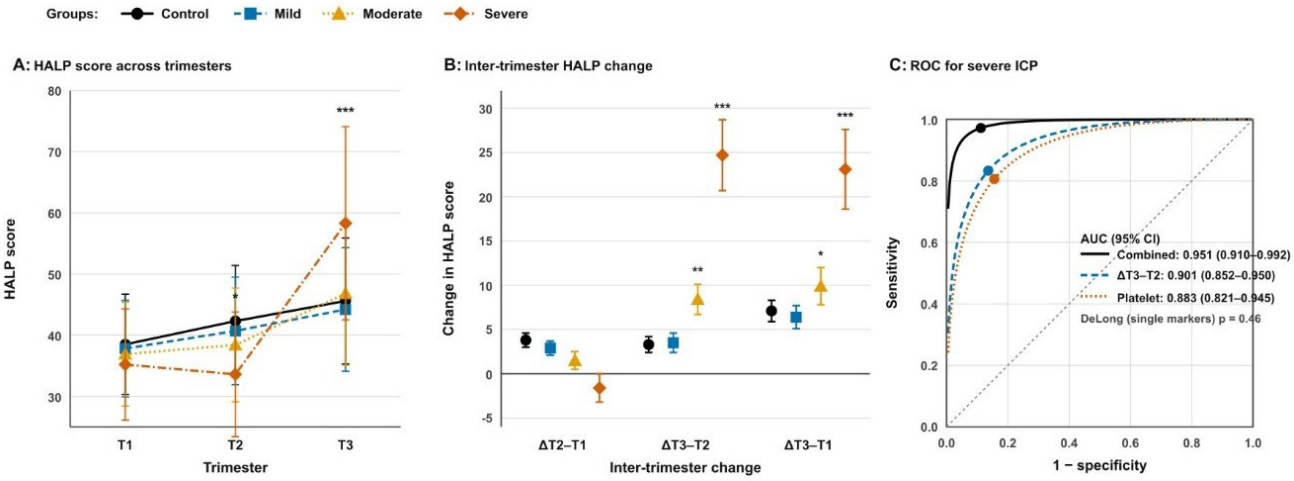

Fig. 2. Trimester-specific HALP behavior and discrimination of severe ICP. (A) HALP score across trimesters by group (mean ± SD); (B) inter-trimester HALP changes by group (mean with 95% CI; Kruskal–Wallis with Dunn post-hoc); and (C) ROC curves for severe ICP—ΔT3–T2, third-trimester platelet count, and a combined model with both markers as continuous variables, with optimal operating points marked and the diagonal denoting no discrimination. The two single markers showed similar discrimination (DeLong $p = 0.46$), whereas the combined model discriminated better than either alone (likelihood-ratio $p < 0.001$). Asterisks denote comparison with the control group in (A) and (B): *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Non-significant comparisons are unmarked. CI, confidence interval; ROC, receiver operating characteristic; AUC, area under the ROC curve.

vere cases, 97.2% of whom had a positive value. Over the whole period (ΔT3–T1), the severe group increased by a mean of 23.1 units (95% CI: 18.6 to 27.6), and 86.1% of these women gained more than 10 units. Because the delta distributions were right-skewed (Shapiro-Wilk $p < 0.05$), the groups were compared with the Kruskal–Wallis test and Dunn post-hoc correction: the ΔT3–T2 and ΔT3–T1 differences were significant ($p < 0.001$), while ΔT2–T1 was not ($p = 0.121$; Table 3; Fig. 2B).

3.4 Changes in HALP Score Components

To clarify the physiological basis of these changes, the components were examined longitudinally within the severe ICP group. Hemoglobin declined from 12.1 ± 1.2 g/dL at T1 to 10.8 ± 1.3 g/dL at T3 (about 10.7%), and albumin fell from 3.8 ± 0.3 to 3.2 ± 0.4 g/dL (about 15.8%). Lymphocytes stayed stable (2.1 ± 0.5 vs. 2.2 ± 0.6 $\times 10^3/\mu L$). Platelets changed the most, falling 34.9% from 218 ± 38 $\times 10^3/\mu L$ in the second trimester to 142 ± 35 $\times 10^3/\mu L$ in the third.

