RESEARCH ARTICLE

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Neutrophil-to-Lymphocyte Ratio (NLR) for Preoperative Differentiation between Uterine Leiomyosarcoma (LMS) and Uterine Leiomyoma: A Case-Controlled Study

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Abstract

Background: Differentiating uterine LMS from uterine leiomyoma is difficult. Therefore, this study aimed to compare preoperative NLR of uterine leiomyosarcoma (LMS) with leiomyoma and secondary objective aimed to identify the clinical characteristics to distinguish between uterine LMS and uterine leiomyoma including the appropriate NLR cut off value to differentiate LMS from leiomyoma. **Methods:** This was a matched case-controlled study with 1:4 ratio. We collected data of patients with uterine LMS and leiomyoma from 2011 to 2020 at King Chulalongkorn Memorial Hospital. Patients with uterine LMS (case group) and leiomyoma (control group) were matched in terms of year of the surgery and size of the uterine mass. Statistical analysis was conducted using SPSS version 22.0 and STATA version 17. Conditional logistic regression analysis with a p-value of <0.05 was used. **Results:** Twenty-seven patients who were diagnosed with uterine LMS met the inclusion criteria; 13 patients who had incomplete data and one patient who was had concurrent breast cancer were excluded. Thirteen patients were included in the final analysis. From 2,587 patients in control group; 52 patients were matched. The baseline characteristics in both groups were comparable except for menopausal status Women with uterine LMS had a higher NLR than those with leiomyoma (mean, 4.56 ± 2.5 and 2.4 ± 1.15 in the case and control groups, respectively). Conditional logistic regression determined that the NLR cut-off value of 2.8 was a statistically significant factor for determining uterine LMS (OR = 3.24; 95% CI 1.01–10.43). No significant difference was found in the other factors. **Conclusions:** Patients who were diagnosed with uterine LMS had a significantly higher NLR than those diagnosed with leiomyoma. The NLR is a simple and effective method for predicting the presence of a uterine LMS in patients who are pre-operatively diagnosed with a uterine mass.

Keywords: leiomyoma- uterine LMS- Leiomyosarcoma- neutrophil-to-lymphocyte ratio- NLR

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Introduction

Uterine leiomyomas are benign neoplasms that commonly occur in the female reproductive system. Most of the women with uterine leiomyomas are asymptomatic; however, those with clinical symptoms can experience heavy menstrual bleeding, pelvic pain and pressure, and a pelvic mass. Ultrasonography is the standard diagnostic test to detect uterine leiomyomas (Cramer et al., 1990; Stewart et al., 2016).

Uterine LMS is a rare and malignant neoplasm that accounts for 1% of all gynecologic malignancies and 3%–7% of all uterine malignancies. Women diagnosed with this neoplasm have a poor prognosis (5-year overall survival rate is approximately 30%). Most of the patients with uterine LMS are asymptomatic; therefore, differentiating uterine LMS from benign condition such as uterine leiomyoma is difficult. Several imaging modalities, including ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-CT (PET-CT), cannot clearly distinguish uterine LMS from uterine leiomyoma (Mallmann, 2018). Most of the cases of uterine LMS are diagnosed through incidental findings after hysterectomy or morcellation of the mass. Approximately 0.17%–0.47% of women diagnosed with uterine leiomyoma before surgery were pathologically diagnosed with uterine LMS after the operation. In cases of misdiagnosis LMS may inadvertently morcellate during laparoscopic surgery (Zhao et al., 2015), which can potentially decrease the survival rate and lead to serious consequences (Ota et al., 2012).

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Currently, there is no reliable preoperative diagnostic test to accurately detect uterine LMS. Many studies have demonstrated that systemic inflammation has been shown to be an important manifestation of malignancy development and progression (Hanahan and Weinberg, 2011). Additionally, recent data have shown that chronic inflammation was involved in 15% to 20% of all malignancies (Chen et al., 2018).

