Original Article
Analysis of changes in platelet parameters and inflammatory markers in intrahepatic cholestasis of pregnancy before disease development

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Abstract: Background: Intrahepatic cholestasis of pregnancy (ICP) is the most common liver condition during pregnancy, associated with adverse outcomes for both mother and fetus. While inflammatory markers are important predictors in oncology and cardiovascular disease, their role in ICP remains unclear. This study investigates changes in platelet parameters and blood-derived inflammatory markers around the onset of ICP and evaluates their potential as independent risk factors. Methods: This retrospective study analyzed inflammatory markers, including the Neutrophil-to-Lymphocyte Ratio (NLR), Derived NLR (dNLR), Monocyte-to-Lymphocyte Ratio (MLR), Neutrophil-Monocyte-to-Lymphocyte Ratio (NMLR), Systemic Inflammation Response Index (SIRI), and Systemic Immune-Inflammation Index (SII) along with variations in platelet parameters in 49 ICP patients and 250 healthy controls during late pregnancy, specifically at disease onset. Additionally, changes in these parameters were assessed among the same 49 ICP patients compared to 1439 healthy controls during early pregnancy. Results: During an episode of ICP, individuals exhibited increased platelet parameters, including PCT, P-LCR, PDW and MPV, compared to those with uncomplicated pregnancies. The levels of WBC, NEUT, NLR, dNLR, NMLR, SIRI, and SII were also elevated in the ICP group relative to the control group. Prior to disease onset, platelet parameters such as PCT and PDW, along with inflammatory markers including NEUT, NLR, NMLR, SIRI, and SII, were significantly higher in ICP patients. Additionally, a notable increase in HGB, HCT, MCV, MCH, and RDW-CV was observed in the ICP group, while MCHC was decreased. Logistic regression analysis identified MCV, PDW and SII as risk factors for developing ICP. Conclusions: PCT, PDW, NEUT, NLR, NMLR, SIRI, and SII levels were significantly elevated both before and during the progression of ICP. Notably, MCV, PDW, and SII were identified as independent risk factors, representing new predictive indicators for the development of ICP.

Keywords: Intrahepatic cholestasis of pregnancy (ICP), platelet parameters, inflammatory markers

Introduction

Intrahepatic Cholestasis of Pregnancy (ICP) is a common liver condition that typically emerges in the third trimester of gestation [1]. This disorder is primarily characterized by severe itching and elevated concentrations of total bile acids (TBA) in the blood. The prevalence of ICP varies widely depending on geographical and ethnic factors, with an estimated occurrence rate between 0.1% and 2% [1, 2]. Recent studies indicate that the overall prevalence of ICP in the Chinese population is approximately 6.06% [3]. Although cholestasis generally poses little threat to the mother's overall health, it does increase the likelihood of various complications during pregnancy, such as preeclampsia (PE) and gestational diabetes mellitus (GDM) [4], while significantly raising the risk of adverse fetal outcomes. For the fetus, elevated levels of bile acids in the mother's blood can lead to complications, including staining of the amniot-

ic fluid, spontaneous preterm labor, fetal distress, fetal growth restriction (FGR), and, in severe cases, stillbirth [5, 6]. Research has demonstrated a clear link between elevated maternal bile acid levels and an increased risk of fetal complications - higher bile acid concentration, which correlates with greater risk [7]. Given these potential complications, current research is focused on identifying new molecular markers for the early diagnosis and intervention of ICP. Recognizing these markers could improve early detection of ICP, allowing healthcare providers to implement preventive strategies that enhance outcomes for both the mother and the fetus.

The traditional clinical diagnostic criteria for ICP rely on elevated total bile acids (TBA) and the presence of pruritus (itching), particularly in the second and third trimesters of gestation. However, the sensitivity and specificity of TBA measurements for diagnosing ICP can be limited, necessitating a search for more accurate and reliable biomarkers [8]. Recent advancements in omics research, particularly high-throughput RNA and protein analyses, have suggested potential new diagnostic biomarkers for ICP. For instance, proteomics studies have identified a combination of four proteins that may serve as promising diagnostic markers [9, 10]. Despite these findings, there is ongoing debate regarding the quantitative reliability of omics technologies in clinical practice.

