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Comparison of Blood NLR and PLR Values Between Pregnant Women Diagnosed with Intrauterine Death (IUEX) After 20 Weeks and a Healthy Control Group

20 Haftadan Sonra İntrauterin Ölüm (IUEX) Tanısı Konulan Hamile Kadınlar İle Sağlıklı Kontrol Grubu Arasında Kan NLR ve PLR Değerlerinin Karşılaştırılması

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ABSTRACT

Aim: The aim of this study is to compare NLR and PLR ratios between pregnant women diagnosed with intrauterine fetal death after 20 weeks and a healthy control group of pregnant women.

Materials and Methods: This was a retrospective, single-center study that included 180 patients, comprising 90 pregnant women diagnosed with intrauterine ex(ıuex)after 20 weeks and an equal number of healthy controls. NLR (NLR = neutrophil/lymphocyte) and PLR (PLR = platelet/lymphocyte) were calculated. Data distribution was compared using the Mann–Whitney U test when not normally distributed. ROC analysis was used to calculate cutoff points for NLR and PLR predicting IUEX.

Results: Both NLR and PLR were significantly lower in the IUEX group compared with controls (NLR: p=0.020; PLR: p<0.001). ROC analysis identified PLR cutoff of 47.31 with 100% sensitivity and 100% specificity (AUC=0.983; p<0.001). For NLR, the best cutoff was 3.95 with 63% sensitivity and 32% specificity (AUC=0.603; p=0.019).

Conclusion: Our findings suggest that PLR may serve as a stronger biomarker for predicting intrauterine death after 20 weeks compared with NLR, though prospective multicenter validation is required to standardize thresholds and assess clinical utility.

Keywords: Intrauterine Death, NLR = nötrofil/lenfosit, PLR = trombosit/lenfosit

ÖZ

Amaç: Bu çalışmanın amacı, 20 haftadan sonra intrauterin fetal ölüm tanısı konulan hamile kadınlar ile sağlıklı kontrol grubu hamile kadınlar arasında NLR ve PLR oranlarını karşılaştırmaktır.

Gereç ve Yöntemler: Retrospektif, tek merkezli bir çalışma olup, 20 haftadan sonra intrauterin ölüm tanısı konulan 90 gebe ile eşit sayıda sağlıklı kontrol içeren 180 hasta dahil edildi. NLR (NLR = nötrofil/lenfosit) ve PLR (PLR = trombosit/lenfosit) hesaplandı. Verilerin dağılımı normal olmama durumunda Mann–Whitney U testi ile karşılaştırıldı. ROC analizi ile NLR ve PLR için IUEX öngörüsü belirleyen kesim noktaları hesaplandı.

Sonuçlar: NLR ve PLR, kontrol grubuna kıyasla IUEX grubunda anlamlı olarak daha düşüktü (NLR: p=0,020; PLR: p<0,001). ROC analizi, %100 duyarlılık ve %100 özgüllük ile 47,31 PLR kesme değerini belirledi (AUC=0,983; p<0,001). NLR için en iyi kesme değeri %63 duyarlılık ve %32 özgüllük ile 3,95 idi (AUC=0,603; p=0,019).

Sonuç: Bulgularımız, PLR'nin NLR'ye kıyasla 20 haftadan sonra intrauterin ölümü öngörmede daha güçlü bir biyomarker olabileceğini göstermektedir, ancak eşik değerleri standartlaştırmak ve klinik yararını değerlendirmek için prospektif çok merkezli bir doğrulama gereklidir.

Anahtar Kelimeler: İntrauterin ölüm, nötrofil lenfosit oranı, platelet lenfosit oranı

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INTRODUCTION

Fetal death is defined by the World Health Organization (WHO) as death occurring at any time during pregnancy. The global stillbirth rate is an average of 13.9 per 1,000 births, and the stillbirth rate for deaths occurring at ≥20 weeks of gestation is 23.0 per 1,000 births (1).

Fetal death is the result of various maternal, fetal, and placental disorders (2).

Fetal mortality is associated with congenital anomalies, infections, growth restriction, and underlying maternal medical conditions. Fetal mortality in late pregnancy is caused by both maternal medical conditions and, more commonly, placental abruption and previa, cord prolapse, other delivery and birth complications, or unexplained obstetric disorders that develop at the time of delivery (3).

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) indicate oxidative stress and associated endothelial dysfunction. These ratios have been found to be elevated in conditions such as preeclampsia and IUGR (3-6).

Endothelial damage and oxidative stress are thought to be possible causes of intrauterine fetal death. The aim of this study is to compare NLR and PLR ratios between pregnant women diagnosed with intrauterine fetal death after 20 weeks and a healthy control group of pregnant women.