The third-trimester rise in the HALP score reflected this fall in platelets: Because platelets are the denominator of the formula HALP = (Hb × albumin × lymphocytes) / platelets, a large reduction raises the score even while hemoglobin and albumin decline. Therefore, whether the HALP-derived change added anything beyond the platelet count was tested directly in the analyses below.

Table 3. Inter-trimester changes in HALP score (delta analysis).

Delta HALP	Control (n = 120)	Mild ICP (n = 96)	Moderate ICP (n = 60)	Severe ICP (n = 36)	*p* value
ΔT2–T1					
Mean ± SD	3.8 ± 4.2	2.9 ± 3.8	1.5 ± 4.1	−1.6 ± 4.8	0.121
95% CI	3.0 to 4.6	2.1 to 3.7	0.5 to 2.5	−3.2 to 0.0	–
Positive change, n (%)	94 (78.3)	70 (72.9)	38 (63.3)	12 (33.3)	–
ΔT3–T2					
Mean ± SD	3.3 ± 5.1	3.5 ± 5.3	8.4 ± 6.8**	24.7 ± 12.3***	<0.001
95% CI	2.4 to 4.2	2.4 to 4.6	6.7 to 10.1	20.7 to 28.7	–
Positive change, n (%)	86 (71.7)	72 (75.0)	50 (83.3)	35 (97.2)	–
ΔT3–T1					
Mean ± SD	7.1 ± 6.8	6.4 ± 6.5	9.9 ± 8.2*	23.1 ± 13.7***	<0.001
95% CI	5.9 to 8.3	5.1 to 7.7	7.8 to 12.0	18.6 to 27.6	–
Increase >10 units, n (%)	30 (25.0)	22 (22.9)	29 (48.3)	31 (86.1)	–

Inter-trimester changes in the HALP score are presented as mean ± standard deviation with the corresponding 95% confidence interval of the mean. Categorical changes are presented as n (%). Because the delta distributions were right-skewed (Shapiro-Wilk $p < 0.05$), between-group comparisons were performed using the Kruskal-Wallis test with Dunn post hoc correction. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ versus the control group.

Table 4. Diagnostic performance of HALP-based parameters (ROC analysis).

Parameter	AUC (95% CI)	Cut-off	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Prediction of severe ICP						
T3 HALP	0.824 (0.762–0.886)	>48.5	77.8	79.6	44.8	94.5
T3 platelet count	0.883 (0.821–0.945)	≤165	80.6	84.4	51.4	95.5
ΔT3–T2	0.901 (0.852–0.950)	>12.0	83.3	87.3	46.2	97.6
ΔT3–T1	0.884 (0.830–0.938)	>15.0	80.6	83.7	50.0	95.6
ΔT3–T2 + T3 platelet count (combined)	0.951 (0.910–0.992)	model	97.2	88.8	64.0	99.4
Prediction of any ICP (n = 192)						
T3 HALP	0.598 (0.528–0.668)	>46.0	49.5	66.7	70.4	45.2
ΔT3–T2	0.654 (0.586–0.722)	>5.0	60.4	69.2	75.8	52.1

Optimal cut-offs by the Youden index; AUCs are reported with 95% confidence intervals. Single-predictor AUCs use the continuous marker, and the combined AUC is from a model with both markers entered as continuous variables. Bootstrap optimism-corrected AUCs were 0.90 for ΔT3–T2 and 0.95 for the combined model. The ΔT3–T2 and platelet-count curves did not differ (DeLong $p = 0.46$). The combined operating point maximizes the Youden index on the predicted probability. PPV, positive predictive value; NPV, negative predictive value.