Bile acids are known to trigger inflammation by affecting hepatocytes, which in turn leads to the secretion of pro-inflammatory mediators and the subsequent activation of neutrophils [11]. Recent research has begun to explore the use of novel inflammatory markers in blood tests as tools for diagnosing and prognosing ICP. Evidence suggests that patients with severe ICP exhibit significantly elevated white blood cell (WBC) counts and higher Neutrophil/Lymphocyte Ratios (NLR) compared to healthy controls. Even those with mild ICP show increased NLR, along with generally reduced lymphocyte levels [12].

In addition to the NLR, other inflammatory markers derived from complete blood cell counts, such as the Derived Neutrophil/Lymphocyte Ratio (dNLR), Monocyte/Lymphocyte Ratio (MLR), Neutrophil-Monocyte/Lymphocyte Ratio (NMLR), Systemic Inflammatory Response Index (SIRI), and Systemic Immune-Inflammation Index (SII), have been associated with various medical conditions, including benign prostatic hyperplasia, heart failure, sarcopenia, and overall mortality [13-15]. However, the specific diagnostic and prognostic significance of these inflammatory markers in ICP is not fully understood, indicating a need for further research to clarify their clinical utility in this context.

This research examines changes in various inflammatory markers obtained from complete blood count (CBC), including NLR, dNLR, MLR, NMLR, SIRI, and SII. Additionally, it explores changes in platelet parameters across different stages of ICP. The goal is to assess the potential of these markers as predictive or diagnostic biomarkers for the early identification and prevention of ICP, aiming to improve maternal and fetal outcomes through more precise risk stratification.

Materials and methods

Data collection

A retrospective analysis was conducted on the clinical data of patients with ICP and healthy pregnant women (control group) who delivered at Suzhou Municipal Hospital between 2015 and 2024. The study included 49 ICP patients and 1439 control subjects in the early or mid-pregnancy stages, as well as 49 ICP cases and 250 controls in late pregnancy. Participants were selected based on specific criteria: a thorough medical history, singleton pregnancies, live births free of defects, and completion of laboratory assessments. Exclusion criteria: missing data; congenital anomalies or chromosomal abnormalities in the fetus; multiple gestations; pre-existing chronic or acute liver disorders (including Wilson's disease, cholecystitis, primary sclerosing cholangitis, primary biliary cirrhosis, alpha-1-antitrypsin deficiency, symptomatic gallstones, cytomegalovirus infection, Epstein-Barr virus infection, autoimmune hepatitis, or acute fatty liver disease during pregnancy); HELLP syndrome; or additional complications during pregnancy.

Indicators and definitions

The criteria for diagnosing ICP include the following: unexplained skin itching, particularly in the palms and soles; increased fasting serum

Table 1. Parameters related to routine blood tests of ICP group and control group during late-pregnancy (mean ± SD)

Clinical parameters	ICP group	Control group	P value
PLT (10^9/L)	195.41±70.75	179.68±47.88	0.326
PCT (%)	0.23±0.06	0.2±0.04	0.003
P-LCR (%)	37.99±11.01	33.61±8.68	0.003
MPV (fL)	11.6±1.53	11.06±1.12	0.028
PDW (fL)	16.32±3.48	14.13±2.72	<0.001
WBC (10^9/L)	10.83±2.99	9.4±2.63	0.002
NEUT (10^9/L)	8.16±3.11	6.92±2.5	0.003
LYMPH (10^9/L)	1.96±1.26	1.81±0.55	0.153
NLR	5.61±3.42	4.21±2.41	0.002
dNLR	0.91±0.08	0.91±0.04	0.002
MLR	0.38±0.19	0.35±0.15	0.480
NMLR	5.99±3.53	4.56±2.52	0.001
SIRI	3.36±2.54	2.62±1.97	0.027
SII	1050.9±720.11	748.87±443.84	0.004

ICP, intrahepatic cholestasis of pregnancy; PLT, platelet count; PCT, plateletcrit; P-LCR, platelet-larger cell ratio; MPV, mean platelet volume; PDW, platelet distribution width; WBC, white blood cell count; NEUT, neutrophil count; LYMPH, lymphocyte count; NLR, Neutrophil-to-Lymphocyte Ratio; dNLR, Derived NLR; MLR, Monocyte-to-Lymphocyte Ratio; NMLR, Neutrophil-Monocyte-to-Lymphocyte Ratio; SIRI, Systemic Inflammation Response Index; SII, Systemic Immune-Inflammation Index.

total bile acids (TBA); and normal bile acid levels in individuals with unaccounted hepatic function abnormalities, predominantly characterized by mild to moderate increases in serum alanine aminotransferase (ATL) and aspartate aminotransferase (AST), along with potentially elevated levels of glutamyl transpeptidase (GGT). Additionally, elevated serum bilirubin levels, primarily direct bilirubin, may be present. It is important to note that itchy skin and liver function issues typically resolve in the postpartum period [16-18].