MATERIALS AND METHODS

Study Population

This study was retrospective, single-center, and conducted at a tertiary care hospital. Patients who were diagnosed with intrauterine fetal ex and treated during pregnancy follow-ups between January 2022 and December 2024 and had a gestational age of over 20 weeks were included in this study.

Approval was obtained from the Ethics Committee (TABED-1-25-1993) for this study. The Helsinki Declaration guidelines were followed at every stage of the study. The gestational age of the patients was determined based on the date of their last menstrual period. Clinical and demographic information, age, parity, gravida, body mass index (BMI), presence of maternal chronic disease, DMH use, smoking status, gestational age at the time of intrauterine ex, history of IUEX in previous pregnancies, routine hemogram levels taken at the time of diagnosis, biochemical values, fetal gestational age, and birth weight were recorded.

NLR: Neutrophil/Lymphocyte

PLR: Platelet/Lymphocyte were calculated.

Patients included in the control group in this study were randomized and selected from healthy pregnant women. One control patient was selected for each patient in the study group. Care was taken to ensure an equal distribution of age, gestational weeks, gravidity, and body mass index (BMI) among patients in the study and control groups.

In this study, patients with multiple pregnancies, organ transplants, immunodeficiency, hypertension, diabetes, active or chronic viral hepatitis and autoimmune hepatitis, and patients with known major fetal chromosomal and cardiac anomalies and structural anomalies, as well as patients with missing or inaccessible data, were excluded from the study.

Statistical Analysis

In this study, the sample size was analyzed using G Power software (version 3.1; Franz Foul, Universitat Kiel, Kiel, Germany). A sample size was calculated for a 0.05 (two-tailed) p-value and 95% power with an effect size of 0.80 (large). A sample size of 43 patients per group was calculated.

The SPSS 22.0 (SPSS Inc., Chicago, IL, USA) statistical program was used for data analysis. The Kolmogorov–Smirnov test and Shapiro–Wilk test was used to analyze the normality of the data distribution. The Mann–Whitney U test was used to compare variables that did not follow a normal distribution. Descriptive analyses used median min-max for non-normally distributed variables. The chi-square test was used to compare categorical variables. The ROC curve was used to determine the cutoff point for NLR and PLR in predicting IUEX.

RESULTS

A total of 180 patients were included in this study, comprising 90 patients diagnosed with IUEX and 90 healthy control groups.

The clinical and demographic data and blood test results for each patient are presented in Table 1. No differences were observed between the two groups in terms of age, parity, or number of abortions ($p>0.05$).

This study was conducted to compare various hematological and biochemical parameters between the IUEX group and the healthy group. The main findings of the study are as follows:

Table 1. Patients' demographic data and blood results

Variables	IUEX group N:90 Median(interquartel)	Heathy Group N:90 Median(interquartel)	P value
Age	29(8)	31(9)	0.603
Gravida	2.0(2.0)	2.0(1.0)	0.222
Parity	1.0(2.0)	1.0(1.0)	0.198
BMI	32(8)	31(6)	0.234
Hb(×10⁹/L)	11.3(1.5)	11.7(2.6)	**<0.001**
WBC(×10⁹/L)	10.64(4.0)	9.51(3.5)	**<0.001**
Neu(×10⁹/L)	7.79(3.0)	7.46(0.39)	**<0.001**
lymphocyte(×10⁹/L)	1.9(1.0)	1.54(0.95)	**<0.001**
monocyte(×10⁹/L)	0.53(0.0)	4.3(0.26)	**<0.001**
eosinophil(×10⁹/L)	0.09(0.0)	0.6(0.5)	**<0.001**
Platelet(×10⁹/L)	253(89)	213(86)	**<0.001**
AST(U/L)	15(6.0)	13(8.0)	0.052
ALT(U/L)	14(9.0)	19(12)	**<0.001**
NLR	4.18(1.72)	4.8(7.0)	0.020
PLR	1.30(0.82)	1.47(1.2)	**<0.001**

Values were given as median (interquartel). Hb: Hemoglobin, Neu:Neuthrophile, WBC: White Blood Cell.AST: Aspartate Transferase, ALT: Alanine Transferase
P value < .05 was considered statistically significant.

No significant differences were found between the groups in terms of demographic and obstetric parameters: When age, gravida, and parity values were compared, P values ranged from 0.222 to 0.603 and were not statistically significant.