3.5 Discrimination of Severe ICP

Because HALP was measured serially and severity was classified by peak total serum bile acids, these analyses describe how well the markers discriminated against severe disease rather than prospective prediction. In ROC analysis, ΔT3–T2 gave the highest discrimination for severe ICP (AUC: 0.901, 95% CI: 0.852–0.950). At a cutoff of 12.0 units, it yielded 83.3% sensitivity and 87.3% specificity, with a negative predictive value of 97.6% (Table 4; Fig. 2C). The third-trimester HALP score alone did not discriminate as well (AUC: 0.824; cutoff: 48.5; sensitivity 77.8%; specificity 79.6%). Discrimination for any ICP was poor (AUC: 0.598–0.654).

To test whether the HALP-derived change simply mirrored the falling platelet count, the ΔT3–T2 was compared with the third-trimester platelet count alone. The platelet count discriminated against severe ICP nearly as well (AUC: 0.883, 95% CI: 0.821–0.945; cutoff ≤165 $\times 10^3/\mu L$; sensitivity 80.6%; specificity 84.4%), and the two curves did not vary significantly (DeLong $p = 0.46$). A model combining the two markers as continuous variables discriminated better than either alone (AUC: 0.951, 95% CI: 0.910–0.992). Regarding internal validation by bootstrapping, the optimism-corrected AUCs were 0.90 for ΔT3–T2 and 0.95 for the combined model, indicating limited overfitting, despite the few severe cases.

3.6 Risk Categories and Clinical Outcomes

When the women were grouped by the longitudinal change in the HALP score (ΔT3–T2), the clinical outcomes diverged across categories. In the low-risk group (ΔT3–T2 <5 units, n = 117), preterm births occurred in 8.5% and fetal complications in 5.1%. In the moderate-risk group (5–12 units, n = 130), the corresponding rates were 16.9% and 10.8%, respectively. The high-risk group (>12 units,

Table 5A. HALP risk categories and clinical outcomes (n = 312).

HALP risk category	n (%)	Preterm birth, n (%)	HELLP/PE, n (%)	NICU admission, n (%)	Fetal complications, n (%)
Low (ΔT3–T2 <5)	117 (37.5)	10 (8.5)	0 (0.0)	1 (0.9)	6 (5.1)
Moderate (ΔT3–T2 5–12)	130 (41.7)	22 (16.9)	3 (2.3)	5 (3.8)	14 (10.8)
High (ΔT3–T2 >12)	65 (20.8)	34 (52.3)***	14 (21.5)***	10 (15.4)**	23 (35.4)***

Outcomes according to HALP risk category were defined by ΔT3–T2. Preeclampsia and HELLP syndrome were absent at diagnosis and were recorded only during follow-ups. Chi-square test: $**p < 0.01$ and $***p < 0.001$ versus the low-risk category. HELLP, hemolysis, elevated liver enzymes, low platelets; PE, preeclampsia; NICU, neonatal intensive care unit.

Table 5B. Multivariable logistic regression for factors associated with severe ICP.

Variable	Odds ratio	95% CI	*p* value
ΔT3–T2 >12.0 units, unadjusted	34.40	12.20–80.20	<0.001
Multivariable model			
Maternal age >35 years	1.78	0.74–4.28	0.198
Nulliparity	1.42	0.66–3.05	0.368
ΔT3–T2 >12.0 units	31.70	12.30–81.80	<0.001

Logistic regression for severe ICP. The unadjusted estimate is displayed for reference; because maternal age and parity were balanced and unrelated to disease severity, adjustment left the ΔT3–T2 odds ratio essentially unchanged. All variance inflation factors were less than 5.

n = 65) had the highest rates of preterm birth (52.3%), preeclampsia or HELLP syndrome (21.5%), neonatal intensive care admission (15.4%), and fetal complications (35.4%). See Table 5A. Preeclampsia and HELLP syndrome were absent at the time of ICP diagnosis and were recorded only during the follow-up; women in whom either condition was present at diagnosis were excluded.

