Systemic immune-inflammatory index and platelet-to-lymphocyte ratio in intrahepatic cholestasis of pregnancy

Nihal Çallıoğlu, MD, Güray Tuna, MD, Özden Tandoğan, PhD, Fırat Ersan, MD, Selçuk Atalay, MD, Kübra K. Bilirer, MD.

ABSTRACT

الأهداف: دراسة دور مؤشر الالتهاب المناعي الجهازي (SII) في تشخيص وشدة الركود الصفراوي داخل الكبد أثناء الحمل (ICP).

المنهجية: اشتملت هذه الدراسة على بحث الحالات والشواهد على 173 امرأة حامل مصابة ببرنامج المقارنات الدولية و266 امرأة حامل تتمتع بصحة جيدة مرتبطة بعمر الحمل كمجموعة مراقبة. كانت معايير تشخيص ICP هي قبول زيادة مستويات حمض الصفراء الكلي في المصل (TBA) (أكبر أو يساوي 10 ميكرومول/لتر). كان لدى مجموعة ICP المعتدلة مستويات TBA تتراوح بين 10 و 39 ميكرومول/لتر (العدد=109)، بينما كان لدى مجموعة ICP الشديدة مستوى TBA أدنى من 40 ميكرومول/لتر (العدد=64). وتمت مقارنة البيانات الاجتماعية والديموغرافية، والنتائج المختبرية، وقيم SII بين المجموعات. قمنا بحساب قيم القطع للتنبؤ ببرنامج المقارنات الدولية. تم حساب SII على أنه عدد الصفائح الدموية × عدد العدلات / عدد الخلايا الليمفاوية.

النتائج: كان عدد الكريات البيض والعدلات أقل (p<0.01)، وكان عدد الوحيدات أعلى (p=0.026) في مجموعة ICP مقارنة بالتحكم. كانت نسبة الصفائح الدموية إلى الخلايا الليمفاوية (PLR) أعلى في مجموعات ICP المعتدلة منها في التحكم (p<0.01). كانت قيمة القطع المثلى لـPRL هي 126.2238، مع حساسية ونوعية 57.2% و57.1% على التوالي.

الخلاصة: قيم SII المرتفعة تدعم الدليل على الخصائص الالتهابية لICP ولكنها لا تساعد في تشخيص وتحديد مدى خطورته. قد يكون PLR علامة مفيدة في تحديد ICP.

Objectives: To investigate the role of systemic immune-inflammation index (SII) in the diagnosis and severity of intrahepatic cholestasis of pregnancy (ICP).

Methods: This case-control research involved 173 pregnant women with ICP and 266 gestational age-related healthy pregnant women as the control group. Criteria for diagnosing ICP were acceptance of increased serum total bile acid (TBA) levels (≥10 µmol/L). The mild ICP group (n=109) had TBA levels ranging between 10-39 µmol/l, while the severe ICP group (n=64) had a minimum TBA level above 40 µmol/l. Sociodemographic data, laboratory results, and SII values were compared between groups. Cut-off values were calculated to predict ICP. The SII was calculated as the platelet count × neutrophil count/lymphocyte count.

Results: The leukocyte and neutrophil counts were lower (p<0.01), and the monocyte count was higher (p=0.026) in the severe ICP group compared to the controls. The platelet-to-lymphocyte ratio (PLR) was higher in mild ICP groups than in controls (p<0.01). The optimum PRL cut-off value was 126.2238, with a sensitivity of 57.2% and specificity of 57.1%.

Conclusion: Elevated SII values support the evidence for the inflammatory properties of ICP but do not aid in diagnosing and determining its severity. Platelet-to-lymphocyte ratio may be a useful marker in determining ICP.