In this study, pregnant women with normal TBA levels in early or mid-pregnancy- and late-pregnancy were classified as the normal group, while those diagnosed with ICP in mid- or late-pregnancy were classified as the ICP group. The ICP group was further divided into the early or mid-pregnancy ICP group (less than 20 weeks of gestation) and the late-pregnancy ICP group (more than 28 weeks of gestation) based on the gestational age at which ICP onset occurred.

Study methods

Blood samples were collected and sent to the laboratory for analysis of whole blood cells dur-

ing the second or third trimester of pregnancy. The cell counts in the whole blood were assessed using a hematology analyzer. The data obtained included maternal age, body mass index (BMI), gravida, parity, calculated gestational age, gestational age at testing, in vitro fertilization (IVF) status, and various blood parameters: platelet count (PLT), plateletcrit (PCT), platelet-larger cell ratio (P-LCR), mean platelet volume (MPV), platelet distribution width (PDW), WBC, neutrophil count (NEUT), lymphocyte count (LYMPH), monocyte count (MONO), and ratios including NLR = NEUT/LYMPH, dNLR = NEUT/(WBC - LYMPH), MLR = MONO/LYMPH, NMLR = (MONO + NEUT)/LYMPH, SIRI = NEUT × MONO/LYMPH, SII = PLT × NEUT/LYMPH, along with hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red blood cell volume distribution width (RDW) were collected and examined.

Statistical analysis

Data were described as mean ± standard deviation and median (minimum-maximum) values [19, 20]. The Wilcoxon rank sum test was used to assess differences between groups [21]. Correlations were analyzed using Spearman's rank-order correlation [22, 23]. All statistical analyses were performed with the R package "Stata" and "car". A *p* value <0.05 was considered statistically significant.

