ORIGINAL RESEARCH

Bagcilar Med Bull
DOI: 10.4274/BMB.galenos.2025.35229

Second-trimester Hemogram-derived Inflammatory Markers for the Prediction and Severity Stratification of SGA Fetuses Based on Doppler and Birthweight Percentiles

İkinci Trimester Hemogram Türevli Enflamatuvar Belirteçlerin Doppler ve Doğum Ağırlığı Persentillerine Dayalı Olarak SGA Fetüslerinin Öngörülmesi ve Şiddet Sınıflandırmasındaki Rolü

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Abstract

Objective: This study aimed to evaluate the predictive value of second-trimester maternal hemogram parameters in identifying small for gestational age (SGA) fetuses and assessing the severity of SGA based on umbilical artery Doppler (UAD) findings and birthweight percentiles.

Method: A total of 150 singleton pregnancies were retrospectively analyzed and divided into three groups: SGA with abnormal UAD, SGA with normal UAD, and non-SGA controls. Maternal white blood cell (WBC) count, neutrophil count, lymphocyte count, platelet count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were compared among groups. SGA cases were further stratified into ≤3rd percentile (high risk) and 4th-10th percentile (lower risk) subgroups based on birthweight percentiles, categorizing them as high-risk and low-risk SGA.

Results: Maternal WBC and neutrophil counts were significantly higher in SGA pregnancies compared to non-SGA controls ($p<0.05$). The highest WBC and neutrophil levels were observed in the SGA group with abnormal UAD and in fetuses ≤3rd percentile. No significant differences were found in lymphocyte count, platelet count, NLR, or PLR across groups. A strong association was noted between elevated maternal WBC and markers of SGA severity, including lower gestational age at delivery, reduced birthweight, and abnormal Doppler findings.

Öz

Amaç: Bu çalışma, ikinci trimesterdeki maternal hemogram parametrelerinin, gestasyonel yaşa göre küçük (SGA) fetüslerin tanımlanmasında ve umbilikal arter Doppler (UAD) bulguları ile doğum ağırlığı persentillerine göre SGA şiddetinin değerlendirilmesindeki öngörücü değerini araştırmayı amaçlamıştır.

Yöntem: Toplam 150 tekil gebelik retrospektif olarak analiz edildi ve üç gruba ayrıldı: anormal UAD bulgularına sahip SGA, normal UAD bulgularına sahip SGA ve SGA olmayan kontrol grubu. Gruplar arasında maternal beyaz kan hücresi (WBC) sayısı, nötrofil sayısı, lenfosit sayısı, trombosit sayısı, nötrofil/lenfosit oranı (NLR) ve trombosit/lenfosit oranı (PLR) karşılaştırıldı. SGA olguları ayrıca doğum ağırlığı persentillerine göre ≤3. persentil (yüksek riskli) ve 4-10. persentil (daha düşük riskli) olmak üzere iki alt gruba ayrıldı.

Bulgular: SGA gebeliklerinde maternal WBC ve nötrofil sayıları, SGA olmayan kontrol grubuna kıyasla anlamlı derecede yüksekti ($p<0,05$). En yüksek WBC ve nötrofil düzeyleri, anormal UAD bulgularına sahip SGA grubunda ve ≤3. persentildeki fetüslerde gözlendi. Lenfosit sayısı, trombosit sayısı, NLR ve PLR açısından gruplar arasında anlamlı fark saptanmadı. Artmış maternal WBC düzeyleri ile daha düşük doğum haftası, azalmış doğum ağırlığı ve anormal Doppler bulguları gibi SGA şiddet göstergeleri arasında güçlü bir ilişki gözlemlendi.

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Received: 05.05.2025 **Accepted:** 02.09.2025 **Epub:** 04.09.2025

Cite this article as: Kayaoğlu Yıldırım Z, Selvi E. Second-trimester hemogram-derived inflammatory markers for the prediction and severity Stratification of SGA fetuses based on Doppler and birthweight percentiles. Bagcilar Med Bull. [Epub Ahead of Print]

Abstract

Conclusion: Second-trimester maternal WBC and neutrophil counts may serve as useful non-invasive markers for both identifying SGA and evaluating its severity. These routinely available parameters could support early risk stratification and management in clinical practice.

