DOI: 10.4274/gulhane.galenos.2025.47855
Gulhane Med J 2026;68(2):102-108

The predictive role of hemoglobin-albumin-lymphocyte-platelet (HALP) score and serum inflammatory markers in intrahepatic cholestasis of pregnancy

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Cite this article as: Öztürk Ö, Yılmaz Ergani S, Ağaoğlu RT, Günday F, Tezcan AY, Yakut Yücel K, et al. The predictive role of hemoglobin-albumin-lymphocyte-platelet (HALP) score and serum inflammatory markers in intrahepatic cholestasis of pregnancy. *Gulhane Med J.* 2026;68(2):102-108.

Date submitted:
13.06.2025
Date accepted:
25.12.2025
Epub:
11.06.2026
Publication Date:
16.06.2026

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Keywords: HALP, SIRI, AISI, intrahepatic cholestasis of pregnancy

ABSTRACT

Aims: To date, no studies have examined the relationship between the hemoglobin-albumin-lymphocyte-platelet (HALP) score and the systemic inflammatory response index (SIRI) in pregnancy. The aim of this study was to compare HALP, SIRI, and other systemic inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and aggregate index of systemic inflammation (AISI), between pregnant women with intrahepatic cholestasis of pregnancy (ICP) and healthy pregnant controls.

Methods: This retrospective cross-sectional study included pregnant women diagnosed with ICP and healthy controls matched for age and pregnancy. Participants were screened using complete blood count data collected at diagnosis. The primary endpoint was a comparison of systemic inflammatory markers, including NLR, MLR, PLR, SII, SIRI, AISI, and HALP score.

Results: A total of 143 pregnant women with a mean age of 29.3 years were included. Of these, 73 were in the ICP group and 70 were in the control group. PLR, SII, and HALP scores were significantly higher in the ICP group than in the control group (p=0.026, p=0.019, and p=0.016, respectively), while NLR, MLR, SIRI, and AISI showed no significant differences between the groups. Weak positive correlations were found between the presence of ICP and each of PLR (r=0.187, p=0.025), SII (r=0.197, p=0.019), and HALP (r=0.201, p=0.016). Receiver operating characteristic analysis showed that HALP [area under the curve (AUC)=0.616, sensitivity 97%, p=0.016], SII (AUC=0.614, specificity 94%, p=0.019), and PLR (AUC=0.608, specificity 89%, p=0.026) had significant predictive value.

Conclusions: HALP and selected systemic inflammatory indices can serve as helpful biomarkers for the diagnosis of ICP.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific condition. It is characterized by impaired bile flow, resulting in elevated maternal bile acid (BA) levels. The underlying causes of ICP are believed to include hormonal changes during gestation, genetic and environmental factors affecting bile transport, and inflammatory mechanisms (1). The literature reports a role for inflammation in the pathogenesis of the disease (2). This condition mainly manifests in the third trimester of pregnancy and is concomitantly associated with severe fetal complications. These include premature labor, fetal distress, and an increased number of stillbirths (3-5). The disease has been observed to resolve spontaneously after delivery; however, it has also been reported to reappear in a more severe form in 45-90% of subsequent pregnancies (6,7). Cholestatic liver injury, whether caused by endogenous or exogenous factors, may present with elevated cholestatic enzymes such as alkaline phosphatase and gamma-glutamyl transferase, and is frequently accompanied by pruritus and hyperbilirubinemia (8).

In recent years, the hemoglobin-albumin-lymphocyte-platelet (HALP) score has demonstrated potential as a predictive biomarker. This score, which involves the analysis of hemoglobin, albumin, lymphocytes, and platelets, has demonstrated its potential to assess systemic inflammation and nutritional status. It is currently being investigated for its ability to predict a range of clinical outcomes associated with various neoplastic diseases (9-12).

