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Comparison of First and Third Trimester Complete Blood Count Parameters for Prediction of Preterm Birth

Preterm Doğum Öngörüsünde Birinci ve Üçüncü Trimester Tam Kan Sayımı Parametrelerinin Karşılaştırılması

ENGİN YURTÇU [1] Orcid ID: 0000-0002-1517-3823
HATİCE ÖZKUL [2] Orcid ID: 0000-0002-2088-6343
VEHBİ YAVUZ TOKGÖZİ [3] Orcid ID: 0000-0002-4113-385X
BETÜL KEYİF [1] Orcid ID: 0000-0002-8521-5486

[1] Department of Gynecology and Obstetric, Faculty of Medicine, Düzce University, Düzce, Turkey

[2] Department of Family Medicine, Faculty of Medicine, Karabük University, Karabük, Turkey

[3] Department of Gynecology and Obstetric, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

ÖZ

Amaç: Tam kan sayımı parametreleri ve nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), ortalama trombosit hacmi (MPV) gibi bu parametrelerin kombinasyonları inflamatuar belirteçlerdir. Bu çalışmada tam kan sayımı parametrelerinin (NLR, PLR ve MPV) erken doğumu tahmin etmedeki olası rolünü değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Birinci ve üçüncü trimesterdeki tam kan sayımı parametreleri kaydedildi ve NLR, PLR değerleri hesaplandı. Çalışma popülasyonu preterm doğumlar (n=94) ve miadında doğumlar (n=953) olarak kategorize edildi. Preterm doğum grubu ayrıca erken preterm (n=11) ve geç preterm (n=83) olmak üzere iki subgruba ayrıldı. İnflamatuvar belirteçler çalışma grupları arasında birinci ve üçüncü trimester için ayrı ayrı karşılaştırıldı. Ayrıca birinci ve üçüncü trimester değerleri arasındaki değişimler de değerlendirildi.

Bulgular: İlk trimester değerleri çalışma grupları arasında benzerdi. Birinci ve üçüncü trimesterler arasındaki MPV değişimi, preterm grupta term gruba göre anlamlı olarak daha düşüktü (0.0 ± 1.1 vs. 0.2 ± 1.1, p = 0.038). Ayrıca birinci ve üçüncü trimesterde NLR değerleri erken preterm subgrupta geç preterm ve term gruplara göre daha yüksekti (ilk trimester; 4.0 ± 1.2 vs. 3.1 ± 2.0 and 3.1 ± 1.3, p = 0.005; üçüncü trimester; 5.3 ± 1.2 vs. 4.0 ± 1.5 and 4.4 ± 2.9, p = 0.013).

Sonuç: NLR ve MPV ilk trimester ve doğum öncesinde preterm doğumları öngörmektedir. Bu da hekimlerin preterm doğumu önlemek için bazı önlemler almasını sağlar.

Anahtar kelimeler: Tam kan sayımı parametreleri, nötrofil lenfosit oranı, ortalama trombosit hacmi, preterm doğum, erken preterm doğum

ABSTRACT

Introduction: The complete blood count parameters and its combinations, such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV), are inflammatory markers. In this study, we aimed to demonstrate the possible role of complete blood count parameters (NLR, PLR, and MPV) in predicting preterm birth.

Material and Methods: The complete blood count parameters in the first and third trimesters were recorded, as well as the corresponding NLR, PLR, and MPV. The study population was categorized as preterm (n = 94) and term births (n = 953). The preterm birth group was further divided into early preterm (n = 11) and late preterm birth (n = 83) groups. The inflammatory markers were compared between the study groups for the first and third trimesters separately. The alterations between the first and third trimester values were also compared.

Results: The first trimester values were similar across the study groups. Moreover, the MPV difference between the first and third trimesters was significantly lower in the preterm group than in the term group (0.0 ± 1.1 vs. 0.2 ± 1.1, p = 0.038). Furthermore, NLR values were higher in the early preterm subgroup than in the late preterm and term groups for the first and third trimesters (first trimester; 4.0 ± 1.2 vs. 3.1 ± 2.0 and 3.1 ± 1.3, p = 0.005; third trimester; 5.3 ± 1.2 vs. 4.0 ± 1.5 and 4.4 ± 2.9, p = 0.013).