Keywords: Blood cell count, Doppler ultrasonography, intrauterine growth restriction, placental insufficiency, small for gestational age, umbilical artery

Öz

Sonuç: İkinci trimesterde ölçülen maternal WBC ve nötrofil sayıları, SGA fetüslerin belirlenmesinde ve şiddetlerinin değerlendirilmesinde faydalı, non-invaziv belirteçler olarak kullanılabilir. Rutin olarak erişilebilen bu parametreler, klinik uygulamada erken risk sınıflaması ve yönetimi açısından destekleyici olabilir.

Anahtar kelimeler: Doppler ultrasonografi, fetal büyüme geriliği, gebelik haftasına göre küçük bebek, kan hücresi sayımı, plasental yetmezlik, umbilikal arterler

Introduction

Small for gestational age (SGA) refers to a condition in which a fetus fails to achieve its genetically expected growth by the time of birth. Together with intrauterine growth restriction (IUGR), SGA is associated with adverse perinatal outcomes affecting both the mother and the newborn (1,2). By definition, SGA is characterized by a birth weight below the 10th percentile for gestational age (1).

Fetal growth restriction (FGR) increases the risk of early neonatal complications such as low birth weight, the need for neonatal intensive care, and perinatal mortality. In addition, it has been linked to long-term health problems, including obesity, neurodevelopmental disorders, cardiovascular diseases, and type 2 diabetes later in life (3-5). These complications may emerge during the neonatal period and often persist into later stages of life (2). The severity of FGR has been shown to correlate inversely with estimated fetal weight; that is, lower fetal weight is typically associated with more profound placental dysfunction and a worse perinatal prognosis (6).

The development of SGA and IUGR is attributed to various maternal and fetal factors, including fetal chromosomal abnormalities, structural anomalies, and maternal infections (1). Notably, increased resistance and abnormal findings in the umbilical artery Doppler are indicative of more severe FGR and are associated with poorer perinatal outcomes. Such Doppler abnormalities reflect impaired placental perfusion, which further contributes to adverse neonatal prognosis (7).

Recent studies have increasingly emphasized a strong association between FGR and inflammation, indicating that inflammatory mechanisms may be central to the initiation and progression of FGR (8,9). Inflammatory states may activate immune responses that impair placental function and hinder nutrient exchange, thereby contributing to FGR (10). Such impairment can result in compromised fetal development, posing serious risks to both immediate and long-term neonatal health.

Previous studies have indicated that elevated levels of first and second trimester maternal serum inflammatory markers—such as neutrophil count, white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)—may serve as significant and predictive biomarkers of impaired intrauterine growth (11-15).

The primary objective of this study was to evaluate the predictive value of second trimester maternal serum inflammatory markers—including WBC count, neutrophil count, lymphocyte count, platelet count, NLR, and PLR—for identifying SGA fetuses; the secondary objective was to investigate the utility of these markers in predicting the severity of SGA based on umbilical artery Doppler findings and birthweight percentiles.

Materials and Methods

This retrospective observational case-control study included a total of 150 pregnant women who were followed at the Perinatology Outpatient Clinic of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital between January 2024 and December 2024.The participants were categorized into three groups based on fetal growth status and umbilical artery Doppler findings. Fetuses with an estimated fetal weight below the 10th percentile on ultrasonographic evaluation were diagnosed with SGA.

Group 1 consisted of 50 pregnant women carrying fetuses diagnosed with SGA accompanied by abnormal umbilical artery Doppler findings, such as an increased resistance index. These cases were considered high-risk SGA pregnancies.

Group 2 included 50 pregnant women carrying fetuses diagnosed with SGA but with normal umbilical artery

Doppler findings, and were therefore considered to have lower-risk SGA pregnancies.

Group 3 served as a control group and consisted of 50 randomly selected pregnant women with appropriately grown fetuses and normal Doppler findings, representing healthy pregnancies. In the control group, all patients delivered at ≥37 weeks of gestation without obstetric or neonatal complications.