Although numerous studies have investigated the association between HALP scores and various types of cancer, the HALP score during pregnancy remains poorly studied. A study was conducted to investigate the sensitivity of the HALP level in predicting preterm delivery. The study included a comparison of the HALP score with other serum markers for the prediction of preterm labor (13). Soykan Sert and Bertizlioğlu (14) found higher HALP scores in patients with severe preeclampsia. Low HALP scores were shown to be associated with hyperemesis gravidarum severity by Bayram et al. (15). However, there are no data on the HALP score and on ICP disease in pregnancy. In addition to pregnancy-related causes such as ICP, drug-induced liver injury must be considered in the differential diagnosis of cholestatic elevations of liver enzymes during gestation. Başgöz et al. (8) reported two cases of cholestatic hepatitis triggered by meropenem, emphasizing the importance of recognizing medication-induced liver injury that may mimic ICP symptoms.

The hematological system plays a pivotal role in preserving the structural integrity and physiological function of the placenta. This system serves as a conduit between the foetus, the placenta, and the maternal circulation. A number of changes associated with post-term pregnancies have been shown to diminish nutrient and oxygen transport to the foetus. Markers such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are strong indicators of an acute inflammatory state. They are commonly used as diagnostic and prognostic markers for cardiovascular events, including myocardial infarction. Recent evidence supports the use of these haematological indices as valuable biomarkers in obstetrics and gynaecology. It has been demonstrated by means of research that as gestation progresses, there is an increase in neutrophil levels and a decrease in lymphocyte levels, which results in an elevated NLR (16). The main objective of the current study was to evaluate the HALP score together with other inflammatory markers obtained from the blood count, such as the systemic inflammatory response index (SIRI), aggregate index of systemic inflammation (AISI), and systemic immune-inflammation index (SII). The aim of this study was to assess the ability of these markers to predict disease severity in pregnant women with ICP.

Methods

Study design, setting, duration, participants, and ethical approval

This cross-sectional study was conducted from October 2022 to February 2024 in the Perinatology Clinic of University of Health Sciences Türkiye, Ankara Etlik City Hospital, a tertiary referral center affiliated with the Turkish Ministry of Health in Ankara. A total of 143 pregnant women were included. Seventy-three women were diagnosed with ICP, and 70 were healthy pregnant women of the same age group and gestational age. Ethical approval was granted by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (approval no: AEŞH-BADEK-2024-069, date: 31.01.2024). All participants provided written informed consent. The study was conducted in accordance with the standards of the Declaration of Helsinki.

Inclusion and exclusion criteria

Pregnant women with ICP, as determined by clinical and laboratory findings, were included. The diagnosis was based on the presence of pruritus (especially on the palms and soles), elevated total BA levels (>10 μmol/L) and/or increased liver transaminases [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)>40 U/L], in the absence of dermatological or other pathological conditions that could explain these symptoms (17,18).

Clinical and laboratory assessments

The clinical parameters collected included maternal age, gravidity, parity, body mass index (BMI) (BMI, kg/m^2), and gestational age at diagnosis. Haematological and biochemical

parameters obtained from maternal peripheral venous blood samples included haemoglobin (g/dL), leukocytes (white blood cell), neutrophils, lymphocytes, monocytes, platelets (10^3/μL), AST, ALT, fasting BAs (μmol/L), and albumin (g/L).

All laboratory data were retrieved from the hospital's electronic medical records system. Based on BA values, patients with ICP were categorised into two groups: mild (10-40 μmol/L) and severe (≥40 μmol/L) (18).

Outcome measures

The primary aim of our study was to compare systemic inflammatory indices between pregnant women with ICP and a healthy control group. The secondary outcome was to determine the diagnostic efficacy of these indices in distinguishing between mild and severe ICP.

Inflammatory index calculations

The systemic inflammatory indices were calculated as follows: (9,19,20)

HALP score=(hemoglobin×albumin×lymphocyte)/platelet

AISI=(neutrophil×monocyte×platelet)/lymphocyte

NLR=neutrophil/lymphocyte

PLR=platelet/lymphocyte

SIRI=(neutrophil×monocyte)/lymphocyte

MLR=monocyte/lymphocyte

SII=(neutrophil×platelet)/lymphocyte

Statistical Analysis

Statistical analyses were conducted using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was utilized to evaluate the distribution of continuous variables. The data concerning variables distributed normally were characterized in accordance with the mean ± standard deviation, after which a comparison was made between said variables using an Independent Samples t-test. Non-normal variables were expressed as medians and interquartile ranges and subsequently evaluated using the Mann-Whitney U test.