Results

Parameters related to routine blood tests during late-pregnancy

In late pregnancy, it is noteworthy that the levels of PCT, P-LCR, MPV, and PDW were elevated in patients with ICP compared to those in the normal pregnant cohort. However, the difference in PLT between the two groups was not statistically significant. Additionally, WBC, NEUT, NLR, dNLR, and NMLR values were high-
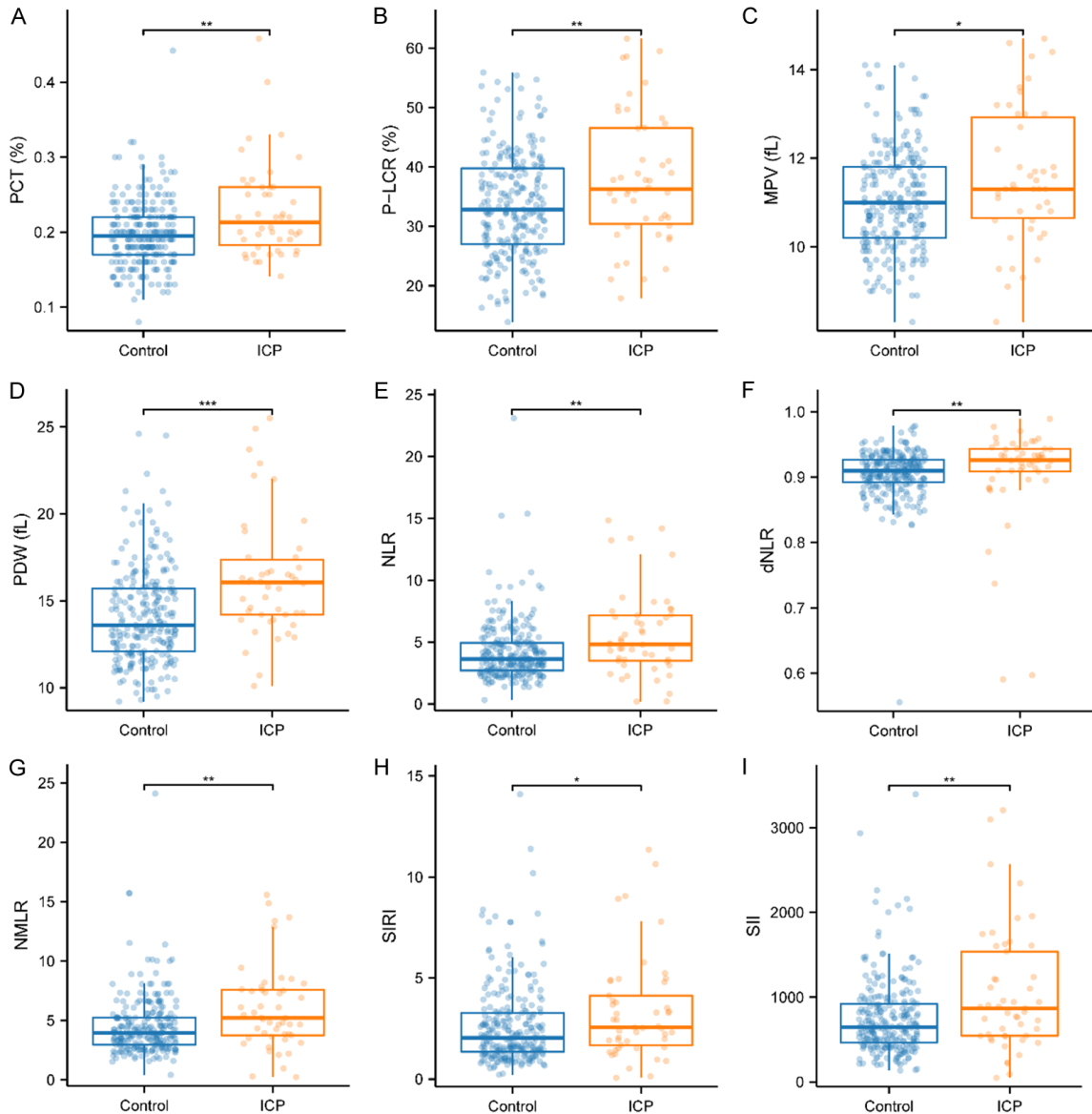
Figure 1. Differences in parameters related to routine blood tests between the ICP group and the control group in late-pregnancy. (A) PCT, (B) P-LCR, (C) MPV, (D) PDW, (E) NLR, (F) dNLR, (G) NMLR, (H) SIRI and (I) SII. ICP, Intrahepatic Cholestasis of Pregnancy; PCT, plateletcrit; P-LCR, platelet-larger cell ratio; MPV, mean platelet volume; PDW, platelet distribution width; WBC, white blood cell count; NEUT, neutrophil count; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil to lymphocyte ratio; NMLR, neutrophil-monocyte to lymphocyte Ratio; SIRI, systemic inflammatory response index; SII, systemic immune inflammatory index. *<0.05, **<0.01, ***<0.001.

er in the ICP group than those in the control group, with no significant difference observed in MLR. Similarly, we observed an increase in SIRI and SII among ICP patients during late pregnancy (**Table 1**; **Figure 1**).

Patient characteristics during early or mid-pregnancy

Table 2 presents the key features of both the control group and the ICP group. No significant differences were observed in terms of age, BMI, or gestational age at testing. Additionally, the ICP group exhibited a higher number of IVF cases.

Routine blood tests during early or mid-pregnancy

During the early to mid stages of pregnancy, patients with ICP exhibited significantly higher levels of PCT and PDW compared to women

Table 2. General data of ICP group and control group during early or mid-pregnancy pregnancy (mean ± SD)

Clinical parameters	ICP group	Control group	P value
Number of cases	49	1939	
Age (year)	31.78±4.78	30.7±4.55	0.111
BMI (kg/m^2)	22.48±2.83	22.25±2.83	0.738
Tested gestational age (week)	12.99±1.91	13.23±1.17	<0.001
IVF conceptions	14.3%	3.82%	<0.001

ICP, intrahepatic cholestasis of pregnancy; BMI, body mass index; IVF, in vitro fertilization.