Conclusion: NLR and MPV predict preterm births in the first trimester and before birth. This enables physicians to take some precautions in preventing preterm delivery.

Keywords: Complete blood count parameters, neutrophil to lymphocyte ratio, mean platelet volume, preterm delivery, early preterm birth

Sorumlu Yazar/ Corresponding Author: Engin Yurtçu
Adres: Düzce University Department of Gynecology and Obstetric, Faculty of Medicine 81620 Merkez/Düzce
E-mail: drenginyurtcu1@hotmail.com

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INTRODUCTION

Defined as delivery before 37 weeks of gestation, preterm birth is one of the leading causes of neonatal mortality and morbidity and is an important complication of both singleton and multiple pregnancies worldwide (1). The incidence of preterm birth varies between 5%–13% among countries, and 15 million preterm births occur every year worldwide (2). Complications of preterm birth are estimated to be responsible for 35% of the 3.1 million annual neonatal deaths worldwide and are now the second most common cause of death in children under 5 years of age after pneumonia. In addition to causing mortality, preterm birth has lifelong effects on neurodevelopmental functions, leading to increased rates of cerebral palsy, learning difficulties, and visual impairments among newborns, as well as an increase in chronic diseases in adulthood (3). Preterm births are evaluated according to clinical causes and gestational week at the time of delivery. In 2013, the preterm birth rate in the USA was 11.4%, and the rate of births before 34 weeks was 3.4%. The risk of neonatal mortality and morbidity increased as the gestational week at delivery decreases (4). For these reasons, the prediction of preterm birth is important to reduce fetal mortality and morbidity and prevent unnecessary interventions.

The pathogenesis of preterm birth is not fully understood, but preterm birth can occur because of early idiopathic activation of the normal birth process or because of pathological processes. Pathological processes involved in preterm birth syndrome include intrauterine infection, uterine ischemia, uterine overstretching, abnormal allogeneic recognition, allergic-like reaction, cervical disease, and endocrine disorders (5). Among all suspected causes of preterm birth, infection and/or inflammation is the only pathologic process for which a solid causal relationship has been established, and whose molecular pathophysiology has been defined (6). One in four preterm infants is born to a mother with intra-amniotic infection, which is largely subclinical (7).

Various biomarkers related to inflammation have been examined as potential predictors of preterm birth (8). Complete blood count includes important parameters indicating inflammatory events. Platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio have prognostic significance in diseases associated with systemic inflammation (9,10). Platelets are involved in the maintenance of hemostasis and thrombosis. However, there is a growing recognition that inflammation and immune response have a critical role (11). Mean platelet volume (MPV) is a measure of platelet size. MPV is a parameter indicating platelet function and activity (12). MPV disturbances reflect changes in the level of platelet stimulation or in the rate of platelet production. MPV has been used as a marker of platelet function in inflammatory diseases (13).

Prediction and prevention of preterm birth are recognized as a public health priority because of it's potential to reduce infant and childhood morbidity and mortality. Unfortunately, the progress in this regard has been limited. The present study investigated the role of complete blood count parameters and their changes in the first and third trimesters in predicting preterm birth.

MATERIALS AND METHODS

A retrospective observational study was conducted at Karabuk University Gynecology and Obstetrics Clinic between 2018 and 2020. The study was approved by the Local Ethics Committee of Karabuk University. We included women between the ages of 18 and 42, who had single pregnancies, were followed up at least once in the first and third trimesters, and whose pregnancy resulted in delivery. We excluded patients with pregestational or gestational conditions such as gestational hypertension, diabetes mellitus, hematological problems, thyroid disorders, hyperemesis gravidarum, active infection, threatened miscarriage, and those with a previous history of preterm birth which may complicate pregnancy and change the paramaters (14).