Spearman's rank correlation coefficient was used to analyze the correlations between the variables. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) and optimal cut-off values were reported. A p-value of less than 0.05 was considered significant

Results

Study population and demographics

A total of 143 pregnant women were included in the study: 73 diagnosed with ICP and 70 healthy pregnant women who served as controls. The median age of the mothers was 28 years [interquartile range (IQR): 25-32] in the ICP group and 26 years (IQR: 23-31) in the control group. No subjects were excluded after enrollment due to data inaccessibility or eligibility issues. Among the patients with ICP, 87.7% (n=64) had mild disease (defined as serum BA levels between 10 and 40 μmol/L), while 12.3% (n=9) had severe ICP (BA levels ≥40 μmol/L).

Basic clinical and laboratory characteristics

The demographic and laboratory data of the study groups are presented in Table 1. The results indicate that there were no statistically significant differences between the two groups regarding maternal age, gravidity, or BMI (p>0.05 for all). However, parity was significantly lower in the ICP group than in the control group (p=0.024).

Regarding the laboratory parameters, the present study found that the liver enzymes, ALT and AST, were significantly elevated in the ICP group (p<0.001 for both). The investigation showed that the concentrations of haemoglobin, neutrophils, monocytes, lymphocytes, platelets, and serum albumin did not differ significantly between groups (p>0.05).

Regarding the calculated inflammatory indices, SII and the PLR were significantly higher in the ICP group than in the control group (p=0.026 and p=0.019, respectively). No significant differences were observed between the groups for the NLR, AISI, SIRI, or MLR. However, the HALP score was significantly higher in the ICP group compared to the controls [26.60 (18.96-36.30) vs. 23.94 (3.21-36.68); p=0.016].

Primary and secondary outcomes

The correlations between the inflammatory indices and the presence of ICP are summarized in Table 2. The correlation analysis showed slight but statistically significant positive correlations of ICP with PLR (r=0.187, p=0.025), SII (r=0.197, p=0.019), and HALP score (r=0.201, p=0.016). No statistically significant correlations were observed between fasting BA levels and biomarkers of inflammation, including SIRI, SII, AISI, NLR, PLR, MLR, and HALP score (p>0.05).

The effectiveness of these measures in identifying ICP was evaluated using ROC analysis. The results are presented in Figure 1 and Table 3. Figure 1 illustrates the ROC analysis. The HALP score demonstrated the highest sensitivity (97%) at a cut-off value of ≥7.565, with an AUC of 0.616 [95% confidence interval (CI): 0.522-0.711; p=0.016]. The SII had a cut-off value of ≥1432.674, resulting in a sensitivity of 30% and a specificity of 94% (AUC=0.614, 95% CI: 0.521-0.706; p=0.019). The PLR had a cut-off of ≥174.820, with a sensitivity of 34% and a specificity of 89% (AUC=0.608, 95% CI: 0.515-0.701; p=0.026).

Table 1. Descriptive and comparative analysis of demographic and laboratory data between ICP and control groups