Table 3. Parameters related to routine blood tests of ICP group and control group during early or mid-pregnancy (mean ± SD)

Clinical parameters	ICP group	Control group	P value
PLT (10^9/L)	232.24±53.9	216.74±48.43	0.071
PCT (%)	0.24±0.04	0.22±0.04	0.004
P-LCR (%)	27.4±10.02	26.88±7.93	0.836
MPV (fL)	10.24±1.35	10.24±0.97	0.943
PDW (fL)	14.84±2.83	12.14±2.12	<0.001
WBC (10^9/L)	9.46±2.24	8.88±1.93	0.090
NEUT (10^9/L)	7.35±2.08	6.7±1.71	0.031
LYMPH (10^9/L)	1.62±0.44	1.71±0.43	0.140
NLR	4.9±2.22	4.11±1.32	0.004
dNLR	0.93±0.02	0.93±0.02	0.440
MLR	0.27±0.11	0.24±0.09	0.139
NMLR	5.17±2.29	4.35±1.37	0.004
SIRI	2.03±1.33	1.64±0.81	0.019
SII	1128.6±545.91	887.32±347.5	<0.001

ICP, intrahepatic cholestasis of pregnancy; PLT, platelet count; PCT, plateletcrit; P-LCR, platelet-larger cell ratio; MPV, mean platelet volume; PDW, platelet distribution width; WBC, white blood cell count; NEUT, neutrophil count; LYMPH, lymphocyte count; NLR, Neutrophil-to-Lymphocyte Ratio; dNLR, Derived NLR; MLR, Monocyte-to-Lymphocyte Ratio; NMLR, Neutrophil-Monocyte-to-Lymphocyte Ratio; SIRI, Systemic Inflammation Response Index; SII, Systemic Immune-Inflammation Index.

with normal pregnancies. In contrast, no notable differences were observed in PLT, P-LCR, and MPV. Significant variations were also noted in NEUT, NLR, and NMLR between the ICP patients and the normal pregnant cohort, with elevated levels in those suffering from ICP. However, there were no statistically significant differences in WBC, LYMPH, dNLR, and MLR between the ICP patients and normal controls. Additionally, an increase in SIRI and SII was recorded in the ICP group (**Table 3**; **Figure 2**). A significant increase in HGB, HCT, MCV, MCH, and RDW-CV was observed in the ICP group, while MCHC showed a decrease (**Figure 3**).

Logistic regression analysis of ICP risk factors during early or mid-pregnancy

This analysis combined alterations in routine blood parameters associated with ICP at and before disease onset. The parameters included were PCT, PDW, NEUT, NLR, NMLR, SIRI and SII. However, due to strong correlations among PCT, NEUT, NLR, NMLR, SIRI and SII, these variables could not be included in the regression analysis due to covariance issues (see **Figure 4**). The subsequent multiple regression analysis revealed that MCV (OR, 1.110; 95% CI, 1.025-1.202), PDW (OR, 1.552; 95% CI, 1.385-1.738), and SII (OR, 1.002; 95% CI, 1.001-1.003) were significantly associated with an increased risk of ICP (refer to **Figure 5**).

Discussion

ICP is a liver disorder that poses significant risks, including preterm labor and fetal death. Early diagnosis is crucial for healthcare providers to implement preventive measures and mitigate these adverse outcomes. The primary goal of this study is to explore platelet-related markers and emerging inflammatory indicators at different stages of ICP development. Understanding these changes will clarify the pathophysiological mechanisms behind ICP and provide valuable clinical markers for its prevention.