Keywords: inflammatory markers, intrahepatic cholestasis of pregnancy, platelet-to-lymphocyte ratio, pregnant, systemic immune-inflammation index

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From the Department of Perinatology (Çallıoğlu, Tuna, Ersan, Bilirer), Başakşehir Çam and Sakura City Hospital, from the Department of Perinatology (Çallıoğlu), Gaziosmanpasa Training and Research Hospital, from the Department of Nursing (Tandoğan), Faculty of Health Sciences, Istanbul Arel University, Istanbul, and from the Department of Perinatology (Atalay), Ordu Training and Research Hospital, Ordu, Turkey.

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Address correspondence and reprint request to: Dr. Nihal Çallıoğlu, Department of Perinatology, Başakşehir Çam and Sakura City Hospital, Istanbul, Turkey. E-mail: niyalcll@gmail.com
ORCID ID: https://orcid.org/0000-0002-4324-692X

Intrahepatic cholestasis of pregnancy (ICP) is a liver disease characterized by widespread pruritus and cholestasis that occurs late in the second half of pregnancy and continues until delivery. According to epidemiological studies, its incidence shows regional differences. It is crucial in that it can lead to serious obstetric complications such as pregnancy-related intrahepatic cholestasis, preterm birth, fetal distress, and sudden intrauterine fetal death.[1] The role of fetal

monitoring carried out to determine fetal well-being in these cases is still controversial because studies are reporting fetal death within 24 hours after normal reactive cardiotocography and within hours after routine antepartum tests. Active interventions to reduce the risk of fetal death will increase the rates of iatrogenic preterm birth and low birth weight babies. In addition, a significant increase in the risk of unexpected respiratory distress syndrome has been detected in cases close to term, even if lung maturation has been achieved.[2] Intrahepatic cholestasis of pregnancy is thought to be caused by a disorder in the hepatic bile acid homeostasis, and the most appropriate diagnostic method is to detect elevated maternal serum bile acids. Additionally, elevated serum bile acids correlate with fetal complications. The techniques used in treatment provide symptomatic improvement and do not affect pathogenesis.[3] Although steroids and antihistamines are an option, the most effective and widely used today of therapy is ursodeoxycholic acid application. However, no factor can affect fetal well-being. Plasmapheresis can be applied in selected cases that start in the early weeks and are resistant to medical treatment.[4]

Although there are new biomarkers that are specific to the disease, most of them involve measuring total bile acid (TBA) levels, which is time-consuming and expensive. However, a retrospective study suggested that more than relying on TBA alone is required as it is neither sensitive nor specific concerning ICP.[5] Therefore, it would be necessary to identify new laboratory markers already existing diseases to facilitate early diagnosis and minimize adverse perinatal outcomes.

Cholestasis result in liver damage and thus increase aspartate aminotransferase (AST), alanine aminotransferase (ALT), total/direct bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) values. Patients may also present with incidental ALP and GGT elevations during routine tests. Alanine aminotransferase and AST may increase 2-3 times, while ALP may increase 10 times normal values. Alkaline phosphatase and GGT elevations are often the first signs of early cholestasis. Alkaline phosphatase is rarely found to be expected in long-term extrahepatic cholestasis. Gamma-glutamyl transpeptidase may also increase 2-4 times.[6] In biliary tract obstruction, GGT and 5'nucleotidase elevations may accompany ALP and bilirubin elevations. On the other hand, cholestasis causes inflammation as hepatocytes generate an inflammatory response due to elevated TBA. However, the increase of inflammatory bio-markers (interleukin-6 (IL-6), IL-8, IL-10, and tumor necrosis factor-α (TNF-α) is far more significant in pregnant women compared to healthy pregnancy cases.[7] Within the scope of this research, we aimed to elucidate the role of the systemic immune-inflammatory index (SII), which is affordable and readily available. We calculated using the neutrophil x platelet/lymphocyte ratio to investigate its role in the diagnosis and severity of ICP.

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Methods. This retrospective case-control study was carried out at the Başakşehir Çam and Sakura Hospital, a tertiary public hospital in Istanbul, Turkey, between June 2020 and August 2022, with 173 pregnant women with ICP and 266 healthy pregnant women without any pathology. Ethical approval was obtained with protocol number 208094421. Since the study was retrospective, no patient consent was required.