3.7 Independent Risk Factors for Severe ICP

In logistic regression, a ΔT3–T2 greater than 12.0 units was strongly associated with severe ICP (unadjusted OR: 34.40, 95% CI: 12.2–80.2). After adjustment for maternal age and parity—the only demographic factors considered, as the groups were otherwise balanced—the association was essentially unchanged (OR: 31.7, 95% CI: 12.3–81.8). Neither maternal age over 35 years (OR: 1.78, $p = 0.198$) nor nulliparity (OR: 1.42, $p = 0.368$) was significant. All variance inflation factors were below 5 (Table 5B).

To check whether this association merely reflected the platelet count, the two markers were modeled together. The platelet count alone had an odds ratio of 22.4 (Model 1). When both were entered, each remained significant (platelet count OR: 10.8; ΔT3–T2 OR: 16.5), and adding ΔT3–T2 augmented the model fit (likelihood-ratio test $p < 0.001$). The markers were only moderately correlated (r = 0.41; variance inflation factor 1.20), so collinearity was not a concern. Thus, the dynamic inter-trimester change and the static platelet level carried comparable but partly complementary information (Table 5C).

3.8 Relationship Between HALP Score and Bile Acid Levels

The HALP scores showed different patterns of association with TSBA levels across pregnancy. A weak negative correlation was present in the first trimester ($r = -0.124$) and became somewhat stronger in the second ($r = -0.287$), while a positive correlation appeared in the third ($r = 0.426$). The strongest association was between ΔT3–T2 and peak TSBA ($r = 0.612$, $p < 0.001$). Because the HALP score and its components are mathematically interrelated, each parameter was examined in its own univariable regression rather than in a single combined model. Of these, ΔT3–T2 explained the largest share of the variance in peak TSBA ($R^2 = 0.375$). See Fig. 3.

4. Discussion

We investigated longitudinal changes in the HALP score across trimesters in pregnancies complicated by ICP and examined how well it discriminated against disease severity. Our findings determined that an increase in the HALP score, particularly during the transition to the later stages of pregnancy, was associated with severe ICP. The score discriminated against severe disease reasonably well, reaching its highest values in the third trimester among patients with severe cholestasis compared with the control group (58.3 ± 15.8 vs. 45.6 ± 10.3; $p < 0.001$).

Although the HALP score in the second trimester was lower in the ICP group than in the control group, a 73.5% increase was observed as these patients transitioned from the second to the third trimester. This longitudinal rise (ΔT3–T2) appeared to discriminate severe disease better than any single-point measurement.

Table 5C. Joint modeling of ΔT3–T2 and the third-trimester platelet count.

Model/Variable	OR	95% CI	*p* value
Model 1—T3 platelet count (≤165 ×10^3/μL)	22.4	9.2–54.5	<0.001
Model 2—T3 platelet count (≤165 ×10^3/μL)	10.8	4.1–28.7	<0.001
Model 2—ΔT3–T2 (>12.0 units)	16.5	6.0–45.0	<0.001
Likelihood-ratio test (Model 1 vs. Model 2)	—	—	<0.001

Logistic regression for severe ICP. Odds ratios use the dichotomized cut-offs (platelet ≤165 × 10^3/μL; ΔT3–T2 >12.0 units). The Model 1 odds ratio equals the diagnostic odds ratio of the platelet cut-off. The combined AUC (0.951; optimism-corrected 0.95) is from a model with both markers entered as continuous variables. Adding ΔT3–T2 improved the model fit (likelihood ratio χ^2 = 37.2, 1 df, p < 0.001). The markers were moderately correlated (r = 0.41, variance inflation factor 1.20).