Variables	ICP (n=73)	Control (n=70)	p-value
Age (year)	28 (25-32)	26 (23-31)	0.407[a]
Gravidity (n)	2 (1-2)	2 (1-3)	0.208[a]
Parity (n)	0 (0-1)	1 (0-2)	**0.024[a]**
BMI (kg/m²)	27.86±2.95	25.03±3.67	0.230[b]
GA at time of blood sampling (weeks)	34 (31-36)	35 (32-36)	0.149[a]
Hb (g/dL)	11.7±1.5	11.6±1.3	0.458[b]
Thrombocyte (10^3/μL)	265.1±65.3	252.7±66.0	0.259[b]
Neutrophile (10^3/μL)	7.31 (6.06-8.76)	6.98 (6.12-8.40)	0.516[a]
Monocyte (10^3/μL)	0.66±0.33	0.7±0.25	0.433[b]
Lymphocyte (10^3/μL)	1.82±0.71	1.96±0.51	0.174[b]
Albumin (g/L)	35.0 (32.7-36.3)	33.0 (31.0-36.0)	0.088[a]
ALT (U/L)	78 (39-190)	15 (12-20)	**<0.001[a]**
AST (U/L)	54 (28-134)	13 (9-17)	**<0.001[a]**
FBA (μmol/L)	27.7±23.4	-	-
Mild ICP (FBA=10-40)	64 (87.7%)	-	-
Severe ICP (FBA>40)	9 (12.3%)	-	-
PLR	141.82 (117.39-190.05)	128.97 (107.65-151.15)	**0.026[a]**
NLR	3.92 (3.24-5.49)	3.80 (3.130-4.405)	0.101[a]
MLR	0.33 (0.25-0.450)	0.35 (0.28-0.43)	0.605[a]
SII (10^9/L)	1007.75 (762.50-1535.76)	857.40 (717.50-1099.58)	**0.019[a]**
SIRI	2.379 (1.54-3.88)	2.58 (1.88-3.32)	0.818[a]
AISI	635.55 (394.25-955.03)	592.50 (423.44-901.66)	0.784[a]
HALP score	26.60 (18.96-36.30)	23.94 (3.21-36.68)	0.016[a]

[a]: The Mann-Whitney U test was used, with results presented as median and quartiles (25^{th}-75^{th} percentiles), [b]: The Student's t-test for independent samples was used to compare the measured values between two independent groups, with the results expressed as mean ± standard deviation
ICP: Intrahepatic cholestasis of pregnancy, BMI: Body mass index, GA: Gestational age, Hb: Hemoglobin, ALT: Alanine aminotransferase, AST: Aspartate amino transferase, FBA: Fasting bile acid, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation, HALP: Hemoglobin-albumin-lymphocyte-platelet

Discussion

This study investigated the association of the HALP score, a novel immune-nutritional biomarker, with ICP and with various systemic inflammatory indices derived from complete blood counts. The main finding was that pregnant women with ICP had significantly higher HALP, SII, and PLR levels than healthy pregnant controls. This is the first study to evaluate the diagnostic potential of the HALP score in the context of ICP.

In this study, inclusion and exclusion criteria were strictly defined to avoid bias, and blood samples were uniformly collected at the time of diagnosis. Although the sample size was modest, it was sufficient to detect statistically significant differences in certain inflammatory indices, which indicates adequate representativeness and internal validity.

The primary endpoint of this study was to determine whether HALP, SII, and PLR values differed significantly between pregnant women with ICP and healthy controls. The present study found that these indices were significantly elevated in the ICP group, supporting the hypothesis that ICP is associated with systemic inflammation. The secondary endpoint included comparison of other inflammatory indices (NLR, MLR, SIRI, AISI), none of which differed significantly. Previous studies have also reported associations between elevated SIRI and ICP (21), and have highlighted PLR as a meaningful marker in ICP diagnosis (22). Moreover, studies by Huang et al. (23) and Gul and Callioglu (24) provided evidence of inflammatory changes in similar cohorts. In this study, Huang et al. (23) demonstrated that increased levels of the pro-inflammatory mediator interleukin-8 (IL-8) and decreased levels of the anti-inflammatory cytokines IL-4, IL-6, and tumor necrosis factor-α (TNF-α) occurred together, thus supporting the notion that ICP is associated with inflammatory processes. The researchers concluded that TNF-α, while providing significant diagnostic value on its own, achieves optimal diagnostic accuracy when used together with IL-4 and IL-8.