Patients in the third trimester (≥28 weeks of gestation) with pruritus and serum TBA levels of ≥10 μmol/L were assigned to the ICP group and classified as mild ICP (TBA between 10-39 μmol/L) and severe ICP (TBA ≥40 μmol/L).[8] The control group consisted of healthy pregnant women whose gestational weeks were matched, who did not show itching and whose TBA level was normal.

To minimize selection bias, we used a systematic sampling approach. Every third eligible patient from the hospital's electronic health records was selected for inclusion, ensuring a representative sample of the hospital's population.

Blood samples were obtained before treatment or intervention during ICP diagnosis in the outpatient clinic. On the other hand, blood samples were taken during routine prenatal outpatient clinic visits in the third trimester from the control group. The groups were matched in terms of age, gestational age, gravity, and parity.

Individuals of <18 years, women with maternal infection, autoimmune and inflammatory diseases, multiple pregnancies, acute/chronic liver and gallbladder diseases, diseases causing high liver enzymes and low platelet count (HELLP and preeclampsia), and comorbidities were excluded.

Patient data and patient files were acquired from the hospital's information system. The data was captured to ensure reliability and validity, and was validated. All blood analyses were carried out in the same laboratory. Sociodemographic data, biochemical tests, and complete blood count (CBC) parameters were

also recorded. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) values, and SII were calculated using neutrophil, platelet, monocyte, and lymphocyte values. A photometric technique was applied to review serum bile acids using a Siemens ADVIA 1800 Chemistry Analyzer. In this study, transparent jelly tubes (serum) were used. Tubes with K3-EDTA (Tripotassium ethylenediaminetetraacetic acid) were used for CBC analysis. Flow cytometry measured the CBC parameters using an automated hematology analysis instrument (XN1000, Sysmex, Roche Corp., Japan).

Statistical analysis. Data were analyzed using the Statistical Package for the Social Sciences, version 26.0 (IBM Corp., Armonk, NY, USA). Power analysis was carried out before the data collection. Descriptive tests, including number (n), percentage (%), means, standard deviation (SD), and minimum and maximum variables, were used in the data analysis. The normality of the data was explored using the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) was used to compare the means of 3 independent groups in parametric distributions, and Kruskal-Wallis analysis was used for nonparametric distributions. Dunnett's T3 test was applied to explore the source of significant differences in variables in univariate analyses. In this study, receiver operating characteristic (ROC) curves, the area under the curve (AUC) of the ROC, sensitivity, and specificity were calculated to determine levels of inflammatory markers that best differentiate ICP versus the control group. The optimal cut-off values for the inflammatory markers were the cut-off values that gives the best sensitivity/specificity balance in ROC curves. The ROC analysis was carried out for SII, PLR, NLR, and MLR values. Sensitivity (%), specificity (%), and likelihood [LR+ = sensitivity/ (1-specificity)] values under the ROC curve were investigated for ICP. A *p*-value of <0.05 was considered significant at a 95% confidence interval.

The sample size was estimated via G*Power 3.1 software. In line with prior studies, the moderate effect size (d=0.5) for the difference in levels of inflammation markers between the ICP and control groups was calculated to be a minimum of 128 participants per group (alpha =0.05 and power =0.80).[8,9]

Results. This research enrolled 439 pregnant women with a mean age of 28.54±5.36 years. There was no difference between the ICP and control groups in terms of maternal age, gestational age, body mass index, gravida, and parity (p>0.05). All participants had a live birth at ≥37 weeks, and no intrauterine fetal death, maternal death, or antenatal severe complications were detected. No statistically significant differences were achieved between the groups regarding platelets, hemoglobin, hematocrit, neutrophils, lymphocytes, and monocytes (p>0.05). Nonetheless, the differences in WBC, neutrophils, monocytes, AST, ALT, and TBA levels were statistically significant (p>0.05, **Table 1**).