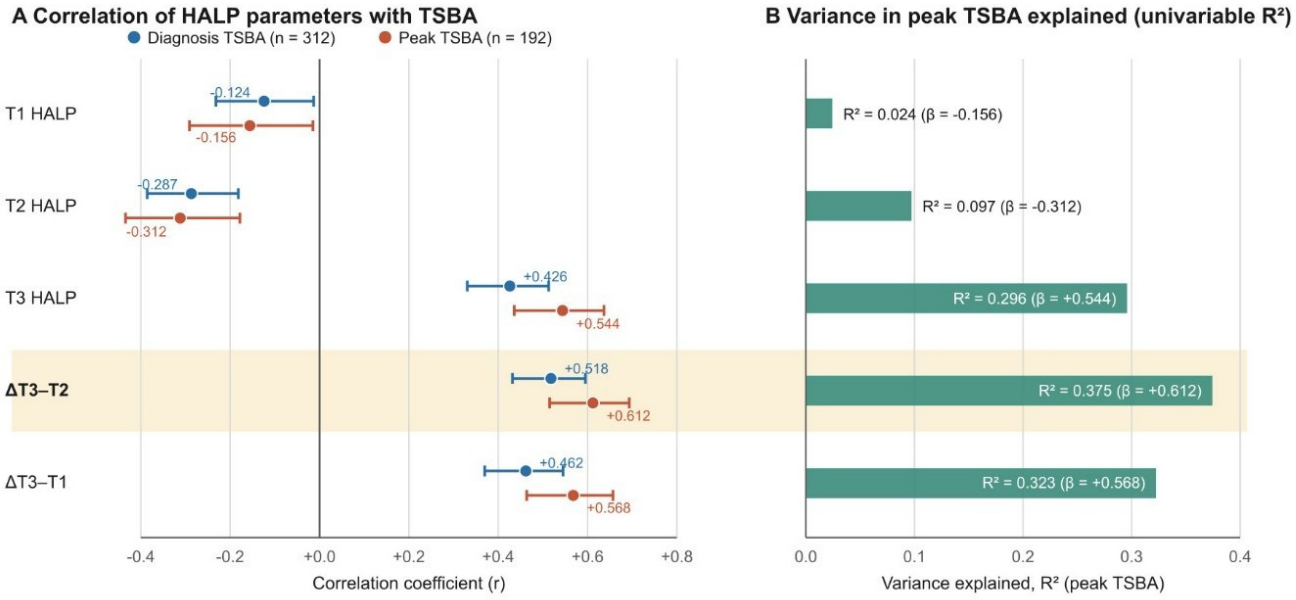

Fig. 3. Association between HALP parameters and TSBA levels. (A) Correlation coefficients (r) of trimester-specific and inter-trimester HALP parameters with TSBA at the diagnosis (n = 312) and peak (n = 192). The bars denote 95% confidence intervals. (B) Variance in the peak TSBA explained by each parameter in separate univariable linear regressions (R^2 with standardized β). The parameters were modeled univariably because the score and its components are mathematically interrelated. ΔT3–T2 illustrated the strongest association (r = 0.612; R^2 = 0.375). All coefficients were significant (T1 HALP, p < 0.05; others, p < 0.001). β, standardized regression coefficient.

The primary explanation for this paradoxical increase in the HALP score is the disproportionate decrease in platelet counts. In the severe ICP group, a 34.9% reduction in platelet counts was observed between the second and third trimesters. Since platelets constitute the denominator of the HALP formula [HALP = (HGB × ALB × LYM) / PLT], their substantial decline leads to a sharp, proportional escalation in the final score. While other components also fluctuated—hemoglobin levels decreased by 10.7% and albumin levels by 15.8%, alongside a 10.0% increase in lymphocyte counts—the magnitude of the platelet drop remained the dominant driver of the score. The decrease in albumin levels in ICP may be attributed to impaired hepatic synthetic function. Specifically, bile acid-induced oxidative stress within the endoplasmic reticulum of hepatocytes can lead to proteotoxic stress and the subsequent impairment of albumin synthesis [18]. This hepatocellular dysfunction, coupled with a systemic inflammatory response, further complicates the biochemical profile of severe ICP cases.