All participants had hemogram parameters measured during the second trimester (between 14-28 weeks of gestation). The maternal complete blood count (CBC) values analyzed included WBC count, neutrophil count, lymphocyte count, platelet count, NLR, and PLR. CBC analyses were performed using the Sysmex XN-1000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). These parameters were assessed to investigate their potential predictive value in identifying IUGR fetuses.

Additionally, within the SGA group (Groups 1 and 2), further stratification was performed based on birth weight percentiles. Fetuses born below the 3rd percentile were defined as higher-risk SGA, whereas those between the 3rd and 10th percentiles were considered lower-risk SGA. The predictive performance of the hemogram parameters for both the identification and risk stratification of SGA was statistically analyzed.

Pregnancies complicated by multiple gestations, congenital anomalies, pre-existing maternal chronic illnesses (e.g., diabetes mellitus, hypertension, autoimmune diseases), or incomplete medical records were excluded from the study.

The study protocol, procedures, and ethical conduct were reviewed and approved by the Local Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: KAEK/12.02.2025.41, date: 04.03.2025). All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Because of the retrospective nature of the study, written informed consent was not required from participants.

Selection and Description of the Participants

This study included 150 pregnant women followed at our tertiary care center. Inclusion criteria were singleton pregnancies between 14-28 weeks of gestation with complete medical and ultrasonographic data, including second trimester hemogram results and umbilical artery Doppler findings. Participants were selected to reflect a spectrum of fetal growth status: High-risk SGA, low-risk SGA, and normal fetal growth.

Exclusion criteria were as follows: Multiple gestations, fetal congenital or chromosomal anomalies, known maternal infections, use of medications influencing hematological parameters, maternal hematologic disorders, and chronic maternal conditions such as diabetes mellitus, hypertension, or autoimmune diseases. Cases with incomplete or missing medical records were also excluded.

The study population was not restricted by maternal age, ethnicity, or parity; however, all participants were selected from the same geographical region and healthcare facility to ensure consistency in clinical protocols and data acquisition. The rationale for this selection was to minimize confounding factors related to clinical variability and to reflect a representative sample of patients typically seen in tertiary obstetric care.

Statistical Analysis

All statistical analyses were conducted using R software (version 4.4.2). The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed variables are presented as mean ± standard deviation, and non-normally distributed variables as median and interquartile range (IQR). Categorical variables are expressed as counts and percentages.

Group comparisons for categorical variables were performed using Fisher's exact test or the chi-square test, as appropriate. For continuous variables, the Wilcoxon Rank-Sum test was used for two-group comparisons, and the Kruskal-Wallis test was applied for comparisons across more than two groups. A p-value of <0.05 was considered statistically significant.

Results

A total of 150 pregnant women were included and categorized into three groups based on fetal growth and umbilical artery Doppler findings. Hematologic and perinatal outcomes were compared between groups to assess the predictive value of maternal second-trimester hemogram parameters for SGA fetuses and SGA severity.

Comparison of SGA and Non-SGA Groups

Patients with SGA fetuses (Groups 1 and 2) demonstrated significantly higher maternal neutrophil counts [7,970.00/µL (IQR: 6,380.00-10,390.00)] compared to the non-SGA control group [6,970.00/µL (IQR: 6,230.00-8,440.00]; p=0.021)]. Similarly, WBC counts were significantly elevated

in the SGA group [11,765.00/µL (IQR: 9,500.00-13,240.00)] compared to controls [9,965.00/µL (IQR: 8,740.00-11,540.00); p=0.004]. There were no statistically significant differences in lymphocyte count, platelet count, NLR, or PLR between groups (p>0.05 for all) (Table 1).

Comparison of Non-SGA, SGA with Abnormal UAD and SGA with Normal UAD Groups

A significant difference in gestational age at delivery was observed across the three groups (p<0.001). Pregnancies complicated by SGA with abnormal UAD had the earliest deliveries [29.71 weeks (IQR: 27.93-32.29)] compared to SGA with normal UAD [37.00 weeks (IQR: 36.00-37.14)] and non-SGA pregnancies [39.00 weeks (IQR: 38.57-40.00)]. Birthweights were lowest in the abnormal UAD group [855.00 g (IQR: 635.00-1,190.00)] compared to the normal UAD group [2,330.00 g (IQR: 1,965.00-2,450.00)] and the non-SGA group [3,425.00 g (IQR: 3,140.00-3,630.00); p<0.001].