There were notable differences in terms of hematological indicators. Differences between the groups in some blood values, such as Hb, WBC, Neu, leukocyte subtypes (lymphocyte, monocyte, eosinophil), and platelet count, were statistically significant (P<0.001 to<0.001). Hb, WBC, Neu, Lymphocyte, Monocyte, and Eosinophil values showed a different distribution in the IUEX group.

When liver function tests were examined, a significant difference was found between the groups in the ALT value (P<0.001), while for AST, a similar borderline or near-significant difference may have been observed (P = 0.052).

Significant differences were also observed between the groups in terms of NLR (neutrophil/lymphocyte ratio) and PLR (platelet/lymphocyte ratio) (figure1). These ratios were found to be lower in the IUEX group (P = 0.020 and P<0.001). The distribution of these ratios in the IUEX group indicates that there may be potential differences in immunological or inflammatory responses.

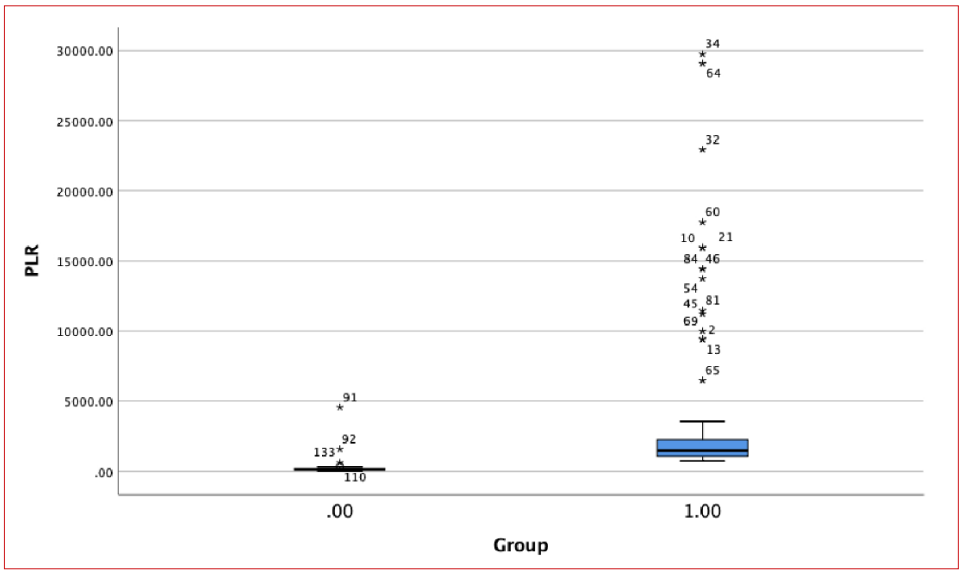

Figure 1. PLR results between the IUEX group and the control healthy group.

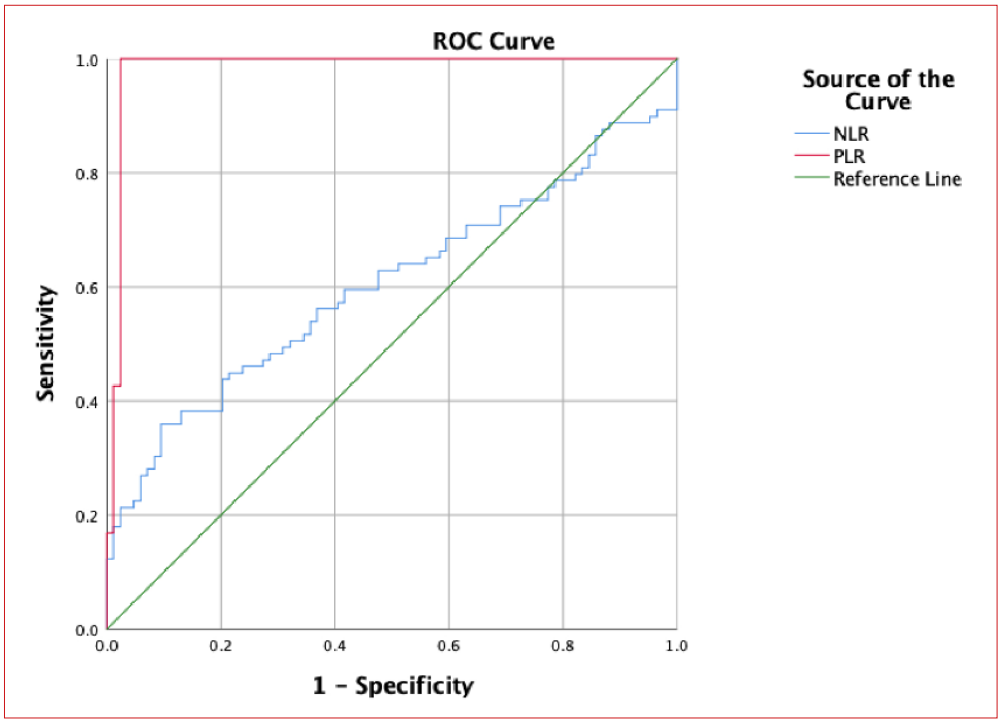

Figure 2. Receiver operating characteristic (ROC) curve analysis of predictors of IUEX