We reviewed the hospital database and collected data of 1047 patients who gave birth at 28 weeks and later. We recorded the maternal age, gravida, parity, the number of births, and body mass indices as baseline data for the patients. We equally examined the complete blood count parameters obtained in the first trimester and recorded the values of white blood cell, neutrophil, lymphocytes, platelet (PLT), red blood cell distribution width, platelet distribution width and MPV. Moreover, we recorded the same parameters in the complete blood count for women during the last trimester as routine follow-up at 1–2 weeks before delivery. We obtained the gestational age at birth, the type of delivery, birth weight of the newborn, and the first and fifth-minute APGAR(Activity-Pulse-Grimace-Appearance-Respiration) scores. The patients were divided into two groups: term (>37 gestational weeks) and preterm births (<37 gestational weeks). Additionally, patients with preterm birth were divided into two subgroups: early preterm birth (<34 gestational weeks) and late preterm birth (34–37 gestational weeks).

NLR and PLR values were calculated according to neutrophil, lymphocyte, and platelet values from complete blood counts. The NLR was obtained by dividing the absolute neutrophil count with the absolute lymphocyte count, while the PLR was calculated by dividing the platelet count with the absolute lymphocyte count. The differences between the third and first trimesters of the NLR, PLR, MPV, RDW, and PDW were also calculated and recorded.

We analyzed data using IBM SPSS Statistics version 21.0. The categorical variables, such as the type of birth, are presented as percentages. The quantitative variables were tested for normal distribution using the Shapiro–Wilk test. Normally distributed variables were analyzed using parametric tests such as T-test and ANOVA, while skewed-distributed variables were analyzed using the Mann–Whitney U and Kruskal–Wallis tests. A p value below 0.05 was considered statistically significant.

RESULTS

We examined 1047 patients, 953 of them had term births, and 94 delivered prematurely. Among this population, 637 underwent cesarean section, and 437 patients delivered pervaginally. While 22 (23%) of the preterm birth cases who had preterm labor did not receive any treatment due to preterm labor before delivery, 72 (77%) cases were hospitalized for preterm labor, received treatment (such as antenatal corticosteroids),

and were discharged during follow-up. They gave birth as preterm on their readmission later on. Delivery occurred before the 34th gestational week in 11 patients (11.7%) who had preterm delivery and between 34 and37 weeks in 83 patients (88.3%). Moreover, 410 patients (39.2%) delivered pervaginally, and 637 patients (60.8%) delivered by cesarean section.

We showed a comparison of the basal parameters and the hematological results detected in the first trimester between term and preterm deliveries in Table 1.

Table 1 Bazal and first trimester complete blood count parameters

	Preterm Birth (-) >37 weeks (n=953)	Preterm Birth (+) <37 weeks (n=94)	p
Gestational age at delivery (days)	272.3 ± 9.0	248.5 ± 9.8	<0.001
Age (years)	28.6 ± 5.5	28.8 ± 5.8	0.807
Gravida	2.2 ± 1.2	2.4 ± 1.3	0.286
Parity	2.0 ± 1.0	2.2 ± 1.1	0.157
Surviving	2.0 ± 1.0	2.2 ± 1.1	0.226
BMI (kg/m^2)	24.8 ± 5.7	25.6 ± 5.4	0.270
First Trimester; Complete blood count parameters			
WBC ($10^3/\mu L$)	8.6 ± 2.2	8.6 ± 2.1	0.758
NEU ($10^3/\mu L$)	5.9 ± 1.9	6.0 ± 1.9	0.717
Lym ($10^3/\mu L$)	2.1 ± 1.0	2.0 ± 0.6	0.621
PLT ($10^3/\mu L$)	254.0 ± 59.3	256.6 ± 55.7	0.765
MPV (f/L)	10.1 ± 1.2	10.1 ± 1.0	0.826
RDW (%)	14.1 ± 2.2	13.9 ± 1.3	0.719
PDW (%)	16.0 ± 0.6	16.0 ± 0.3	0.430
N/L ratio (NLR)	3.1 ± 1.3	3.3 ± 1.9	0.930
P/L ratio (PLR)	130.8 ± 39.3	135.9 ± 43.4	0.290

We could not detect significant differences between the groups. Although NLR and PLR values were higher in the preterm group, this difference was not significant. Table 2 shows the third trimester values and the differences between the third and first trimester data between the term and preterm birth groups. We found that the mean RDW values in the third trimester were significantly higher in cases with preterm delivery. Moreover, the difference between the third and first trimester values for MPV was lower in the preterm group. The first and third trimester values were similar, revealing possibly lower third trimester values. This shows that the low level of MPV could predict higher inflammation in the third trimester of the preterm group.