Similarly, WBC counts were highest among patients with SGA and abnormal UAD [12,430.00/µL (IQR: 10,750.00-14,835.00)], followed by those with normal UAD [10,075.00/µL (IQR: 9,030.00-12,625.00)] and non-SGA pregnancies [9,965.00/µL (IQR: 8,740.00-11,540.00); p<0.001]. Neutrophil counts were also significantly different among groups (p=0.012), while lymphocyte counts, platelet counts, NLR, and PLR did not show significant differences (p>0.05) (Table 2).

Comparison Based on Birthweight Percentiles Among SGA Fetuses

Further stratification of SGA fetuses by birthweight percentiles revealed that those born at ≤3rd percentile had significantly lower gestational age at birth [32.36 weeks (IQR: 29.29-35.29)] compared to those between the 4th-10th percentile [37.00 weeks (IQR: 36.86-37.14); p<0.001]. Birthweights were also significantly lower in the ≤3rd percentile group [1,095.00 g (IQR: 715.00-1,630.00)] compared to the 4th-10th percentile group [2,390.00 g (IQR: 2,340.00–2,470.00); p<0.001]. Maternal WBC counts were significantly higher in the ≤3rd percentile group [12,110.00/µL (IQR: 9,720.00-13,390.00)] compared to the 4th-10th percentile group [9,760.00/µL (IQR: 8,800.00-12,500.00); p=0.021]. No significant differences were observed in other hematological parameters (Table 3).

Discussion

The pathophysiological basis of SGA is multifactorial, with increasing attention directed toward the potential role of inflammation in placental dysfunction and suboptimal fetal growth. Although the association between inflammation and FGR has been hypothesized—particularly due to

Table 1. This table presents a comparison of patients with and without SGA based on the parameters listed below, along with the corresponding p-values

Variable	Group 3 n=50[1]	Group 1+2 n=100[1]	p-value[2]
Age	30.00 (25.00-35.00)	28.00 (24.00-31.00)	0.067
Birthweek	39.00 (38.57-40.00)	35.00 (30.00-37.00)	**<0.001**
Birthweight	3,425.00 (3,140.00-3,630.00)	1,625.00 (880.00-2,360.00)	**<0.001**
Lymphocyte	2,005.00 (1,750.00-2,450.00)	2,080.00 (1,715.00-2,600.00)	0.4
Neutrophil	6,970.00 (6,230.00-8,440.00)	7,970.00 (6,380.00-10,390.00)	**0.021**
Platelets	227,000.00 (184,000.00-268,000.00)	233,000.00 (196,500.00-270,000.00)	0.6
WBC	9,965.00 (8,740.00-11,540.00)	11,765.00 (9,500.00-13,240.00)	**0.004**
NLR	3.60 (2.97-4.29)	3.65 (2.84-4.87)	0.5
PLR	109.08 (95.60-136.73)	114.44 (81.49-138.15)	0.7
UAD	0 (NA%)	40 (40%)	-
Birthweight percentile			**<0.001**
≤3	0 (0%)	66 (66%)	
4-10	0 (0%)	27 (27%)	
11-90	48 (96%)	7 (7.0%)	
>90	2 (4.0%)	0 (0%)	

[1]: Median (Q1-Q3); n (%), [2]: Wilcoxon Rank-Sum test; Fisher's exact test, -: Cannot be obtained, SGA: Small for gestational age, UAD: Umbilical artery Doppler, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.
Maternal neutrophil and WBC counts were significantly higher in the SGA group compared to the non-SGA group (p=0.021 and p=0.004, respectively). No significant differences were observed in lymphocyte count, platelet count, NLR, or PLR between the groups (p>0.05)

