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Diagnostic utility of the systemic immune-inflammatory index in preterm neonates with late-onset sepsis

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ABSTRACT

Objective: To assess if systemic immune-inflammatory index (SII) has a diagnostic role for late-onset sepsis (LOS) in premature neonates.

Patients and Methods: A single-center retrospective observational study including preterm infants with culture-proven LOS and controls was conducted between January 2017 and December 2022. SII was derived using complete blood count values acquired at the beginning of and three to five days before LOS. SII was compared between the LOS group and controls.

Results: A total of 144 infants were included in the study. The SII values of the LOS group were found to be significantly increased in comparison to the control group [376.74 (11.11 – 15170) vs. 235.24 (46.83 – 1214.38) (median, min-max), P =0.018]. The SII values significantly increased when pre-sepsis and LOS values were compared [200.6 (0 – 1295.78) vs. 328.28 (0 – 14678, P<0.001]. As determined using the receiver operating characteristic analysis, the area under the curve for SII was 0.621 (44.4% sensitivity, 83.3% specificity, 72.7% positive predictive value, and 60% negative predictive value) for predicting LOS.

Conclusion: Although, further research is required, SII may be used with other biomarkers to identify LOS in preterm infants and may constitute a readily accessible additional diagnostic parameter.

Keywords: Late-onset sepsis, Systemic immune-inflammatory index, Neonate, Biomarker

1. INTRODUCTION

Neonatal sepsis is described as an immune system dysregulation induced by bacterial, viral, or fungal bloodstream infection accompanied by hemodynamic abnormalities [1,2].

Neonatal sepsis is classified as early or late onset sepsis (LOS), depending on the onset time. LOS occurs after 72 hours of life, according to the pathophysiology and etiology of the responsible microorganisms [3].

Despite advances in clinical management and laboratory diagnosis methods, LOS remains the major reason for morbidity and mortality in preterm neonates receiving care in neonatal intensive care units (NICUs) [4]. LOS is a common consequence of extreme prematurity due to low immunoglobulin concentrations and poor neutrophil function, which makes preterm infants more vulnerable to infection [2]. Contact with hospital personnel, family members, contaminated equipment, nutritional sources, increased hospital stay, a necessity for invasive interventions, central venous access, and use of broad-spectrum antibiotics are multiple factors that put preterm neonates at increased risk for LOS. Infants with extremely low birth weight are reported to have an incidence of LOS ranging from 12.2% to 24.4% [4].

Each laboratory test has yet to be identified as having high enough sensitivity and specificity for the early recognition of LOS. The gold standard for LOS diagnosis is appropriately collected cultures (blood, urine, cerebrospinal fluid, etc.). In over 99% of patients, the causative bacterium may be identified within 36 hours [5]. Immediate commencement of therapy is vital and lifesaving. On the other hand, overdiagnosis is associated with the harmful effects of neonatal antibiotic exposure [6]. C-reactive protein (CRP), procalcitonin (PCT), as well as the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR), are considered to be crucial markers in diagnosing neonatal sepsis [7-9]. Several parameters from a complete blood count (CBC) – peripheral lymphocyte, neutrophil, and platelet counts, are used to derive the systemic immune-inflammatory index (SII). Both inflammation and

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ischemia are reported to lead to an increase in SII [10]. The purpose of this study was to evaluate, if any, the role that SII plays in assessing LOS in preterm infants when there is a clinical suspicion that it may be present. We are unaware of any previous study on the predictive efficacy of SII in diagnosing LOS in premature infants.

2. PATIENTS and METHODS

Study design, ethical considerations, and participants

This retrospective analysis involving preterm neonates with culture-proven sepsis and controls was undertaken between January 2017 and December 2022 in the NICU of Marmara University Research and Training Hospital in Istanbul, Turkey. The Marmara University School of Medicine's Clinical Studies Ethics Committee approved the study (Date: 01.06.2023, No: 09.2023.105).

