

## Original Article

## Can Preoperative Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and APRI Score Reliably Differentiate Uterine Sarcomas from Leiomyomas?

### Preoperatif Nötrofil Lenfosit Oranı, Platelet Lenfosit Oranı ve APRİ Skoru Uterin Sarkomları Myomlardan Ayırt Edebilir mi?

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#### ABSTRACT

**Aim:** Uterine sarcomas are one of the aggressive gynecologic malignancies. There is still no optimal test for preoperative diagnosis of uterine sarcomas. The aim of this study was to evaluate the role of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and APRI score in predicting preoperative uterine sarcoma.

**Materials and Methods:** Patients operated on between January 2010 and December 2020 histopathologically diagnosed as sarcoma were included in the study group. Patients who were histopathologically diagnosed with myoma uteri were included as the control group during the same period. Age, BMI (body mass index), gravida, parity, preoperative mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width (RDW), NLR, PLR and APRI scores were recorded.

**Results:** When comparing patients with fibroids and sarcomas, hemoglobin [12.3 g/dl (6.4-15.4) vs. 11.3 g/dl (6-17), p=0.008, respectively], hematocrit [38.5% (22-48.7) vs. 35.9% (21.4-52.1), p=0.002, respectively] and lymphocyte levels [2.2 10<sup>3</sup>/L (0.9-13.8) vs. 1.8 10<sup>3</sup>/L (1-2.6), p=0.001, respectively] were significantly lower and NLR [1.7 (0.2-10.1) vs. 2.3 (1.4-5.9), p=0.001, respectively] and PLR [124 (10.9-352.1) vs. 180.4 (84.9-284.3), p=0.001, respectively] were significantly higher in sarcoma group. The optimal cut-off value for NLR and PLR was calculated to be 2.04 with sensitivity and specificity of 59.4% and 59.5%, respectively, and 150.7 with sensitivity and specificity of 65.6% and 64.7%, respectively.

**Conclusion:** Preoperative NLR and PLR rates can be useful markers for diagnosing uterine sarcoma. Randomized controlled large series studies are necessary to make a definitive statement.

**Keywords:** Uterine sarcoma, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, APRI score

#### ÖZET

**Giriş ve Amaç:** Uterin sarkomlar nadir görülen, agresif seyirli jinekolojik kanserlerden biridir. Preoperatif optimal tanı testi hala bulunmamaktadır. Çalışmamızın amacı preoperatif uterin sarkomu öngörmeye nötrofil-lenfosit oranı (NLR), platelet-lenfosit oranı (PLR) ve APRİ skoru değerlendirmektir.

**Yöntem ve Gereçler:** Ocak 2010 ile Aralık 2020 tarihleri arasında histopatolojik sarkom tanısı alan hastalar çalışmaya dahil edildi. Aynı dönemde histopatolojik myom uteri tanısı alan hastalar kontrol grubu olarak alındı. Yaş, vücut kitle indeksi, gravida, parite, preoperatif ortalama platelet hacmi (MPV), platelet dağılım genişliği (PDW), kırmızı hücre dağılım genişliği (RDW), NLR, PLR and APRİ skoru kaydedildi.

**Bulgular:** Sarkom ve myom tanılı hastalar karşılaştırıldığında, sarkom hastalarında hemoglobin [sırasıyla 12.3 gr/dl (6.4-15.4) ve 11.3 gr/dl (6-17), p=0.008], hematokrit [sırasıyla %38.5 (22-48.7) ve %35.9 (21.4-52.1), p=0.002] ve lenfosit seviyeleri [sırasıyla  $2.2 \times 10^3/L$  (0.9-13.8) ve  $1.8 \times 10^3/L$  (1-2.6), p=0.001,] anlamlı olarak düşük, NLR [sırasıyla 1.7 (0.2-10.1) ve 2.3 (1.4-5.9), p=0.001] ve PLR [sırasıyla 124 (10.9-352.1) ve 180.4 (84.9-284.3), p=0.001] anlamlı olarak yüksek saptandı.