Table 2. Comparison of non-SGA, SGA with normal UAD, and SGA with abnormal UAD

Variable	Non-SGA n=50[1]	SGA + Normal UAD n=60[1]	SGA + Abnormal UAD n=40[1]	p-value[2]
Age	30.00 (25.00-35.00)	27.00 (24.00-30.50)	29.00 (24.00-32.50)	0.10
Birthweek	39.00 (38.57-40.00)	37.00 (36.00-37.14)	29.71 (27.93-32.29)	**<0.001**
Birthweight	3,425.00 (3,140.00-3,630.00)	2,330.00 (1,965.00-2,450.00)	855.00 (635.00-1,190.00)	**<0.001**
Lymphocyte	2,005.00 (1,750.00-2,450.00)	1,980.00 (1,660.00-2,355.00)	2,320.00 (1,755.00-2,975.00)	0.079
Neutrophil	6,970.00 (6,230.00-8,440.00)	7,280.00 (6,365.00-9,815.00)	9,070.00 (6,590.00-11,105.00)	**0.012**
Platelets	227,000.00 (184,000.00-268,000.00)	235,000.00 (201,500.00-267,500.00)	229,000.00 (189,000.00-279,500.00)	0.9
WBC	9,965.00 (8,740.00-11,540.00)	10,075.00 (9,030.00-12,625.00)	12,430.00 (10,750.00-14,835.00)	**<0.001**
NLR	3.60 (2.97-4.29)	3.69 (3.09-4.73)	3.57 (2.48-5.44)	0.6
PLR	109.08 (95.60-136.73)	123.75 (95.10-142.47)	94.81 (75.57-129.42)	0.10
Birthweight percentile				**<0.001**
≤3	0 (0%)	27 (45%)	39 (98%)	
4-10	0 (0%)	26 (43%)	1 (2.5%)	
11-90	48 (96%)	7 (12%)	0 (0%)	
>90	2 (4.0%)	0 (0%)	0 (0%)	

[1]: Median (Q1-Q3); n (%), [2]: Kruskal-Wallis Rank-Sum test; Fisher's exact test, SGA: Small for gestational age, UAD: Umbilical artery Doppler, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.

Gestational age at delivery and birthweight differed significantly among the three groups, with the earliest deliveries and lowest birthweights observed in the SGA with abnormal UAD group (p<0.001). WBC and neutrophil counts were also significantly higher in this group (p<0.001 and p=0.012, respectively). No significant differences were found in lymphocyte count, platelet count, NLR, or PLR (p>0.05)

Table 3. Comparison of SGA patients with birthweight <3rd vs. 4th-10th percentile

Variable	BW=4-10 n=27[1]	BW≤3 n=66[1]	p-value[2]
Age	26.00 (23.00-29.00)	29.00 (25.00-32.00)	**0.038**
Birthweek	37.00 (36.86-37.14)	32.36 (29.29-35.29)	**<0.001**
Birthweight	2,390.00 (2,340.00-2,470.00)	1,095.00 (715.00-1,630.00)	**<0.001**
Lymphocyte	1,870.00 (1,650.00-2,600.00)	2,235.00 (1,760.00-2,840.00)	0.3
Neutrophil	6,900.00 (6,220.00-9,660.00)	8,570.00 (6,710.00-10,880.00)	0.086
Platelets	231,000.00 (189,000.00-270,000.00)	237,500.00 (195,000.00-271,000.00)	0.8
WBC	9,760.00 (8,800.00-12,500.00)	12,110.00 (9,720.00-13,390.00)	**0.021**
NLR	3.56 (3.13-4.35)	3.67 (2.54-4.98)	>0.9
PLR	127.48 (80.43-135.76)	110.51 (80.13-136.57)	0.4
UAD			<0.001
	1 (3.7%)	39 (59%)	
	26 (96.3%)	27 (41.0%)	
Birthweight percentile			**<0.001**
≤3	0 (0%)	66 (100%)	
4-10	27 (100%)	0 (0%)	
11-90	0 (0%)	0 (0%)	
>90	0 (0%)	0 (0%)	

[1]: Median (Q1-Q3); n (%), [2]: Wilcoxon Rank-Sum test; Fisher's exact test; Pearson's chi-squared test, SGA: Small for gestational age, BW: Birthweight, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, UAD: Umbilical artery Doppler, SGA fetuses with birthweights at or below the 3rd percentile had significantly lower gestational age at delivery and birthweight compared to those between the 4th-10th percentile (p<0.001 for both). Maternal WBC counts were also significantly higher in the ≤3rd percentile group (p=0.021). No significant differences were found in other hematologic parameters

impaired placental function and nutrient exchange—this mechanism has yet to be fully substantiated with definitive causal evidence.