In light of previous research, this study makes several contributions. First, the assessment of HALP and AISI scores in the context of ICP is novel, as no previous studies have addressed this relationship (25,26). Second, our finding of elevated PLR is consistent with previous results by Çallıoğlu et al. (22) and Irak et al. (27), confirming its association with ICP. Third, our results contrast with those of Wang et al. (28), who reported significantly increased NLR values in ICP patients. The absence of NLR elevation in our study may be attributed to differences in population characteristics, sample size, or timing of sampling. Furthermore, MLR was investigated in studies such as Shen (29), but produced varying conclusions. As demonstrated by Shen (29), there was a considerable increase in platelet parameters and inflammatory indices in pregnant women with ICP. It was reported that the MLR increased; although there was an upward trend in the early period, its predictive value was not as strong as that of the NLR and SII. However, when the MLR is evaluated alongside these indices, it supports the immunological mechanisms of ICP as a complementary marker reflecting the systemic inflammatory response (30).

The HALP score has previously demonstrated predictive value in oncological and obstetric conditions, such as preeclampsia and hyperemesis gravidarum (9,14,15). In these contexts, both increased and decreased HALP levels were associated with disease severity, depending on the inflammatory profile of the disease. In the present study, the higher HALP scores observed in ICP cases may reflect an inflammatory phenotype distinct from that of chronic inflammatory diseases, indicating disease-specific immune responses. The diagnostic utility of the HALP score was further emphasized by the ROC analysis, which showed higher sensitivity compared to other indices. In addition, previous studies have suggested an association between ICP and gestational diabetes mellitus overlap syndromes, which may provide a rationale for future investigations evaluating composite inflammatory biomarkers such as HALP (31).

Recent evidence suggests an association between systemic inflammatory indices and hepatic and immune dysregulation

Table 2. Correlation analysis of inflammatory markers with ICP and fasting bile acid levels

Variables	r	p-value
ICP		
PLR	0.187	**0.025**[a]
SII	0.197	**0.019**[a]
HALP	0.201	**0.016**[a]
FBA levels		
NLR	-0.064	0.591[b]
MLR	0.078	0.512[b]
PLR	-0.024	0.841[b]
SII	-0.085	0.476[b]
SIRI	-0.010	0.935[b]
AISI	0.011	0.928[b]
HALP	-0.096	0.419[b]

[a]: Spearman's rank correlation analysis was used. Statistically significant correlations are shown in bold, [b]: Pearson correlation analysis was used to assess the relationship between inflammatory markers and FBA levels
ICP, Intrahepatic cholestasis of pregnancy, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, HALP: Hemoglobin, albumin, lymphocyte, and platelet, FBA: Fasting bile acid, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

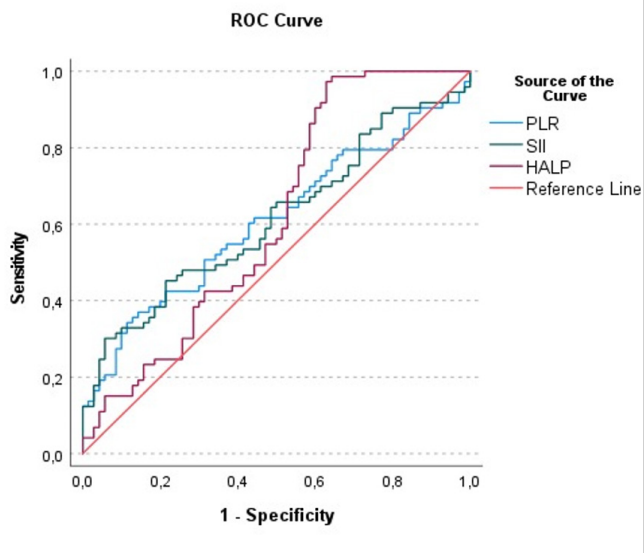

Figure 1. ROC curve analysis of biomarkers for ICP prediction
ICP: Intrahepatic cholestasis of pregnancy, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-Lymphocyte Ratio, SII: Systemic Immune Inflammation Index, HALP: Hemoglobin, albumin, lymphocyte, and platelet score, ROC: Receiver-operating characteristic

Table 3. Logistic regression analysis of data for the prediction of cholestasis and ROC analysis table for the cut-off value of the HALP score for the prediction of ICP