**Tartışma ve Sonuç:** Preoperatif NLR ve PLR oranları uterin sarkom tanısında kullanılabilecek markırlardır. Bu konuda kesin konuşabilmek adına randomize kontrollü geniş serili çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Uterin sarkom, nötrofil lenfosit oranı, platelet lenfosit oranı, APRI skoru

## Introduction

Uterine sarcomas account for 1% of all gynecologic malignancies and 3-7% of uterine malignancies [1,2]. The most common histological types are leiomyosarcoma and endometrial stromal sarcoma. With the last published classification, carcinosarcoma was excluded from the classification of uterine sarcomas [3]. Patients usually present to the clinic with postmenopausal bleeding or premenopausal abnormal uterine bleeding less commonly, they complain of an abdominal mass and pain [4].

The definitive diagnosis of uterine sarcoma is made by histopathologic examination of the hysterectomy material. Unfortunately, there is still no optimal finding or test for preoperative differentiation of fibroids from sarcomas. Clinically, postmenopausal, rapidly growing uterine masses are suspicious [5], but some studies have shown that fibroids can also grow rapidly [6,7]. Although the sensitivity of preoperative diagnostic imaging is high in studies with small numbers of cases, there are not enough studies on this topic [8].

There are publications showing that parameters such as platelet count, mean platelet volume (MPV), platelet distribution width (PDW), neutrophil count, red cell distribution width (RDW) indicate the diagnosis and severity of some hematological diseases [9-11]. In addition, inflammation and oxidative stress are also thought to play a role in the diagnosis of many gynecologic malignancies [12-14].

In this study, we investigated whether preoperative MPV, PDW, neutrophil-to-lymphocyte ratio (NLR), RDW, platelet-to-lymphocyte ratio (PLR), and AST to Platelet ratio Index (APRI) score have any value in predicting uterine sarcoma.

## Materials and Method

### Study population

Permission for the study was obtained from the Ethics Committee of our hospital (29.09.2021/ 2021/93). Patients operated on between January 2010 and December 2020 with a provisional diagnosis of myoma uteri (M. uteri) and histopathologically diagnosed as leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), and adenocarcinoma were included in the study group. Patients who underwent surgery with a provisional diagnosis of M. uteri and were pathologically diagnosed with M. uteri were included as the control group during the same period. Patients with other gynecological malignancies and known inflammatory diseases, ovarian cysts, endometriosis, pelvic inflammatory disease or adenomyosis were excluded from the study.

Age, BMI (body mass index), gravida, parity, preoperative whole blood parameters [hemoglobin, hematocrit, lymphocytes, neutrophil granulocytes, monocytes, platelet count, MPV, PDW, RDW], and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were retrospectively obtained from medical records.

Measurement of NLR, PLR, and APRI score:

The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. The APRI score was defined as  $\text{AST} / \text{upper limit of normal range} / \text{platelet count} (10^9/\text{L}) \times 100$ . The upper limit of normal range for AST was taken as 40 U/L.

Demographic characteristics, hematologic parameters, whether NLR, PLR, and APRI scores differed between fibroid and sarcoma patients, and the role of NLR, PLR, and APRI score in predicting preoperative uterine sarcoma were investigated.

#### Statistical Analysis

The statistical analysis was performed using the Statistics Package for Social Sciences software (ver. 22.0; SPSS Inc., Armonk, NY: IBM Corp). The distribution of all variables were determined using Shapiro Wilk normality test. Mann-Whitney U test was used for nonparametric variables and expressed as median (min-max). Spearman correlation analyses were used to determine the degree of associations among the variables. Receiver operating Characteristics (ROC) curve analysis was used to determine the optimal cut off values of statistically significant variables to predict the treatment modality. Optimal cut-off value was determined according to Youden's index (sensitivity + specificity -1). The results were evaluated in 95% confidence interval and  $p < 0.05$  was considered as significant.