Previous studies have highlighted the association between systemic inflammation and FGR. Elevated maternal inflammatory markers have been implicated in placental dysfunction, which is a key pathophysiological mechanism underlying SGA (14,15). Consistent with these findings, our study showed significantly higher maternal WBC and neutrophil counts in the SGA group compared to controls. These results align with the findings of Kırmızı et al. (11), who also reported higher WBC counts in pregnancies complicated by FGR.

When SGA pregnancies were further stratified by UAD results, our study revealed that those with abnormal UAD—representing higher-risk SGA—had the earliest gestational age at delivery and the lowest birthweights. This group (Group 1) also exhibited the highest WBC and neutrophil levels, supporting the hypothesis that inflammation may be more pronounced in severe cases of SGA. These findings are in agreement with prior research indicating that elevated WBC levels are linked not only to the presence of SGA but also to the extent of placental insufficiency (16).

Additionally, subgroup analysis based on birthweight percentiles revealed that fetuses below the 3rd percentile had significantly earlier gestational ages at delivery and lower birthweights compared to those between the 4th and 10th percentiles. Notably, WBC counts were significantly higher in the ≤3rd percentile group. The high rate of abnormal UAD findings (59%) in this subgroup, compared to only 3.7% in the 4th-10th percentile group, further emphasizes the clinical value of WBC as a potential marker for severe SGA.

Importantly, in contrast to several previous studies in the literature (13-15), this study did not find a significant association between other hematologic parameters—such as lymphocyte count, platelet count, NLR, and PLR—and the presence or severity of SGA. These findings suggest that while WBC and neutrophil counts may have predictive value, the broader range of hemogram parameters may have limited diagnostic utility in this context. Further large-scale studies are warranted to determine whether these markers could contribute meaningfully to SGA prediction.

As in the present study, various previous investigations have assessed the predictive ability of different maternal serum hemogram parameters for identifying SGA (17,18). However, to the best of our knowledge, this is the first study to comprehensively evaluate multiple second-trimester hemogram parameters specifically for predicting the severity of SGA. Taken together, these findings suggest that routine, non-invasive parameters such as CBC-derived inflammatory markers may hold clinical promise in the early identification of high-risk SGA cases. This could be particularly beneficial in settings with limited access to advanced diagnostic tools. However, prospective, large-scale studies are warranted to validate their utility in broader clinical practice.

Study Limitations

Limitations of our study include its retrospective design and single-center setting, which may limit the generalizability of the findings. Future prospective studies with larger cohorts are warranted to validate our findings and to explore the potential integration of these biomarkers into SGA screening protocols.

Conclusion

In conclusion, maternal WBC and neutrophil counts in the second trimester appear to be promising non-invasive markers for predicting SGA and identifying its severity. These parameters, readily available through routine antenatal care, may enhance current screening strategies when combined with fetal biometric and Doppler assessments.

Ethics

Ethics Committee Approval: The study protocol, procedures, and ethical conduct were reviewed and approved by the Local Ethics Committee of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: KAEK/12.02.2025.41, date: 04.03.2025).

Informed Consent: The retrospective nature of the study, written informed consent was not required from participants.

Acknowledgments

The authors would like to thank the staff of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital for their help and support.

Footnotes

Authorship Contributions

Concept: Z.K.Y., E.S., Design: Z.K.Y., E.S., Data Collection or Processing: E.S., Analysis or Interpretation: Z.K.Y., Literature Search: Z.K.Y., E.S., Writing: Z.K.Y., E.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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