Seven hundred fifty-five of the 2268 infants that were followed up in the NICU were born prematurely. Of these, 110 preterm infants <37w gestational age (14.5%) had culture-proven LOS. The study group was comprised of preterm infants ≤35w gestation with culture-proven sepsis that occurred after 72 hours of life (n=101, 13.3%). The control group was comprised of premature children born in our hospital during the same period of time, which matched the inclusion criteria and were free of infection. Control SII was calculated at day 19, corresponding to the LOS group's median first sepsis day. In cases of several LOS episodes, only the initial incident was included. The following exclusion criteria were applied: (1) incomplete laboratory data, (2) any episode of early-onset sepsis, (3) preterm infants with a gestational age >35 weeks, (4) major congenital and chromosomal anomalies, (5) hypoxic-ischemic encephalopathy, and (6) cyanotic heart disease. Following these criteria, 29 patients were excluded; consequently, the study consisted of 72 (9.5%) infants (Figure 1).

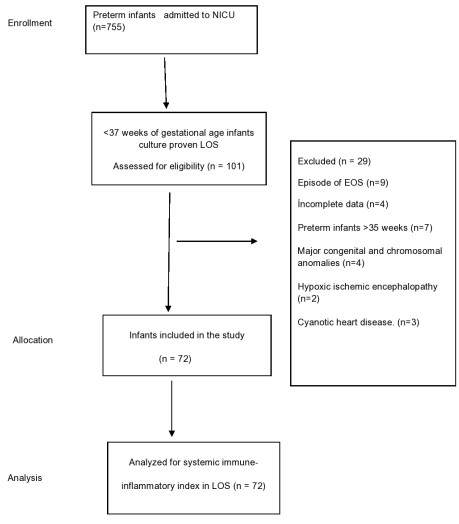

Figure 1. *Flow chart for selection of eligible infants in the study*

Data collection and definitions

Data were extracted from patient records. The demographic, perinatal, and neonatal characteristics of patients were analyzed. A positive blood culture was required to define LOS. Two positive blood cultures were required to diagnose sepsis caused by coagulase-negative staphylococci. Blood culture isolates were analyzed using a fully automated BACTEC method – the BACT/ALERT 3D system (bioMerieux, SA, France).

For all patients, white blood cells (WBC) (/mm3), absolute neutrophil count (ANC) (/mm3), lymphocyte count (/mm3), platelet count (103/mm3), CRP (mg/L) and PCT ((g/L) obtained at the beginning of the LOS episode (6h before or 24h after blood culture samples were obtained when clinical findings were present) and three to five days before sepsis (pre-sepsis) were collected. Hematologic indices that were calculated using this data were: NLR (neutrophil count/lymphocyte count), PLR (platelet count/lymphocyte count), and SII (neutrophil count x platelet count/lymphocyte count).

Neonatal morbidities were analyzed. Severe intraventricular hemorrhage (IVH) included stages ≥ III, classified according to Volpe's cranial ultrasound classification [11]. Bronchopulmonary dysplasia (BPD) was defined according to oxygen and ventilator support requirements at 36w of gestation [12]. Severe retinopathy of prematurity (ROP) included standardized international criteria stages ≥3 or any stage requiring cryotherapy or laser photocoagulation [13]. Bell criteria were used for severe necrotizing enterocolitis (NEC) [14].

Outcomes

The primary outcome was the diagnostic value of SII in preterm infants with LOS. Secondary outcomes were duration of ventilation, BPD, NEC, ROP, IVH, hospitalization days, and mortality.

Statistical analysis

IBM SPSS Statistics for Windows was utilized for statistical analysis (IBM Corp. Released 2017, Version 25.0. Armonk, NY, USA). The sample size was determined with G*Power version 3.1.9.7 (Franz Faul, Germany). Power analysis using alpha = 0.05, effect size = 0.419, and power = 0.80 revealed a required sample size of 144 participants for the two groups. The Pearson's chi-square test was used to compare categorical variables expressed as n (percent). Continuous variables were reported using mean ± standard deviation (SD) or medians and ranges (min-max). The normality of data was evaluated using the Kolmogorov-Smirnov test. Continuous variables were compared using the t-test or the Mann-Whitney U test on independent samples. The Spearman correlation analysis assessed the relationship between continuous variables. For intragroup comparisons, the Wilcoxon Test was utilized. Using receiver operating characteristic (ROC) analysis, the SII values used to predict LOS were investigated. For the appropriate cut-off value, the sensitivity and specificity with positive likelihood ratio (+LR) and negative likelihood ratio (-LR) ratios were computed. The cut-off values exhibited

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the greatest sensitivity. A P-value of <0.05 was considered to be statistically significant.