In post hoc analysis, WBC and neutrophil levels were significantly lower (p<0.01), while monocyte levels were significantly higher (p=0.026) in the severe ICP group. The AST and ALT values were similar between the mild and severe ICP groups (p>0.05); however, they were significantly higher in both the mild and severe ICP groups (p<0.01 for both comparisons). No statistically significant differences were achieved between the groups regarding the SII, NLR, and MLR (p>0.05). In post hoc analysis, PLR was significantly higher in the mild ICP group than in the control group (p=0.02, **Table 2**).

The Youden index was utilized to detect the sensitivity and specificity for diagnosing ICP via the ROC curve (**Table 3**). The best result was achieved with PLR, which had an optimal sensitivity/specificity balance at a cut-off of 126.2238 (sensitivity of 57.2%, specificity of 57.1%; AUC=0.587±0.029; 95% CI: [0.531-0.644], **Figure 1**).

Discussion. Previous studies elaborated that the oxidative response in neutrophils in patients with intrahepatic cholestasis was increased, and stimulatory cytokines such as IL-6, IL-8, and TNF-α increased in circulation. Increased cytokine levels have been shown to cause liver dysfunction. It has been shown that the level of endotoxin in circulation was increased in these patients and that the release of IL-6 and TNF-α cytokines from monocytes in peripheral blood is increased accordingly.[10,11] Chen et al[12] reported that the levels of proinflammatory cytokines IL-1, IL-6, and TNF-α significantly increased. These chemical mediators affect hepatic metabolism, stimulate hepatic regeneration, lead to scar formation, and, most importantly, cause monocyte accumulation and proliferation. Although these monocytes clear endotoxins and microbial agents from the portal circulation, they cause progressive damage as they stimulate hepatic macrophages.[13] Since detecting these inflammatory markers is only possible in advanced laboratory settings, we aimed to retrospectively examine the groups using routinely measured but newly defined inflammatory markers in this case-control study. In our research, some serum inflammatory markers were found to be associated with ICP; however, these markers were not definitive in measuring the severity of the disease.

Table 1 - Intergroup comparisons in terms of socio-demographic, obstetric characteristics, and laboratory values.

Variables	Control group (n=266)	Group with mild cholestasis (n=109)	Group with severe cholestasis (n=64)	*P*-values†
Age (year)	28.6±5.0	28.2±5.4	29.0±6.5	0.668
Gestational week***	33.0±3.5	32.6±3.4	33.1±2.9	0.350
Gravida (number)	2.4±1.4	2.2±1.4	2.3±1.5	0.321
Parity (number)	1.0±1.0	0.8±1.0	0.9±1.1	0.288
Height (cm)	162.4±4.4	162.5±3.9	162.3±4.5	0.725
Weight (kg)	74.7±8.4	75.8±8.6	74.6±9.0	0.342
BMI (kg/m^2)	28.3±2.8	28.7±2.8	28.3±2.9	0.246
WBC (/mm×10)	10.15±2.52[a]	9.51±2.86	9.35±3.56[b]	0.002**
PLT (/mm×10)	236.74±61.56	246.18±79.55	249.97±82.92	0.637
Hb (g/dL)	11.41±1.29	11.26±1.47	11.47±1.20	0.568
Hct (g/dL)	34.22±3.36	34.26±3.86	34.04±5.11	0.927††
Neutrophil (×10/uL)	7.41±2.27[a]	7.13±3.51	6.95±3.26[b]	0.009**
Neutrophil (%)	71.69±7.85	70.96±8.45	70.19±11.45	0.272
Lymphocyte (×10/uL)	1.98±0.57	1.88±0.64	2.02±1.53	0.150
Lymphocyte (%)	20.04±6.00	20.96±8.08	21.58±9.32	0.444
Monocytes (×10/uL)	0.69±0.21b	1.06±3.48	1.36±5.93[a]	0.032*
Monocytes (%)	6.79±1.48	6.92±2.31	6.72±2.74	0.609
AST (U/L)	17.24±27.17[c]	86.57±116.17[d]	122.11±205.37[e]	<0.01
ALT (U/L)	16.18±58.62[c]	125.30±171.60[d]	180.03±281.10[e]	<0.01
TBA	5.23±2.14[f]	21.11±8.21[g]	65.95±26.93[h]	<0.01