#### Results

A total of 192 patients were enrolled in this study. The final pathology result was fibroids in 158 (81.9%) of all study participants and sarcoma in 34 (18.1%).

The median age of the patients included in the study was 46 (28-71), their gravida was 3 (0-

9), parity was 2 (0-7), and BMI was 30  $\text{kg}/\text{m}^2$  (17-45  $\text{kg}/\text{m}^2$ ). When comparing patients with fibroids or sarcomas, hemoglobin [12.3 g/dl (6.4-15.4) vs. 11.3 g/dl (6-17),  $p=0.008$ , respectively], hematocrit [38.5% (22-48.7) vs. 35.9% (21.4-52.1),  $p=0.002$ , respectively] and lymphocyte levels [ $2.2 \times 10^3/\text{L}$  (0.9-13.8) vs.  $1.8 \times 10^3/\text{L}$  (1-2.6),  $p=0.001$ , respectively] were significantly lower in the sarcoma group.

NLR [1.7% (0.2-10.1) vs. 2.3% (1.4-5.9),  $p=0.001$ , respectively] and PLR [124 (10.9-352.1) vs. 180.4 (84.9-284.3),  $p=0.001$ , respectively] were found to be significantly higher in sarcoma group. Age, gravida, BMI, neutrophil count, monocyte count, platelet count, MPV, RDW, PDW, ALT, and AST and APRI values were similar in both groups ( $p > 0.05$ ). The comparison of the two groups is summarized in Table 1.

In the ROC-analysis, NLR (AUC= 0.696,  $p=0.001$ ) and PLR (AUC= 0.719,  $p=0.001$ ) ratios significantly predicted the diagnosis of sarcoma. The optimal cut-off value for NLR and PLR was calculated to be 2.04 with sensitivity and specificity of 59.4% and 59.5%, respectively, and 150.7 with sensitivity and specificity of 65.6% and 64.7%, respectively (Figure 1).

#### Discussion

This study investigated the role of preoperative inflammatory markers in predicting sarcoma diagnosis in women operated for myoma uteri. In the present study, hemoglobin, hematocrit, and lymphocyte count were low, and NLR and PLR were high in patients with sarcoma as the final pathology outcome. Moreover, pre-operative NLR and PLR ratios predicted sarcoma diagnosis with a sensitivity of 59.4% and specificity of 59.5% and a sensitivity of 65.6% and specificity of 64.7%, respectively.

Sarcomas are a rare but aggressive disease arising from uterine smooth muscle cells. The 5-year survival rate of FIGO stage 3-4 uterine

Table 1. Comparison of groups in terms of demographic and laboratory parameters.

	FIBROID (n=158) Median (min-max)	SARCOMA (n=35) median (min-max)	p
Age (year)	45.5 (28-58)	47 (28-71)	NS
Gravity	3 (0-9)	3 (0-9)	NS
Parity	2 (0-6)	3 (0-7)	0.03
BMI (kg/m <sup>2</sup> )	30 (17-41)	31.2 (24-45)	NS
Hemoglobin (g/dl)	12.3 (6.4-15.4)	11.3 (6-17)	0.008
Hematocrit (%)	38.5 (22-48.7)	35.9 (21.4-52.1)	0.002
Lymphocyte(10 <sup>3</sup> /L)	2.2 (0.9-13.8)	1.8 (1-2.6)	<0.001
Neutrophil(10 <sup>3</sup> /μL)	3.9 (2-14.9)	3.7 (2.1-12.7)	NS
Monocyte (10 <sup>3</sup> /μL)	0.3 (0.1-3)	0.3 (0.2-1.1)	NS
Platelet (10 <sup>3</sup> /mm <sup>3</sup> )	282 (29-664)	284 (164-493)	NS
MPV (fL)	8.4 (6.3-11.4)	8.5 (6.2-12.6)	NS
RDW(%)	15.3 (12.3-49.8)	14.9 (2-42.9)	NS
PDW(%)	48.4 (13.7-68.8)	49.7 (12.5-70.4)	NS
ALT (U/L)	14 (6-251)	16 (7-106)	NS
AST (U/L)	17 (10-102)	18 (11-139)	NS
NLR	1.7 (0.2-10.1)	2.3 (1.4-5.9)	<0.001
PLR	124 (10.9-352.1)	180.4 (84.9-284.3)	<0.001
APRI score	0.1 (0.02-0.5)	0.1 (0.03-0.4)	NS