Table 2 Third trimester complete blood count parameters and the differences between these values among groups

	Preterm Birth (-) >37 weeks (n=953)	Preterm Birth (+) <37 weeks (n=94)	p
Third Trimester; Complete blood count parameters			
WBC ($10^3/\mu L$)	10.4 ± 2.5	10.3 ± 2.6	0.733
NEU ($10^3/\mu L$)	7.7 ± 2.2	7.7 ± 2.3	0.501
Lym ($10^3/\mu L$)	1.9 ± 0.8	2.0 ± 0.5	0.246
PLT ($10^3/\mu L$)	228.4 ± 62.7	233.6 ± 62.8	0.333
MPV (f/L)	10.2 ± 1.2	10.2 ± 1.3	0.603
RDW (%)	15.2 ± 3.0	14.6 ± 2.5	0.002
PDW (%)	16.4 ± 0.4	16.4 ± 0.4	0.617
N/L ratio (NLR)	4.4 ± 2.9	4.1 ± 1.4	0.321
P/L ratio (PLR)	127.0 ± 70.9	125.5 ± 51.5	0.751
Differences between third and first trimester complete blood count parameters			
N/L ratio (NLR)	1.3 ± 2.8	0.9 ± 2.0	0.536
P/L ratio (PLR)	-3.6 ± 70.6	-4.8 ± 51.5	0.973
MPV (f/L)	0.2 ± 1.1	0.0 ± 1.1	**0.038**
RDW (%)	1.0 ± 3.0	0.8 ± 2.4	0.098
PDW (%)	0.4 ± 0.6	0.3 ± 0.3	0.155

[a] p=0.004 [b] p=0.003 [c] p=0.004 [d] p=0.006

In Table 3, the early and late preterm groups were compared with the term group. The mean NLR value for first trimester was significantly higher in the <34-week group. Likewise, the third trimester NLR value was significantly higher in the <34-week group compared with the other groups.

Table 3 First and third trimester complete blood count paramteres and the differences between these values among subgroups

	>37 weeks (n=953)	34-37 weeks (n=83)	<34 weeks (n=11)	p
Gestational age at delivery (days)	272.5 ± 9.4	251.4 ± 4.9	225.7 ± 9.4	<0.001
First Trimester the complete blood count parameters				
N/L ratio (NLR)	3.1 ± 1.3 [a]	3.1 ± 2.0 [b]	4.0 ± 1.2[a, b]	**0.005**
P/L ratio (PLR)	130.8 ± 39.3	131.9 ± 46.3	158.9 ± 55.9	0.210
MPV (f/L)	10.1 ± 1.2	10.1 ± 1.0	10.0 ± 1.1	0.920
RDW (%)	14.1 ± 2.2	14.0 ± 1.2	13.9 ± 1.4	0.630
PDW (%)	16.0 ± 0.6	16.0 ± 0.3	16.0 ± 0.4	0.650
Third Trimester the complete blood count parameters				
N/L ratio (NLR)	4.4 ± 2.9 [c]	4.0 ± 1.5 [d]	5.3 ± 1.2 [c, d]	**0.013**
P/L ratio (PLR)	127.0 ± 70.9	126.7 ± 49.3	149.2 ± 91.5	0.774
MPV (f/L)	10.2 ± 1.2	10.2 ± 1.3	10.1 ± 1.6	0.547
RDW (%)	15.2 ± 3.0	14.9 ± 2.9	14.3 ± 1.4	0.143
PDW (%)	16.4 ± 0.4	16.4 ± 0.4	16.4 ± 0.3	0.790
Differences between third and first trimester complete blood count parameters				
N/L ratio (NLR)	1.3 ± 2.8	0.9 ± 2.0	1.3 ± 1.8	0.679
P/L ratio (PLR)	-3.6 ± 70.6	-5.1 ± 46.9	-9.7 ± 81.7	0.787
MPV (f/L)	0.2 ± 1.1	0.1 ± 1.1	0.1 ± 1.5	0.235
RDW (%)	1.0 ± 3.0	0.9 ± 2.5	0.3 ± 1.3	0.174
PDW (%)	0.4 ± 0.6	0.3 ± 0.3	0.4 ± 0.4	0.434

Although the differences in third and first trimester MPV values were similar between the groups, they were lower in preterm cases. Gestational age at birth, birth weights of the babies, and APGAR values were also compared between the study groups and are shown in Table 4. As we expected, the gestational age at birth, birth weights, and APGAR values were significantly higher in the group with term delivery.