Values are presented as mean ± standard deviation (SD). †Kruskal-Wallis test. ††One-way analysis of variance. ***Gestational week at the time of initial itching for ICP patients and corresponding time for matched controls. *p<0.05, **p<0.01. Dunnett's T3 test: a>b, d>c, e>c, g>f, h>f, h>g. BMI: body mass index, WBC: white blood cell count, Hb: hemoglobin, Hct: hematocrit, PLT: platelet count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TBA: total bile acid

Table 2 - Comparison of intergroup laboratory ratio values.

Variables	Control group (n=266)	Group with mild cholestasis (n=109)	Group with severe cholestasis (n=64)	*P*-values†
SII (109/L)	963.66±541.31	1041.46±790.77	1081.14±1044.98	0.823
PLR	127.51±48.08[a]	144.16±61.99[b]	146.65±73.83	<0.01
NLR	4.08±1.98	4.15±2.25	4.12±2.77	0.593
MLR	0.37±0.16	0.63±2.08	1.24±7.19	0.221

Values are presented as mean ± standard deviation (SD). †Kruskal-Wallis test. **p<0.01. Dunnett's T3 test: b>a. SII: systemic immune-inflammation index, PLR: platelet lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocytes-to-lymphocyte ratio

Notably, in our research, there was a significant decrease in WBC and neutrophil levels but an increase in monocyte levels for the severe ICP group compared to the control group. This outcome was contrary to the study of Abide et al,[9] which had previously reported that WBC values were increased for ICP patients. Conversely, Silva et al[14] indicated a decline in WBC and neutrophil counts among ICP patients, consistent with our results.

High TBA, AST, and ALT levels were the most common laboratory abnormalities in ICP.[15] In line with previous research, this study found that AST and ALT were significantly higher in the ICP group than in the control group. However, there is no diagnostic threshold for liver enzyme levels.[8]

The SII is a systemic inflammatory marker suggested by platelet, neutrophil, and lymphocyte count.[16] The SII has been associated with malignant tumors, premature membrane rupture, and miscarriage.[17-19] We observed that SII values were increased in patients with ICP compared to healthy controls but failed to show any statistical association between them, which implies that while SII may serve as a potential index for the diagnosis of ICP, its clinical value needs further verification.

Previous literature has conflicting results regarding NLR values in ICP. The present study also showed an

Table 3 - Receiver operating characteristic analysis results of systemic immune-inflammation index, platelet lymphocyte ratio, neutrophil-to-lymphocyte ratio, and monocytes-to-lymphocyte ratio values.

Variables	AUC (95% CI)	SE	Cut-off values	*P*-values	Sensitivity (%)	Specificity (%)	LR+
SII	0.517 (0.461-0.574)	0.029	833.8611	0.538	52.6	53.8	1.14
PLR	0.587 (0.531-0.644)	0.029	126.2238	<0.01	57.2	57.1	1.34
NLR	0.527 (0.470-0.584)	0.029	3.6874	0.343	53.8	50.0	1.08
MLR	0.522 (0.466-0.578)	0.029	0.3419	0.436	55.5	50.8	1.13

AUC: area under the curve, CI: confidence interval, SE: standard error, LR: likelihood ratio, SII: systemic immune-inflammation index, PLR: platelet lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocytes-to-lymphocyte ratio