NS: Non-significant MPV; Mean Platelet volume, RDW; Red Cell Distribution Width ALT, Alanine aminotransferase, AST; Aspartate aminotransferase NLR; Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, APRI: AST to Platelet ratio Index

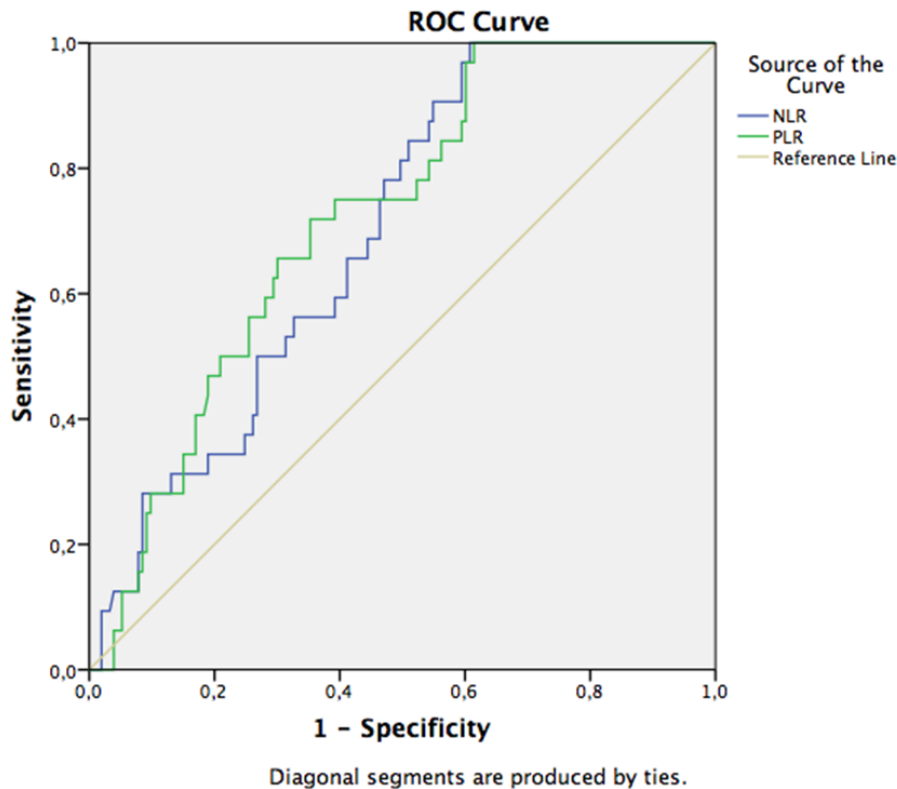


Figure 1. ROC analyses of NLR and PLR

leiomyosarcomas is 25-33% [15]. In recent years, preoperative myoma-sarcoma differentiation has become more critical than ever due to the increase in minimally invasive surgery and the risk of sarcoma spread during laparoscopic myomectomy and morcellation [16].

Sarcomas are often diagnosed incidentally by examination of hysterectomy or myomectomy material [17]. Diffusion-weighted MRI, one of the imaging modalities used in preoperative evaluation, successfully differentiates between sarcoma and fibroma in studies of a small number of patients [18,19]. Goto et al. studied 130 patients with uterine fibroids and ten sarcomas and diagnosed sarcoma with a specificity of 93.8% and a sensitivity of 95.2% using MRI with gadolinium contrast [20]. In addition, they published preliminary results with the combined use of T2-weighted and diffusion-weighted 3-T MRI in eight sarcoma patients with a sensitivity of 100% and a specificity of 100%. Despite the high success rates, this type of MRI in preoperative diagnosis needs to be supported by further studies due to the small number of patients, accessibility, and high cost [21].