The study identified notable increases in various markers such as PCT, PDW, NEUT, NLR, NMLR, SIRI, and SII, prior to and at the onset of ICP. These alterations suggest a heightened inflammatory response as ICP progresses. Additionally, logistic regression analysis identified MCV, PDW, and SII as significant risk factors associated with the onset of ICP, indicating that monitoring these markers in expectant mothers could be a valuable method for the early detection of those at high risk.
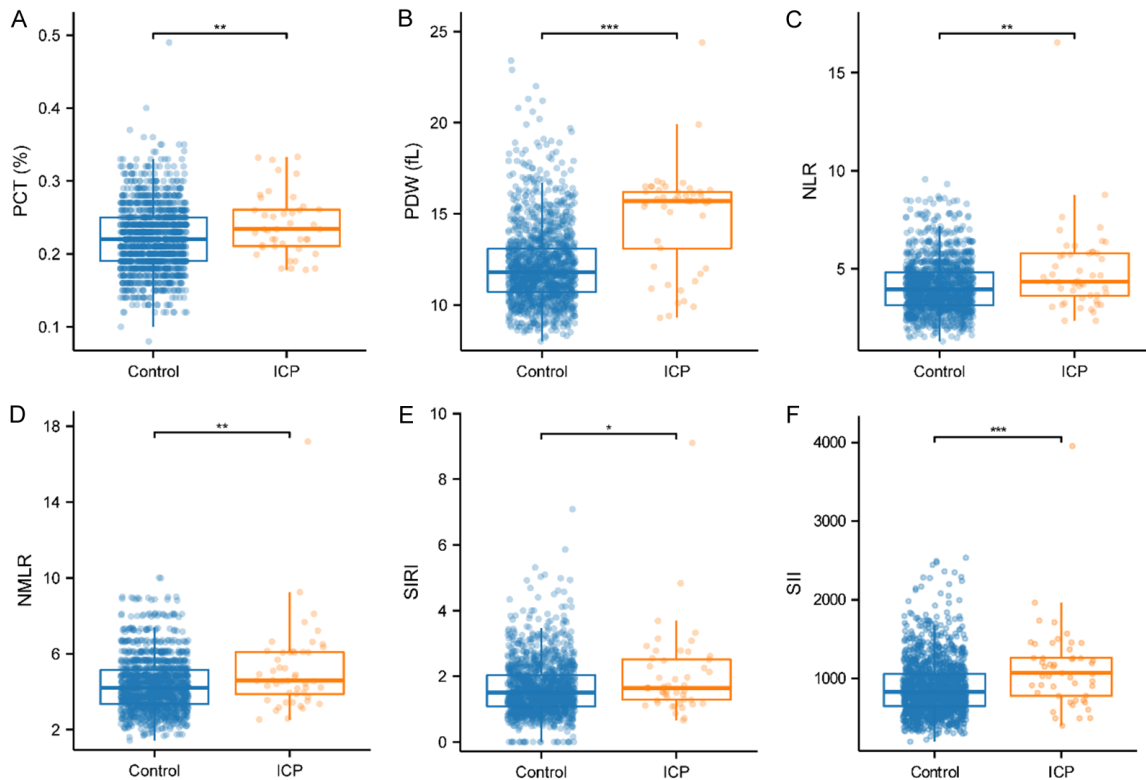
Figure 2. Differences in parameters related to routine blood tests between the ICP group and the control group in early or mid-pregnancy. (A) PCT, (B) PDW, (C) NLR, (D) NMLR, (E) SIRI and (F) SII. ICP, Intrahepatic Cholestasis of Pregnancy; PCT, plateletcrit; PDW, platelet distribution width; NLR, neutrophil to lymphocyte ratio; NMLR, neutrophil-monocyte to lymphocyte Ratio; SIRI, systemic inflammatory response index; SII, systemic immune inflammatory index. *<0.05, **<0.01, ***<0.001.

This research highlights the potential of MCV, PDW and SII as predictive biomarkers for ICP. Since these indicators can be obtained from routine blood tests, they provide a cost-effective, accessible, and rapid approach for assessing ICP risk. This practical method allows healthcare providers to take timely action, ultimately improving outcomes for both pregnant women and their fetuses.

MPV and PDW are critical markers for evaluating platelet characteristics, providing insights into their size, morphology, and functional properties [24, 25]. Variations in platelet size, indicated by changes in MPV and PDW, reflect differences in platelet structure, metabolism, and activity [26]. In this study, elevated levels of MPV and PDW were observed both at the onset and prior to the onset of ICP, suggesting altered platelet functionality. Larger platelets are known to have heightened enzymatic and metabolic activity, producing more serotonin and thromboxane A2 [27]. This increased activity can contribute to pregnancy-related conditions such as preeclampsia. Additionally, activated platelets influence vascular health by affecting vascular permeability, modulating vasoconstriction or vasodilation, and releasing substances that attract macrophages, generate reactive oxygen species (ROS), and reduce the availability of nitric oxide (NO), which impacts vascular elasticity and blood pressure regulation [27]. Furthermore, larger and more active platelets possess more adhesion molecules, and elevated PDW levels may enhance platelet adhesion, increasing the risk of thrombosis in pregnant women with ICP [28]. These findings suggest that MPV and PDW, as indicators of platelet size, morphology, and function, may be associated with the development of ICP complications, such as an elevated risk of thrombosis, and may serve as important markers for monitoring disease progression.