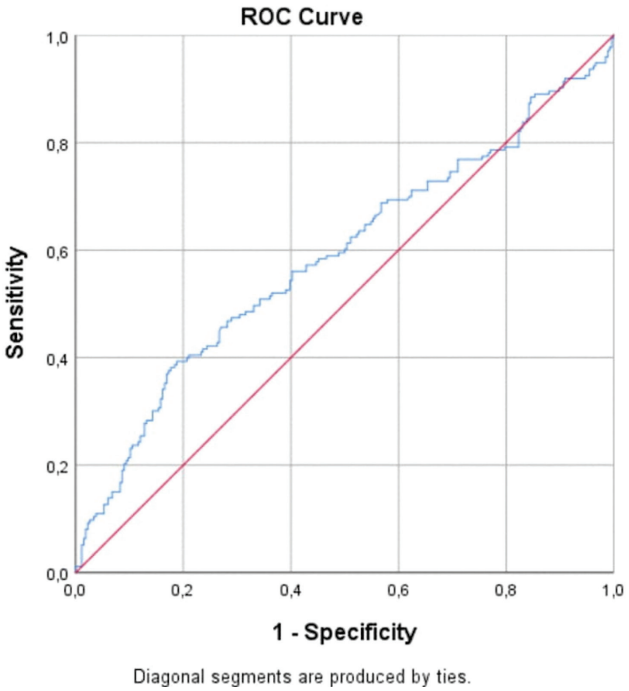

Figure 1 - Receiver operating characteristic analysis (the effect of platelet lymphocyte ratio value in predicting intrahepatic cholestasis of pregnancy). ROC: receiver operating characteristic

increase in NLR values of both mild and severe ICP groups compared to the control group, but this was not statistically significant. Some previous studies have suggested that NLR is a marker for ICP, and this trend supports these earlier findings, even if not definitively so.[15,20]

Abide et al[9] found that significantly higher PLR values were observed in ICP patients than in non-cholestatic pregnant women in the third trimester of pregnancy.[15] Our study, consistent with other studies, found a statistically significant increase in PRL value in the mild ICP group compared to the control group. These findings show that PLR has predictive value in the diagnosis of ICP. Uysal et al[21] noted that the MLR values were significantly lower in the ICP group than in healthy pregnant women, and there were moderately significant negative correlations between TBA and MLR. In contrast, although MLR values were higher in the mild and severe ICP groups than in the control group in our research, the difference was not statistically significant.

Study strengths & limitations. The main limitation of this research could be attributed to its retrospective nature, with a single-center experience. Additionally, SII might be affected by autoimmune diseases and metabolic conditions independent of the ICP. On the other hand, this study has several significant strengths. The exclusion of individuals with comorbidities eliminated the risk of potentially biased outcomes. The relatively large sample size and inclusion of a wide range of hematological inflammatory parameters were the main assets of this article.

In conclusion, this research has indicated that the SII and other markers of inflammation could be related to ICP. Still, they are insufficient for making a definite diagnosis or differentiating among various degrees of severity of ICP. Even though our results imply that PLR can be a useful marker in predicting ICP development, more significant patient cohorts, including people from various races and obstetric groups, must be investigated to validate these findings. Subsequent research will help us understand the clinical importance of these inflammatory markers in diagnosing and treating ICP.

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References

1. Hague WB, Williamson C, Beuers U. Intrahepatic cholestasis of pregnancy: introduction and overview 2024. *Obstet Med* 2024; 17: 138-143.
2. Roediger R, Fleckenstein J. Intrahepatic cholestasis of pregnancy. *Clin Liver Dis (Hoboken)* 2024; 23: e0119.
3. Obiegbusi CN, Dong XJ, Obiegbusi SC, Jin X, Okoene IK. Predictors of adverse fetal outcomes in intrahepatic cholestasis of pregnancy (ICP): a narrative review. *Reprod Sci* 2024; 31: 341-351.