3. RESULTS

The study included 72 preterm neonates that had culture-proven sepsis. On the other hand, the control group was made up of 72 preterm infants who were infection free. Table I shows the demographic and laboratory parameters of the study population. The LOS and the control group were similar concerning gestational age (P=0.052), gender (P=0.739), and IVH (P=0.286). When LOS and control groups were compared, vaginal delivery (P=0.006), presence of venous catheter (P=0.006), ventilator-associated pneumonia (VAP) (P<0.001), duration of ventilation (P<0.013), days on parenteral nutrition (P<0.001), hospitalization (P<0.001), NEC (P<0.001), ROP (P<0.010), and mortality (P <0.001) were observed to be statistically significantly higher in the LOS group. Birth weight (P<0.001) and Apgar scores were significantly lower at the first minute (P=0.002) and fifth minute (P=0.001), respectively, in the LOS group when compared to the control group.

When laboratory parameters were compared, median serum levels of CRP (p<0.001), PCT (p<0.001), WBC (p=0.01), ANC (p<0.001), NLR (p<0.001), SII (p=0.018) were significantly higher in the LOS group whereas, median lymphocyte count (p<0.028), and platelet count (p=0.001) were lower. However, the median PLR (p=0.979) was similar between groups.

Gram-positive microorganisms led to more LOS when compared to (53/77, 68.8%) gram-negative microorganisms [50/72 (69.4%) vs. 20/72 (27.8%)] and fungus (2/72, 2.8%). *Coagulase-negative staphylococci* were the most commonly observed gram-positive organisms that caused LOS (n=31, 43.1%), followed by *Staphylococcus aureus* (n=13, 18.1%), other gram-positive organisms (n=6, 8.3%), *Stenotrophomonas maltophilia* (n=5, 6.9%), *Klebsiella spp.* (n=4, 5.6%), *Enterobacter spp.* (n=3, 4.2%), other gram-negative organisms (n=8,11.2%), and fungus (n=2, %2.8).

The laboratory data of the study population three to five days before sepsis (pre-sepsis), and when sepsis was diagnosed (sepsis) have been summarized in Table II. Lymphocyte count, platelet count, and PLR were similar at pre-sepsis and sepsis measurements. On the other hand, when pre-sepsis values were compared to sepsis values, WBC, PNL, CRP, PCT, NLR, and SII were found to be higher in sepsis (p=0.003, p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001 respectively).

ROC revealed that SII, CRP, PCT, and NLR are predictive when defining culture-proven LOS among preterm infants (Figure 2). The AUC of SII, CRP, PCT, and NLR was 0.621 (0.526-0.716) (44.4% sensitivity, 83.3% specificity), 0.948 (0.912-0.984) (83.3% sensitivity, 97.3% specificity), 0.909 (0.845-0.973) (88.2% sensitivity, 100.0% specificity), and 0.697 (0.609-0.785) (43% sensitivity, 91.6% specificity) respectively (Table3).

SII level was found to be significantly lower in preterm neonates with BPD [511.15 (10.3-14678)] vs. [246.09 (0-4107.3) p=0.038]. SII values were similar for patients with IVH [560.36 (10.33-14678)] vs. [258.57 (0-5474) p=0.104], ROP [387 (5.77-14678)] vs. [270 (0-6549.7) p=0.631], NEC [314.15 (0-14678)] vs. [381.6(10.3-5474) p=0.626], and when mortality was compared [242.1 (0-1534.74)] vs. 381.6 (5.77-14678) p=0.231].

Additionally, no correlation was found between SII and CRP levels. PCT demonstrated a weak positive correlation with SII levels (r=0.464, P<0.001). NLR was highly correlated with SII levels (r=0861, P<0.001).