The results from previous studies have demonstrated the correlation between chronic inflammation and various types of malignancies, including breast, ovarian, endometrial, and cervical cancer. The inflammatory process around the tumor microenvironment promotes the increase in neutrophils in peripheral blood, resulting in neovascularization, tumor growth, and tumor metastasis (Lin and Pollard, 2004). Liu et al. studied the pretreatment neutrophil-to-lymphocyte ratio (NLR) in patients with soft tissue sarcoma and showed that the NLR was a poor prognostic factor in these patients. It could be described by high neutrophils infiltration in a high-density tumor which stimulates TNF-α and VEGF secretion and results in a suitable environment for tumor progression (Liu et al., 2018). Therefore, higher neutrophil levels in peripheral blood may be found in patients with malignant tumors.

Moreover, a previous study in patients with solid malignant neoplasm showed that those with higher lymphocyte levels had better clinical outcomes than those with lower lymphocyte levels (Hendry et al., 2017). The results from this study can be attributed to immune suppression by the malignant neoplasm, which suppresses lymphocytic activity and T-cell response, especially that of the T-helper four lymphocytes, and leads to lower lymphocyte levels or lymphopenia in these patients.

As described above, higher neutrophil and lower lymphocyte levels in patients diagnosed with malignant neoplasm result in a higher NLR ratio, which can be used as a tool for cancer prediction. Hence, the NLR has also been suggested as a simple index of inflammatory response and a helpful method for the preoperative diagnosis and prediction of prognosis in patients with cancer.

This study aimed to identify the preoperative NLR and clinical characteristics of patients with uterine LMS compared with those with uterine leiomyoma. The primary outcome of this study was to compare the preoperative NLR of patients who were diagnosed as having uterine LMS compared with those diagnosed as having uterine leiomyoma. The secondary outcomes of this study were to compare the clinical characteristics of patients diagnosed as having uterine LMS compared with those diagnosed as having uterine leiomyoma and to identify the appropriate cut off value of NLR to use as differentiating tool to separate LNS from leiomyoma.

Materials and Methods

The design of this study was a matched case-controlled study. Data were collected from the database of King Chulalongkorn Memorial Hospital, a tertiary care University hospital in Bangkok, Thailand. We collected data of women who were diagnosed with a uterine mass and underwent surgery between January 2011 and December 2020. Women who were pathologically diagnosed with uterine LMS were assigned to the case group, whereas women who were pathologically diagnosed with uterine leiomyoma were assigned to the control group.

For sample size calculation, the matched case-control for binary data formula was used from Kim H.S. et al (2010). The proportion of exposure was defined as 0.358, and the odds ratio was 6.79. The case group-to-control group ratio was 1:4, and the alpha and beta errors were 0.05 and 0.2, respectively. The calculated sample size was 13 subjects in the case group and 52 subjects in the control group. The inclusion criteria were as follows: 1) women more than 18 years of age who were diagnosed with a uterine mass and underwent total abdominal hysterectomy between 2011 and 2019 at King Chulalongkorn Memorial Hospital; 2) had completed medical data, including preoperative complete blood count, physical examination, or imaging that described the size of the mass; and 3) a pathological report of the mass. The exclusion criteria were women who were diagnosed with other malignancies and had incomplete medical data. To confirm the diagnosis, the pathological reports of all women in both groups were reviewed by one pathologist. The pathologic criteria of uterine LMS were the presence of tumor necrosis, mitotic figure count more than 10 per 10 high power field, and the presence of nuclear atypia.

The patients in the case and control groups were matched by year of surgery and size of the uterine mass in a 1:4 ratios (one patient who was diagnosed with uterine LMS was matched with four patients who were diagnosed with uterine leiomyoma). The size of uterine LMSs was matched with uterine leiomyomas by a physical examination in three uterine LMS cases, whereas the other cases were matched by imaging. The matched patients underwent total abdominal hysterectomy within 12 months from the operation date of patients in the case group. The size of the uterine mass was measured via physical examination or imaging studies, and the difference in the uterine size between the matched patients in both groups should not exceed 2 cm. After matching, there were 13 patients in the case group and 52 patients in the control group.