4. Tang M, Xiong L, Cai J, Fu J, Liu H, Ye Y, et al. Intrahepatic cholestasis of pregnancy: insights into pathogenesis and advances in omics studies. ***Hepatol Int*** 2024; 18: 50-62.
5. Kondrackiene J, Kupcinskas L. Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems. ***World J Gastroenterol*** 2008; 14: 5781-5788.
6. Obut M, Kından A, Ibanoğlu MC, Çayönü Kahraman N, Arat Ö, Keleş A, et al. Liver damage parameters and peripheral blood parameters for prediction and diagnosis of intrahepatic cholestasis in pregnancy. ***J Obstet Gynaecol Res*** 2024; 50: 196-204.
7. Luo X, Li SX, Hai L, Liu SW, Ding XC, Liu XY, et al. [Exploring potential serum metabolite markers of intrahepatic cholestasis based on liquid chromatography-mass spectrometry metabolomics technology]. ***Zhonghua Gan Zang Bing Za Zhi*** 2024; 32: 753-760. [In Chinese].
8. Mays JK. The active management of intrahepatic cholestasis of pregnancy. ***Curr Opin Obstet Gynecol*** 2010; 22: 100-103.
9. Yayla Abide Ç, Vural F, Kılıççı Ç, Bostancı Ergen E, Yenidede İ, Eser A, et al. Can we predict severity of intrahepatic cholestasis of pregnancy using inflammatory markers? T***urk J Obstet Gynecol*** 2017; 14: 160-165.
10. Zeng W, Hou Y, Gu W, Chen Z. Proteomic biomarkers of intrahepatic cholestasis of pregnancy. ***Reprod Sci*** 2024; 31: 1573-1585.
11. Liu W, Chen L, Miao K, You Y, Li J, Lu J, et al. Identification and validation of diagnostic biomarkers for intrahepatic cholestasis of pregnancy based on untargeted and targeted metabolomics analyses of urine metabolite profiles. ***BMC Pregnancy Childbirth*** 2023; 23: 828.
12. Chen J, Zhang S. The role of inflammation in cholestatic liver injury. ***J Inflamm Res*** 2023; 16: 4527-4540.
13. İpek G, Tanaçan A, Peker A, Ağaoğlu Z, Kara Ö, Şahin D. Systemic inflammation response index as a diagnostic and prognostic predictor of intrahepatic cholestasis of pregnancy: a case-control study from a tertiary center. ***Int J Gynaecol Obstet*** 2024; 165: 717-722.
14. Silva J, Magenta M, Sisti G, Serventi L, Gaither K. Association between complete blood count components and intrahepatic cholestasis of pregnancy. ***Cureus*** 2020; 12: e12381.
15. Ozgen L, Ozgen G, Karasin SS, Bayram F. Fibrinogen levels and total serum bile acids in intrahepatic cholestasis of pregnancy. ***J Coll Physicians Surg Pak*** 2022; 32: 1404-1409.
16. Lagunas-Alvarado M, Mijangos-Huesca FJ, Terán-González JO, Lagunas-Alvarado MG, Martínez-Zavala N, Reyes-Franco I, et al. [Systemic immune inflammatory index in sepsis]. ***Medicina Interna de México*** 2017; 33: 303-309. [In Spanish].
17. Ji P, He J. Prognostic value of pretreatment systemic immune-inflammation index in patients with endometrial cancer: a meta-analysis. ***Biomark Med*** 2024; 18: 345-356.
18. Tanacan A, Uyanik E, Unal C, Beksac MS. A cut-off value for systemic immune-inflammation index in the prediction of adverse neonatal outcomes in preterm premature rupture of the membranes. ***J Obstet Gynaecol Res*** 2020; 46: 1333-1341.
19. Turgut E, Yildirim M, Sakcak B, Ayhan SG, Tekin OM, Sahin D. Predicting miscarriage using systemic immune-inflammation index. ***J Obstet Gynaecol Res*** 2022; 48: 587-592.
20. Kirbas A, Biberoglu E, Daglar K, İskender C, Erkaya S, Dede H, et al. Neutrophil-to-lymphocyte ratio as a diagnostic marker of intrahepatic cholestasis of pregnancy. ***Eur J Obstet Gynecol Reprod Biol*** 2014; 180: 12-15.
21. Uysal NŞ, Karakaş LA, Gülümser Ç, Esin S, Yanık F. Are complete blood count indices different in twins with the diagnosis of intrahepatic cholestasis of pregnancy? ***J Clin Obstet Gynecol*** 2020; 30: 85-91.