Beyond this arithmetic effect, the behavior of individual components is biologically plausible, which speaks to why a composite score should be related to ICP at all. Elevated bile acids induce oxidative stress and apoptosis in

hepatocytes [18]; the resulting loss of synthetic capacity provides a direct explanation for the fall in albumin. The same toxic load plausibly underlies the changes in platelet and lymphocyte behavior discussed below. Because the HALP score synthesizes these nutritional (hemoglobin, albumin) and hematological–immune (lymphocyte, platelet) axes in a single value, its trajectory can reflect this multisystemic effect even though no individual component is specific to ICP.

Our findings largely corroborate the existing literature, yet they provide a more nuanced perspective of the cellular dynamics of ICP. Shen et al. [15] demonstrated that platelet parameters, such as platelet distribution width (PDW) and mean platelet volume (MPV), significantly increase in patients with ICP during late pregnancy, signaling heightened platelet activation. Furthermore, Arslanoğlu et al. [16] reported increased platelet aggregation and endothelial dysfunction in ICP patients, suggesting that these changes contribute to maternal vascular dysfunction.

Regarding inflammatory markers, Luo et al. [17] reported that lymphocyte counts in the ICP group were significantly lower than in healthy controls. Interestingly, in our study, lymphocyte values remained relatively constant throughout the trimesters. This discrepancy suggests that ICP may not align with a classic systemic inflammatory profile, but rather reflects a complex metabolic disorder primarily driven by bile acid toxicity and subsequent hepatocellular stress. This distinction is relevant because it supports the utility of the HALP score—which incorporates both nutritional and cellular markers—as a broader indicator of the disease's metabolic and hematological impact.

Differentiating ICP-associated thrombocytopenia from HELLP syndrome is clinically important. In our study, all participants remained normotensive and exhibited no clinical or laboratory evidence of hemolysis (e.g., elevated LDH or schistocytes on peripheral smears). This must be read relative to the proper time frame. At the point when ICP was diagnosed and the third-trimester HALP score was measured, every patient was normotensive and free of hemolysis. Women in whom preeclampsia or HELLP syndrome was already present at diagnosis were excluded. The cases of preeclampsia or HELLP recorded in the high-risk group (Table 5A) developed later during follow-up, after the HALP assessment. Hence, the thrombocytopenia analyzed here reflected ICP itself at the time of measurement and was not a feature of HELLP, even though a subset of these women subsequently developed hypertensive complications. Consequently, the observed decline in platelet counts appears to be an isolated phenomenon secondary to bile acid toxicity, rather than a consumptive process typical of HELLP syndrome.

Bile acid levels exceeding physiological ranges are known to induce systemic tissue damage through the activation of oxidative stress pathways and the triggering of pro-apoptotic signaling [18]. This isolated toxic effect on bone marrow or peripheral platelet survival, independent of hypertensive disorders, may underlie the bile acid-related hematological changes captured by the HALP score.

In the ROC analysis, the ΔT3–T2 variable revealed good discrimination of severe ICP, with an AUC of 0.901. By establishing a threshold value of 12.0 units, we achieved 83.3% sensitivity and 87.3% specificity. The NPV was 97.6%, so a delta below this threshold made a severe disease unlikely. This might help identify lower-risk pregnancies, although such use would require prospective validation before it could guide triage. Unlike previous research, which generally relied on single-time point (static) data collection, our study employed a longitudinal delta-based analysis. This systematic assessment allows the detection of dynamic pathophysiological shifts that static measurements often fail to capture, providing a more comprehensive view of the disease's progression.