Variables	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	95% CI	p-value*
PLR	≥174.820	0.608	34	89	0.515-0.701	**0.026**
SII	≥1432.674	0.614	30	94	0.521-0.706	**0.019**
HALP	≥7.565	0.616	97	37	0.522-0.711	**0.016**

*: ROC analyses were performed, and the results were accepted with a 95% CI, with statistical significance set at p<0.05
ICP: Intrahepatic cholestasis of pregnancy, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII, Systemic immune-inflammation index, HALP: Hemoglobin, albumin, lymphocyte, and platelet, AUC: Area under the curve, ROC: Receiver-operating characteristic, CI: Confidence interval

in cases of ICP. Elevated PLR and SII values in our cohort may indicate increased platelet activation and neutrophil-driven inflammation. These, in turn, contribute to cholestatic hepatocellular injury and microcirculatory disturbance. It has been established that platelet-derived mediators can amplify oxidative stress and cytokine release, thereby exacerbating BA-induced hepatocyte damage. Our findings are consistent with previous research indicating that indices of platelet function reflect subclinical inflammatory changes associated with pregnancy-related hepatic disorders.

The HALP score, which integrates haemoglobin, albumin, lymphocyte, and platelet counts, demonstrated the highest diagnostic sensitivity among the evaluated markers. This may be attributable to the dual nutritional and inflammatory components in its formula. Decreased albumin and lymphocyte levels, commonly observed in cholestatic conditions, indicate hepatic synthetic dysfunction and systemic inflammation. In contrast, reactive thrombocytosis leads to an elevated HALP value. Therefore, the hypothesis that HALP may serve as a composite biomarker reflecting both inflammatory and metabolic stress in ICP is supported by these results and the literature. These findings highlight the potential clinical relevance of HALP, alongside PLR and SII, as a cost-effective method for identifying systemic inflammatory activity in cases of ICP.

Study Limitations

Despite the revealing results, the study has some limitations. The retrospective design, combined with the absence of longitudinal follow-up, limits the ability to draw causal conclusions and establish temporal relationships. In addition, the lack of subgroup analysis based on disease severity and the absence of dynamic biomarker measurements restrict the generalizability and depth of the conclusions. However, the strengths of the study lie in its structured methodology, well-matched control group, and novel investigation of HALP and AISI in ICP.

Conclusion

The primary objective of this study was to evaluate the diagnostic value of haematological indices reflecting the systemic inflammatory response, particularly HALP and SIRI, in pregnant women with ICP. The findings of this study demonstrated that the HALP score was significantly higher in the ICP group and exhibited high diagnostic potential and sensitivity. This result demonstrates, for the first time in the literature, an association between the HALP score and ICP, suggesting that the HALP score—previously examined only in obstetric conditions such as preeclampsia and hyperemesis gravidarum—may also be useful in pregnancy-related hepatobiliary pathologies. In addition, classical inflammatory indices, such as NLR, MLR, and SIRI, do not always show significant differences in diagnosing ICP, whereas immune-nutritional parameters, such as HALP, may provide a stronger diagnostic contribution. In this context, this study emphasizes that the HALP score, a novel biomarker in ICP, can be used as a cost-effective, easily accessible, and complementary diagnostic tool in clinical practice, especially in cases where BA measurements are delayed or inaccessible.

Ethics

Ethics Committee Approval: Ethical approval was granted by the University of Health Sciences Türkiye, Ankara Etlik City Hospital ethics committee (approval no: AEŞH-BADEK-2024-069, date: 31.01.2024). The study was conducted in accordance with the standards of the Declaration of Helsinki.

Informed Consent: All participants provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.Ö., S.Y.E., R.T.A., F.G., A.Y.T., K.Y.Y., Z.V.Y., Concept: Ö.Ö., K.Y.Y., Z.V.Y., Design: Ö.Ö., K.Y.Y., Z.V.Y., Data Collection or Processing: Ö.Ö., R.T.A., F.G., A.Y.T., Analysis or Interpretation: S.Y.E., R.T.A., Literature Search: Ö.Ö., Writing: Ö.Ö., R.T.A., K.Y.Y., Z.V.Y.

Conflict of Interest: The authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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