This study reveals that patients with ICP exhibit significantly increased levels of NEUT, NLR,
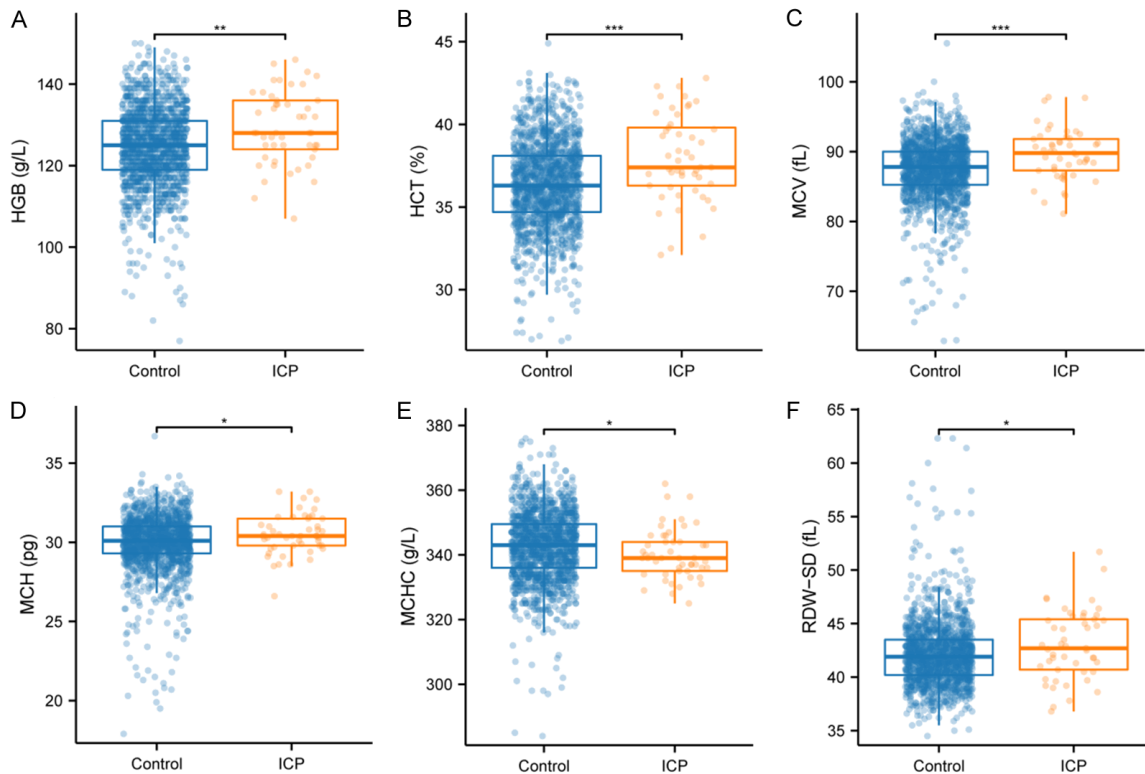
Figure 3. Differences in parameters related to erythrocyte examination between the ICP group and the control group in early or mid-pregnancy. (A) HGB, (B) HCT, (C) MCV, (D) MCH, (E) MCHC and (F) RDW-SD. HGB, hemoglobin; HCT, hematocrit; MCV, mean corpusular volume; MCH, mean corpusular hemoglobin; MCHC, mean corpusular hemoglobin concentration; RDW, red blood cell volume distribution width. *<0.05, **<0.01, ***<0.001.
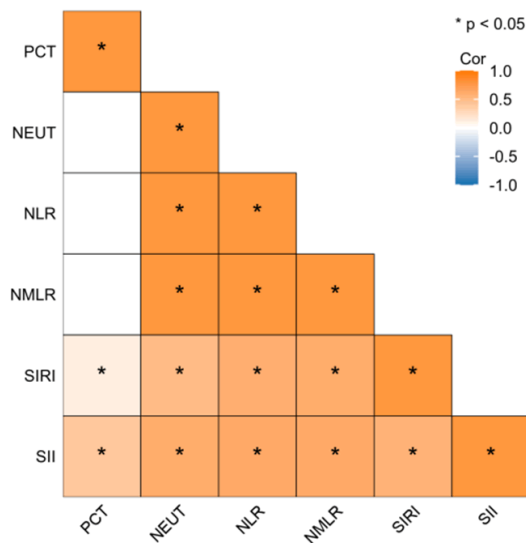

Figure 4. PCT, NEUT, NLR, NMLR, SIRI and SII are strongly correlated. PCT, plateletcrit; NEUT, neutrophil count; NLR, Neutrophil-to-Lymphocyte Ratio; NMLR, Neutrophil-Monocyte-to-Lymphocyte Ratio; SIRI, Systemic Inflammation Response Index; SII, Systemic Immune-Inflammation Index.