Because the platelet count dominates the HALP score, we tested whether the longitudinal change merely reproduced the information already in the platelet level. The third-trimester platelet count alone discriminated severe ICP almost as well (AUC 0.883), and the two curves did not differ significantly (DeLong $p = 0.46$). Accordingly, the HALP-derived change itself was not superior to the platelet count. When the two were combined, discrimination improved (AUC 0.951), which suggests that the dynamic inter-trimester change and the static platelet level carry partly complementary, rather than identical, information. Upon internal validation by bootstrapping, the optimism-corrected AUCs were 0.90 for ΔT3–T2 and 0.95 for the combined model, indicating limited overfitting. Given the few severe cases, however, these estimates should be regarded as preliminary and confirmed by an external cohort.

The identification of severe ICP cases is important for optimizing both maternal and neonatal outcomes. The clinical weight of this is underscored by evidence that the gestational timing at which bile acids reach the severe range (≥100 μmol/L) is related to the risk of stillbirth [9]. Huang et al. [19] demonstrated that ICP significantly escalates the risk of preterm birth by approximately 2.64 times. A similar, yet more pronounced, trend was observed in our proposed risk classification; the rate of preterm birth was 52.3% in the high-risk group (ΔT3–T2 >12), compared to only 8.5% in the low-risk group. This approximately sixfold difference illustrates the clinical impact of HALP-based risk stratification in identifying pregnancies at the highest risk of adverse events. In multivariable logistic regression, a ΔT3–T2 above 12 units was the strongest independent factor associated with severe ICP, with an odds ratio of 31.7 after adjustment for maternal age and parity (Table 5B). When ΔT3–T2 and the third-trimester platelet count were entered together, both remained significant, corresponding to the comparable but complementary information noted above. Overall, the dynamic change in HALP score added information beyond a single static measure-

ment while performing on a par with the platelet count alone rather than clearly surpassing it.

Limitations

It was retrospective and conducted at a single center, which may limit the generalizability of the findings. In addition, because the HALP measurements and the bile acid peak fell within overlapping time windows, our analyses describe the cross-sectional discrimination of severity rather than true prospective prediction; the score should not yet be regarded as an early-warning test applied before diagnosis. The number of severe cases was small (n = 36). Although internal bootstrapping suggested limited optimism, the cutoffs and AUCs may still be optimistic until they are confirmed in an independent population. Finally, as noted above, the HALP-derived change discriminated against severe disease only as well as the platelet count alone, so its value lies in complementing simpler markers rather than replacing them.

However, these limitations are mitigated by several key strengths. The study employed a highly standardized clinical protocol and implemented strict patient selection criteria. By explicitly excluding patients with evidence of infection and utilizing blood samples obtained before corticosteroid administration, we reduced potential confounding factors that could affect hematological parameters. These rigorous methodological steps help ensure that the observed changes in the HALP score reflect the pathophysiological process of ICP rather than these external influences.

5. Conclusions

This study found that the longitudinal change in the HALP score between the second and third trimesters (ΔT3–T2) was associated with and helped distinguish severe ICP. Rather than acting as a stand-alone test, it appeared to track worsening disease and to add information that complemented the third-trimester platelet count rather than surpassing it. Because the study was retrospective and the number of severe cases was small, these findings should be read as generating a hypothesis: HALP-based change is best regarded as a candidate marker that might help flag pregnancies deserving closer attention, not as an established screening or triage tool. Before it could be recommended for routine obstetric use, its value would need to be confirmed in prospective, multicenter studies with external validation, ideally defining and testing any threshold in an independent cohort.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

EM, GA contributed to the study conception and design. Material preparation and data collection were performed by the EM. Statistical analysis and interpretation were performed by all authors. The first draft of the manuscript was written by the EM. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki. This study was approved by the Kahramanmaraş Sütçü İmam University Medical Research Ethics Committee (Protocol code: 382, Date: November 17, 2025). For this type of retrospective study, formal consent is not required as per the institutional ethics committee's guidelines, provided that data are analyzed anonymously.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG53524.

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