Area Under Curve

Variables	Area	Std. Error[a]	Asymptotic Sig.[b]	Cut-off	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
NLR	,603	,044	,019		,518	,688
PLR	983	.012	.000		.960	1.000

The ROC analysis revealed that the optimal cutoff point for NLR in predicting IUEX was determined to be 3.95, with a sensitivity of 63% and a specificity of 32% (AUC=0.603; p=0.019) (Figure 2).

The optimal cutoff point for the PLR value was determined to be 47.31 with 100% sensitivity and 100% specificity (AUC=0.983; p<0.001) (Figure 2).

DISCUSSION

In this study, the first trimester blood results of pregnant women diagnosed with intrauterine ex (IUEX) after 20 weeks were compared with the NLR and PLR ratios of healthy control pregnancies. It was found that NLR and PLR ratios were lower in pregnancies diagnosed with IUEX. It was determined that PLR was a better predictor of IUEX than NLR.

Among pregnancy complications, intrauterine death occurring after the 20th week of pregnancy is the most emotionally devastating for patients and clinicians. There is a racial difference in stillbirth rates. The stillbirth rate is higher in black mothers compared to white mothers (7).

Determining the cause of stillbirth is difficult, and despite intensive investigation of potential causes, many cases remain unexplained. The first attempt to classify causes of perinatal death was published by Baird using the Aberdeen clinicopathological classification (8). This classification was based on clinical information. In 1958, Butler and Bonham developed a new classification based on the British perinatal death survey and including post-autopsy findings (9). In 1977, Naeye added placental findings to a proposed new classification (10). In 1980, Wigglesworth introduced the nine-category classification system currently most widely used in reporting perinatal mortality rates (11,12). Most of this classification system consists of unexplained

deaths. Finding a marker that could be detected in the first trimester was the goal of our IUEX study.

Many parameters such as fetoplacental proteins, combined tests, antiphospholipid antibodies, and placental pathologies have been examined to predict SB (13,14). In a study examining blood parameters, NLR and PLR were examined in the 1st and 3rd trimesters, but no differences were found (15). In our study, these parameters were examined at the time of diagnosis, and both ratios were found to be significantly lower.

The relationship between NLR and PLR and miscarriages, IUGR, preeclampsia, birth weight, and stillbirths due to placental abruption has been investigated in the literature. detected in birth weight and preeclampsia (4,5). This indicates that NLR and PLR values change in conditions related to nutrition. In this study, since these values were examined at the time of diagnosis, the values differ. This indicates that nutrition is impaired in IUEX.

This study has limited generalizability of findings due to its retrospective design and single-center nature; missing records and uncertainties may lead to potential bias. Sample size may result in insufficient statistical power, and residual confounders (such as nutritional status, socioeconomic differences, micronutrient deficiencies) may not be fully controlled. The fact that NLR and PLR were measured only at the time of diagnosis limits the causal relationship. In addition, variations in laboratory reference ranges and measurement methods may affect generalizability. For all these reasons, it is recommended that the results be confirmed in prospective, multicenter studies in the future.

In conclusion, this study shows that NLR and PLR measured at the time of diagnosis are significantly lower in pregnant women diagnosed with intrauterine death after 20 weeks compared to healthy controls; this finding can be interpreted as a potential biomarker associated with endothelial dysfunction and changes in the inflammatory response. However, prospective, multicenter, and large-scale studies are needed to definitively support the clinical use of these markers for early diagnosis and risk stratification. Considering the varying results in the literature, there is also a need for a clinical roadmap showing how these parameters can be used in management decisions, along with the standardization of NLR and PLR and the determination of their reference ranges. Therefore, our studies point to a potential prognostic value in pregnant women diagnosed with IUEX, and further evidence is waited for reliable clinical application.

Ethical approval statement: The study received ethical approval from the Ethics Committee of Ankara City Hospital (TABED-1-25-1993). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

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Author contribution: BBÖ: Design the method to achieve results,Data collecting and processing,Literature scan,Article writing; DS: Article writing, Critical examination,Critical examination

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