Table 4 Delivery weeks and perinatal outcomes

	Preterm Birth (-) >37 weeks (n=953)	Preterm Birth (+) <37 weeks (n=94)	p
Gestational age at delivery (days)	272.3 ± 9.0	248.5 ± 9.8	<0.001
Newborn Weight	3316.1 ± 431.1	2734.4 ± 539.3	<0.001
APGAR 1 min.	8.8 ± 0.7	8.2 ± 1.2	<0.001
APGAR 5 min.	9.7 ± 0.6	9.4 ± 0.8	<0.001
C/S rate(%)	58.55	85.10	<0.001

DISCUSSION

In this study, the complete blood count parameters in the first and third trimesters in the preterm and term birth groups were similar. However, the difference in MPV between the first and third trimesters was significantly lower in the preterm delivery group compared with the term delivery group (p=0.038). When the preterm delivery group was further divided into early preterm and late preterm subgroups, the MPV differences were similar between the first and third trimesters (p=0.235). This finding demonstrates that the differences in MPV can predict preterm and term deliveries; however, it cannot discriminate early and late preterm deliveries. When NLR was considered in the first and third trimesters, although it was higher in the preterm delivery group, it was not significant. When the subgroups were analyzed, NLR values were significantly higher in the first and third trimesters of

the early preterm group (p=0.005 and p=0.013). However, the differences in NLR between the trimesters were not significant in any group. These findings suggest that a high NLR value in the first and third trimesters may predict possible preterm birth.

Preterm births are responsible for 75% of perinatal mortality and more than half of the long-term morbidity (15). Although preterm labor is currently accepted as a syndrome that can be initiated by infection or inflammation, uteroplacental hemorrhage, uterine overstretching, and different mechanisms; the only process whose molecular pathophysiology has been demonstrated is infection and/or inflammation (5,6).

Normal pregnancy relies on a fine balance between immune tolerance and suppression. It is known that tight regulation of maternal immune function in addition to its inflammatory components is crucial for a successful pregnancy, and that any imbalance between proinflammatory and anti-inflammatory cytokines and chemokines can lead to aberrant inflammation, often seen in complicated pregnancies such as preterm birth. Cytokines play a central role in preterm labor due to inflammation/infection (16). Inflammation is characterized by several basic processes, including exudation of plasma proteins, recruitment of leukocytes, and activation of cell- and plasma-derived inflammatory mediators (17). Infection and infection-induced activation of the inflammatory response are thought to be the leading risk factor for spontaneous preterm birth. As a result, increased production of proinflammatory cytokines is associated with uterine activation and preterm birth, whereas the production of anti-inflammatory cytokines plays an important role in the uterine quiescence during pregnancy (18).

Complete blood count is a simple, inexpensive, and readily available laboratory test in clinical practice. In pregnancy, it contains important parameters indicating inflammatory events in many pathological conditions. Especially, platelet and neutrophil counts elevate and lymphocyte counts decrease (19).