Table I. *Demographic and laboratory parameters of the study population*

	Late-onset sepsis group (n=72)	Control group (n=72)	P
**GA[a] at birth, week	27 (22-35)	28 (23-35)	0.052
**BW[b], g	947 (315-3460)	1452 (515-2660)	**<0.001**
*Gender, male	34 (47.2)	36(50)	0.739
*Vaginal delivery	28 (38.9)	13 (18.06)	**0.006**
**Apgar 1	5 (0-9)	6 (2-9)	**0.002**
**Apgar 5	7 (3-10)	8 (2-10)	**0.001**
*Presence of venous catheter	53 (73.6)	37 (51.3)	**0.006**
*VAP[c]	21 (29.2)	4 (5.7)	**<0.001**
*BPD[d]	40 (55.5)	20 (27.7)	**<0.001**
*IVH[e]	16 (22.22)	11 (15.28)	0.286[3]
*NEC	43 (59.72)	14 (19.72)	**<0.001**[3]
*ROP[g]	33 (45.83)	10 (14.08)	**<0.001**[3]
**Ventilation days	17 (0-200)	8 (0-118)	**<0.013**
**Parenteral nutrition days	20 (0-220)	10 (3-120)	**<0.001**
**Hospitalization days	84 (3-373)	45 (0-142)	**<0.001**
*Mortality	11(15.3)	0 (0)	**<0.001**
**WBC (/mm3)[h]	12400 (1100-79600)	10000 (1200-20300)	**0.01**
**ANC (/mm3)[i]	7200 (100-67600)	3450 (600-12800)	**<0.001**
**Lym count (/mm3)[j]	3200 (500-15500)	4050 (1200-11800)	**<0.028**
**Plt count (10^3/mm^3)[k]	165 (15-686)	226 (66-456)	**0.001**
**NLR [m]	1.8 (0.08-41)	0.73 (0.16-5)	**<0.001**
**PLR [n]	60 (10-740)	70 (20-200)	0.979
**Crp (mg/L)[o]	41.7 (0.60-245)	1.59 (0.04-10.8)	**<0.001**
**Pct (µg/L) [r]	3 (0.07-100)	0.3 (0.10-2.0)	**<0.001**
**SII [s]	376.74 (11.11-15170)	235.24 (46.83-1214.38)	**0.018**

**Values are given as percentage, **Values are given as median (min–max), [a]GA gestational age, [b]BW birth weight, C/S cesarean section, [c]VAP ventilator – associated pneumonia, [d]BPD bronchopulmonary dysplasia, [e]IVH intraventricular hemorrhage, [f]NEC necrotizing enterocolitis, [g]ROP retinopathy of prematurity, [h]WBC: White blood cell; [i]ANC:Absolute neutrophil count; [j]Lym: Lymphocyte count ; [k]Plt: Platelet count; [m]NLR: Neutrophil-to – lymphocyte ratio; [n]PLR: Platelet-to-lymphocyte ratio; [o]CRP: C reactive protein,; [r]Pct : Procalcitonin; [s]SII: Systemic immune-inflammatory index*

Table II. *The laboratory data prior to sepsis and at the time of the diagnosis of sepsis.*

	Pre-sepsis	Sepsis	P
WBC[a]	10300 (3400-24700)	12350 (1100-79600)	**0.003***
PNL[b]	4000 (600-10700)	7200 (100-67600)	**<0.001***
LENFO[c]	2900 (400-8500)	3150 (500-15500)	0.402*
PLT[d]	175 (54-249)	158.5 (15-686)	1.000*
CRP[e]	3.11 (0.5-11)	40.17 (0.6-245)	**<0.001***
PCT[f]	0.3 (0.05-5)	3 (0.07-100)	**<0.001***
SII[g]	200.6 (0-1295.78)	328.28 (0-14678)	**<0.001***
NLR[h]	1.08 (0-5.44)	1.92 (0-41)	**<0.001***
PLR[i]	60 (0-260)	60 (10-720)	0.236*

[a]WBC: White blood cell; [b]PNL:Neutrophil count; [c]Lym: Lymphocyte count ; [d]Plt: Platelet count; [h]NLR: Neutrophil-to – lymphocyte ratio; [i]PLR: Platelet-to-lymphocyte ratio; [e]CRP: C reactive protein,; [f]Pct : Procalcitonin; [g]SII: Systemic immune-inflammatory index
**Wilcoxon test*