Uterine sarcomas are most commonly seen clinically in the postmenopausal period, with a median age of onset of 60 years [22]. Hosh et al. reported that the incidence of sarcoma (6.4/10 vs. 1.5/10,  $P < 0.0001$ ) is approximately 4-fold higher in women older than 50 years compared with younger patients [23]. However, it can also occur at a young age [24]. Chen et al. clinically compared 66 patients with uterine sarcoma and patients with 66 fibroid. They found that the sarcoma patients had postmenopausal, solitary, rapidly growing masses [25]. In our study, the mean age of the patients with myoma and leiomyosarcoma was 45.5 and 47 years, respectively, which is consistent with the literature.

Obesity is known to increase cancer risk for all gynecologic cancers, especially

endometrial cancer [26]. Borge et al. found that the risk of uterine sarcoma was increased 1.88-fold in patients with  $BMI \geq 30$  [27]. In our study, BMI was above 30 in both fibroid and sarcoma patients, which may be due to the gradual increase in obesity in society in recent years, the fact that fibroids are estrogen-dependent tumors, and thus the increased estrogen produced by peripheral adipose tissue.

It has been shown that malignancies may be associated with systemic inflammation [28]. A decrease in lymphocyte count has been noted in cancer patients [29]. It has also been shown that inflammatory markers can be used in the diagnosis of gynecologic malignancies [30,31]. Inflammatory markers have been studied in the preoperative diagnosis of uterine sarcomas. Cho et al. showed that an elevated neutrophil-to-lymphocyte ratio (NLR 2.1), large tumor size (8.0 cm), and low body mass index ( $BMI \leq 20$ ) were independent risk factors for uterine sarcoma ( $p = 0.014$ , 0.048, and 0.048, respectively) [32]. Kim et al. studied 55 uterine sarcoma patients and found that a cut-off value of  $NLR \geq 2.12$  could be used in the diagnosis of preoperative uterine sarcoma with a sensitivity of 75.5% and a specificity of 70.3% [33]. Zhang et al. used a new scoring system in which a cut-off value of  $NLR \geq 2.8$  (OR 3.032, 95%CI 1.288-7.13) predicted preoperative sarcoma with a sensitivity of 0.800 and a specificity of 0.778 using age, tumor size, NLR, platelets, and LDH [34]. Our study found that preoperative hemoglobin, hematocrit and lymphocyte rates were significantly lower in sarcoma patients than in myoma patients. Sarcoma was detected by NLR ratio with sensitivity of 59.4% and specificity of 59.5% and PLR ratio with sensitivity of 65.6% and specificity of 64.7%; this result proves that these parameters are diagnostic markers for sarcoma unlike other studies. In our study, unlike other studies, the APRI score was also evaluated, and it was found that the preoperative APRI

score was similar in patients with fibroids and sarcomas.

The association of inflammatory markers with survival in sarcoma patients has also been investigated. Five-year progression-free survival was 69.0% and 94.4% in cases with high and low preoperative lymphocyte/monocyte ratios (cut-off value of 5.86), respectively ( $p = 0.024$ ) [35]. On the other hand, Jeong et al. found that overall survival and disease-free survival were worse in sarcoma patients with an NLR of 2.60. Moreover, PLR, CA125, and LDH had no effect on survival [36].

Considering the frequency of sarcomas, a large number of patients and the combined evaluation of NLR, PLR and APRI scores are the strengths of the study. The limitations of the study are its retrospective design and the lack of evaluation of serum markers such as CA125 and LDH.

Uterine sarcomas are rare but aggressive malignancies. Preoperative diagnosis cannot be definitively established yet. Preoperative NLR and PLR rates can be useful for diagnosing uterine sarcoma. Randomized controlled large series studies are necessary to make a definitive statement.

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