NMLR, SIRI and SII both before and during the disease compared to normal pregnant women. NEUT and NLR, consistent with previous findings [29], underscore the importance of inflammation in progression of ICP. Central to ICP progression is inflammation, in which serum bile acids associated with liver injury directly affect hepatocytes, leading to the release of pro-inflammatory mediators and activation of neutrophils [29, 30]. The NMLR, which indicates the ratio of neutrophils and monocytes to lymphocytes, along with the index calculated by multiplying the counts of neutrophils and monocytes and then dividing by the lymphocyte count-serves as a measure of both innate and adaptive immune responses. These indices have proven valuable in predicting outcomes in inflammation-related conditions. Elevated NMLR, in particular, has been linked to poor prognoses in diseases such as acute myocardial infarction and multiple myeloma [8]. In this study, the significantly increased NMLR in ICP patients suggests substantial shifts in leuko-
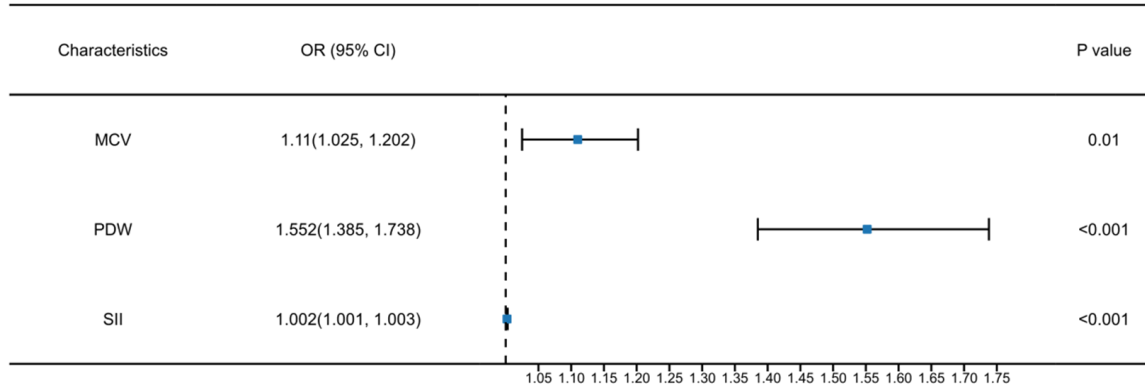
Figure 5. Multiple regression analysis found that MCV, PDW and SII were associated with an increased risk of ICP. ICP, Intrahepatic cholestasis of pregnancy; MPV, ean platelet volume; PDW, platelet distribution width; SII, Systemic Immune-Inflammation Index.

cyte subtypes, specifically neutrophils and monocytes, reflecting inflammatory changes critical for the early detection of ICP. SII, another novel marker that integrates neutrophil, lymphocyte, and platelet counts, provides a comprehensive view of immune and inflammatory status. Elevated SII levels have been correlated with higher mortality in various diseases, including coronary artery disease [31]. This study finds that SII levels increase both before and during the disease in ICP patients. Regression analysis further identifies SII as a significant risk indicator for ICP, suggesting that bile acid accumulation prior to ICP onset could profoundly affect leukocyte subtypes and platelet function. These changes may contribute to the adverse outcomes often observed in ICP, making SII a valuable marker for predicting and monitoring the disease.

This study reveals that in patients with ICP, platelet-related indices and inflammatory markers are significantly elevated. Specifically, PCT, PDW, NEUT, NLR, NMLR, SIRI, and SII were significantly increased prior to and at the onset of ICP. Notably, MCV, PDW and SII emerged as independent risk factors for the occurrence of ICP. These markers may serve as valuable predictive indicators in the future, although further large-scale research is needed to further validate these findings.

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Disclosure of conflict of interest

None.

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