Neutrophils are the most abundant leukocytes in the peripheral blood. Neutrophils with antimicrobial effector mechanisms are deemed the central effectors of acute inflammation, forming the first line of defense of the innate immune response against most bacterial agents. Neutrophils are by far the most dominant leukocyte population in acute chorioamnionitis and in other infectious conditions associated with preterm birth (18). In addition to their role in the maintenance of pregnancy, the role of neutrophils in the induction of parturition remains controversial. Studies have shown that decidual neutrophils contribute to preterm birth by producing various inflammatory mediators and matrix metalloproteinases that promote rupture of fetal membranes (20). Recently, NLR has emerged as a new potential inflammatory biomarker and has been shown to be associated with adverse outcomes in obstetric complications, particularly in preeclampsia, gestational diabetes mellitus, and in different diseases (21,22). There are studies investigating the relationship between preterm birth and NLR in the literature. Akgün et al. showed that high NLR values may be associated with preterm births and newborns with low birth weight. They suggested that the maternal hyperinflammatory state accompanied by high NLR cause low birth weight and preterm birth by affecting the maternal placental fetal unit (14). Tolunay et al. also stated that high NLR may predict preterm delivery in pregnant women presenting with a threat of preterm birth (23). Similarly, in the study by Kurban et al., NLR was found to be higher in the preterm group compared with the term group, and when the preterm labor groups were divided into two subgroups as early and late, it was found that NLR was even higher in the early preterm group (24). We found that the NLR values of both the first and third trimesters were higher than in the early preterm groups. In a recent meta-analysis of 15 studies investigating the relationship between NLR and preterm birth, studies reported high and low levels of NLR. There is heterogeneity in the studies included in this meta-analysis due to differences in the gestational week at which blood samples were collected and in the definition of preterm labor. Nevertheless, the meta-analysis concluded that high NLR was associated with preterm birth (25). In our study, high NLR levels were found in both the first and third trimesters in the early preterm birth group. Therefore, high NLR levels in the first and last trimesters may be used as predictors of preterm birth.

While platelets are involved in the maintenance of hemostasis, many studies have shown that increased platelet count is associated with infection, inflammation, and malignancy (11,12,26). It has been reported that platelet activation increases after tissue damage and release of inflammatory mediators (12). MPV is a parameter indicating platelet function and activity (12). MPV is used as a marker of platelet function in inflammatory diseases. In inflammatory diseases, the number of circulating large platelets increases, and large numbers of large platelets migrate to sites of inflammation. The depletion of large platelets at the site of inflammation leads to an inverse relationship between MPV and platelet count. Cardio- and cerebrovascular disorders and low-grade inflammatory conditions prone to arterial and venous thrombosis are associated with high MPV, whereas low MPV levels are found in high-grade inflammatory diseases, such as active rheumatoid arthritis or familial Mediterranean fever attacks (27). In normal pregnancies, an increase in MPV is observed in the third trimester, but increased or decreased MPV levels have been reported in different pathologic conditions complicating pregnancy. In two different meta-analyses investigating MPV levels in preeclampsia and gestational diabetes mellitus, an increase in MPV was reported in both conditions (28,29). On the other hand, Ekin et al. found that low MPV level in the first trimester could be used as a more effective marker rather than platelet count in the prediction of preterm premature rupture of membranes (30). Similarly, in the study by Ersak et al. investigating platelet indices in placental abruption, low MPV levels were associated with a high degree of inflammation and accompanying platelet depletion (31). Because inflammation plays a critical role in the pathogenesis of preterm labor, changes in platelet function and thus in MPV are expected. In their study, Kurban et al. suggested that low MPV values predict preterm birth (24). In our study, no difference was observed between the first and third trimester MPV levels in the term and preterm birth groups; however, when the MPV change between the first and third trimesters was investigated, the increase in MPV was significantly lower in the preterm group. To our knowledge, this study is the first to evaluate MPV levels between the trimesters by taking serial complete blood count in the literature.

Because of the retrospective design of our study, there may be unidentified confounding variables that can affect the outcome of the study. Our study cohort consisted of women from a single hospital; therefore, it may be difficult to generalize our results to the entire female population. Additionally, the small number of patients in the preterm birth group may be considered a li-

mitation in terms of the study results. A strength of our study is that the sample size is larger than the studies in the literature. Another is that this is the first study in the literature that we know of in which the complete blood count in pregnant women is examined separately in the first and third trimesters, and the differences in these measurements are compared.

In conclusion, a complete blood count is a routine test for pregnancy, which is simple and cheap. To the best of our knowledge, this study is the first to evaluate the first and third trimester values of complete blood count parameters and its combinations, and the association between the differences in these parameters with preterm delivery. In our study, the increase in MPV between the first and third trimesters was significantly lower in the preterm group, and NLR was higher in both the first and third trimesters in the early preterm group. We think that NLR value in the first and third trimesters and MPV changes between trimesters can be used in the prediction of preterm birth due to inflammatory processes. Further studies are needed to validate these findings in clinical practice.

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