Table III. *Accuracy of biomarkers for prediction of late-onset sepsis*

TEST	AUC (%95CI)	Cut-off	p	Sensitivity	Specificity	PPV	NPV
SII[a]	0.621 (0.526-0.716)	>450	**0.014**	44.4	83.3	72.7	60.0
CRP[b]	0.948 (0.912-0.984)	>9.5	**<0.001**	83.3	97.2	96.7	85.3
PCT[c]	0.909 (0.845-0.973)	>0.62	**<0.001**	88.2	100.0	100.0	89.8
NLR[d]	0.697 (0.609-0.785)	>2.8	**<0.001**	43.0	91.6	83.7	61.6
PLR[e]	0.484 (0.384-0.584)		0.742				

[a]SII: Systemic immune-inflammatory index; [b]CRP: C reactive protein,; [c]Pct : Procalcitonin; [d]NLR: Neutrophil-to – lymphocyte ratio; [e]PLR: Platelet-to-lymphocyte ratio; AUC: Area under the curve; PPD: Positive predictive value; NPV: Negative predictive value

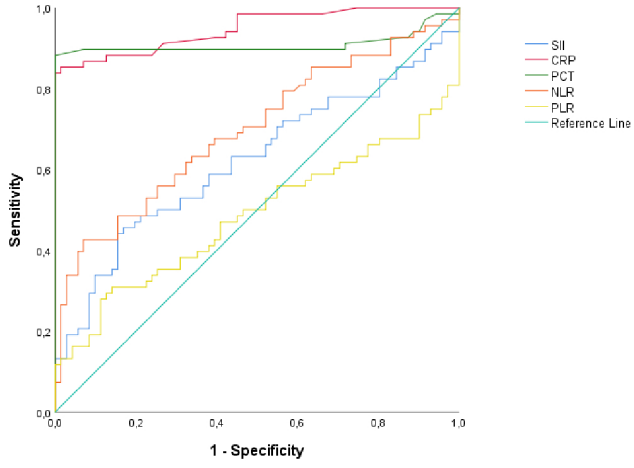

Figure 2. *ROC curves for SII, CRP, PCT, NLR and PLR. SII: Systemic immune-inflammatory index, CRP: C reactive protein, PCT : Procalcitonin, NLR: Neutrophil-to – lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.*

4. DISCUSSION

In this retrospective observational study, the predictive value of SII in the early diagnosis of LOS in preterm infants was investigated. CRP, PCT, NLR, PLR, and SII are the most frequently utilized biomarkers used for diagnosing neonatal sepsis, and they were compared in this study.

Neonatal sepsis remains the leading reason for mortality and morbidity among NICU patients [15], especially in developing countries [16]. Additionally, premature neonates are more prone to infectious diseases. Neonatal sepsis increases as gestational age decrease, and the risk of death in the preterm population has been reported as 120-fold more than in the term population (17). Humoral and cellular deficiencies arising from an immature innate immune system, dysbiotic gut microbiota, lack of total enteral nutrition, requirement for central venous catheters, invasive operations, prolonged hospitalization, and broad-spectrum antibiotics are risk factors for LOS in premature infants [4,18]. Similar to reports in the literature, prolonged hospitalization, the requirement for ventilation devices, central venous access, and long time spent on total parenteral nutrition before switching to complete enteral feeding were the numerous risk factors for developing LOS in preterm infants in our study. *Coagulase-negative staphylococci*, which cause neonatal sepsis in preterm infants associated with the duration of central line exposure and parenteral nutrition [19], were predominant in our group of preterm infants with LOS.

Sepsis manifests in various ways, depending on the region, gestational age, severity, and causative agent. Although blood culture remains the gold standard for diagnosing sepsis [20], it requires at least 48h, and the bacterium is identified in

only 60-80% of neonates with sepsis [21]. On the other hand, delayed diagnosis and treatment may lead to further morbidity and mortality in these patients [17]. Researchers have been encouraged to investigate novel indicators due to the lack of an early diagnostic marker that can provide definitive conclusions in diagnosing neonatal sepsis. No laboratory indicators have been demonstrated to have sufficient sensitivity and specificity in diagnosing sepsis in preterm newborns [22]. CRP is currently the most commonly utilized first-line biomarker in diagnosing neonatal sepsis. It does, however, have certain limitations. First, it elevates in non-sepsis circumstances such as NEC, hypoxia, shock, IVH, meconium aspiration, and surgery [8,17]. Second, levels of CRP start to elevate 10-12 hours following infection onset. Thus, if the test is administered early in the course, it may remain the same. Thirdly, CRP can respond differently in early-onset and LOS in preterm and full-term newborns, with values rising by 0.40 mg/L [17]. A meta-analysis of 10 trials reported CRP's median sensitivity, and specificity to be 70% and 89%, respectively [23]. CRP's median sensitivity and specificity were found to be higher in our study: 83.3% and 97.2%, respectively.

According to a meta-analysis, the diagnostic accuracy of PCT was shown to be greater in neonates with LOS than in those with early-onset sepsis [24]. PCT begins to be released two hours after stimulation and peaks between 12 and 24 hours, with a half-life of approximately 24 hours [25]. It has been reported that PCT has a median sensitivity and specificity of 85% and 54%, respectively; however, there is very little information regarding LOS [26]. Our study's median PCT sensitivity and specificity were 88.2% and 100%, respectively.

Since, neutrophil numbers increase in sepsis while lymphocyte counts drop, NLR has been deemed a promising biomarker. However, it is recommended to be used in conjunction with CRP to evaluate sepsis [8]. Although, varied cut-off values, sensitivity, and specificity rates have been published in the literature, we determined that preterm infants with LOS had a cut-off value of 2.8, with sensitivity and specificity rates of 43.0% and 91.6%, respectively.

Although, PLR has been advocated in diagnosing early-onset sepsis, a newly published meta-analysis found insufficient trials demonstrating its diagnostic value in sepsis [9, 27, 28]. In our study, there was no significant rise in PLR during LOS. This may be due to the decrease in platelets and lymphocyte counts during the sepsis episode.

SII is an index derived from platelet, lymphocyte, and neutrophil counts that reflects the systemic immune-inflammation status. Its role in the clinical outcomes of patients with coronary artery disease and several types of cancer has previously been examined [29, 30]. At the same time, Ceran et al., demonstrated that SII might predict hypoxic-ischemic encephalopathy in neonates [31]. Based on the available data, the cut-off range of SII is 200 to 1375. According to a recent study by Aydogan et al., SII may be used with other biomarkers to diagnose sepsis in neonates with congenital heart disease using a cut-off value of 517.19, with a sensitivity of 70.5% and a specificity of 70.2% [10]. In a study on newborns with urinary tract infections and renal involvement, SII's cut-off value, sensitivity, and specificity were determined to be 217.2, 60.8%, and 60.8%, respectively [32]. In our study, we have demonstrated that a cut-off value of 450 for SII has a sensitivity of 44.4% and a specificity of 83.3%, PPD of 72.7%, and NPD of 60% for diagnosing LOS. Sadly, this is relatively low compared to CRP and PCT. Hence, it can be considered close to NLR.

Moreover, we found no significant relationship between SII and IVH, NEC, ROP, and mortality. However, SII levels were found to be lower in preterm infants with BPD. Since, inflammation is a major risk factor in BPD pathogenesis, NLR was shown to be an early predictor of BPD in 72h [33]. In contrast, different theories of BPD etiology and disease drivers other than LOS may explain our findings [34].

According to our findings, SII levels increased significantly in premature newborns with LOS. We are unaware of any previous investigation that has evaluated SII levels in conjunction with well-known septic biomarkers such as CRP, PCT, NLR, and PLR in preterm infants with LOS. SII can be calculated, at no additional cost, from a CBC and is simple to use in clinical settings. In contrast to CRP and PCT, its diagnostic value is relatively poor. This research has several limitations. In the first place, it was a retrospective study conducted at a single center, and in the second place, we could not measure the SII at multiple periods.

Conclusion

Herein, we have demonstrated that SII increases in premature newborns with LOS. However, compared to CRP and PCT, the diagnostic value is relatively low. Prospective studies are required to determine if the diagnostic value increases if more biomarkers are included. Further research with larger sample sizes may fill in the gaps in our understanding of its involvement in LOS.

Compliance with Ethical Standards

Ethical approval: The Marmara University, School of Medicine Clinical Research Ethics Committee approved the project (Date: 01.06.2023, No: 09.2023.105).

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

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

Authors' Contributions: GV and E O: Concept and design, GV: Data collection or processing, GV and EO: Analysis, interpretation and literature search, GV: Writing. Both authors read and approved the final version of the manuscript.

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