After completing the matching process, preoperative laboratory data, baseline clinical characteristics, and other medical data were collected from all patients in both groups. NTR was calculated by dividing the number of neutrophil by number of lymphocyte. The latest preoperative complete blood count was used to calculate NLR. The baseline clinical characteristics included age, marital status, parity, menopausal status, body mass index (BMI), underlying diseases, history of heavy menstrual bleeding, and dysmenorrhea.

This study has been approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No. 340/63).

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA) and STATA version 17 (Statacorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Numbers, percentages, and mean ± standard deviation were used for the descriptive

statistics. The unpaired t-test was used to compare a normally distributed continuous variable when comparing baseline characteristics between patients with LMS and leiomyoma. For categorical variables, Fisher's exact test was used. Conditional logistic regression analysis was used to test the association between the NLR and uterine LMS. Significance variables at a p-value of <0.2 in the univariable analysis were used as potential confounders in the multivariable logistic regression analysis. Statistical significance was considered when p-value < 0.05. Receiver operating characteristic (ROC) curve analysis was used to investigate sensitivity, specificity, and the optimal cut-off value of NLR.

Results

There were 27 patients who were pathologically diagnosed with uterine LMS and met the inclusion criteria. Thirteen cases had incomplete medical data and one with concurrent breast cancer were excluded. Finally, 13 cases of uterine LMS were included in the analysis. In the control group, 2,587 patients met the inclusion criteria; 52 patients were matched with patients in the case group by the year of surgery and size of the uterine mass. Flow chart 1 shows the recruitment diagram.

Table 1 summarizes the baseline characteristics of the patients in the case (uterine LMS) and the control groups (uterine leiomyoma). The patients in both groups had comparable baseline characteristics (mean BMI and mean age: 24.4 ± 3.8 kg/m^2 and 23.6 ± 4.5 kg/m^2, and 47.9 ± 8.8 years and 45.1 ± 8.9 years in the case (LMS) and control (Leiomyoma) groups, respectively) except for the menopausal status, as there was a higher proportion of patients in the case group who were menopause than those in the control group (38.5% in the case group vs. 13.5% in the control group).

The age, marital status, parity, menopausal status, BMI, and complete blood count parameters including NLR were compared between the case group and control group, as shown in Table 2. Women who were diagnosed can decrease the variables associated with pathological report This study categorized the suitable NLR values on the basis of previous studies. The study of Kim et al., (2010) that compared the NLR with serum CA-125 as preoperative diagnostic markers for uterine sarcoma. In other words, the research was conducted in a form of a retrospective matched case-control on the basis of matching from ages, BMI, and uterine volume, whereby the matching conditions were different from those in our research. The results of their study found that NLR of ≥2.12 had a 74.5% sensitivity and 70.3% specificity for the preoperative diagnosis of uterine sarcoma. Furthermore, the NLR predicted recurrence and progression more accurately than CA-125.

Later, the study of Cho et al., (2010), with the same research form of matched case-control, used the matching

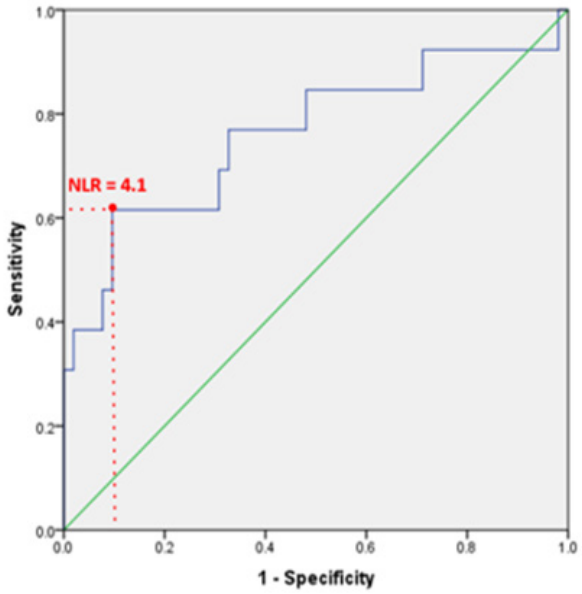
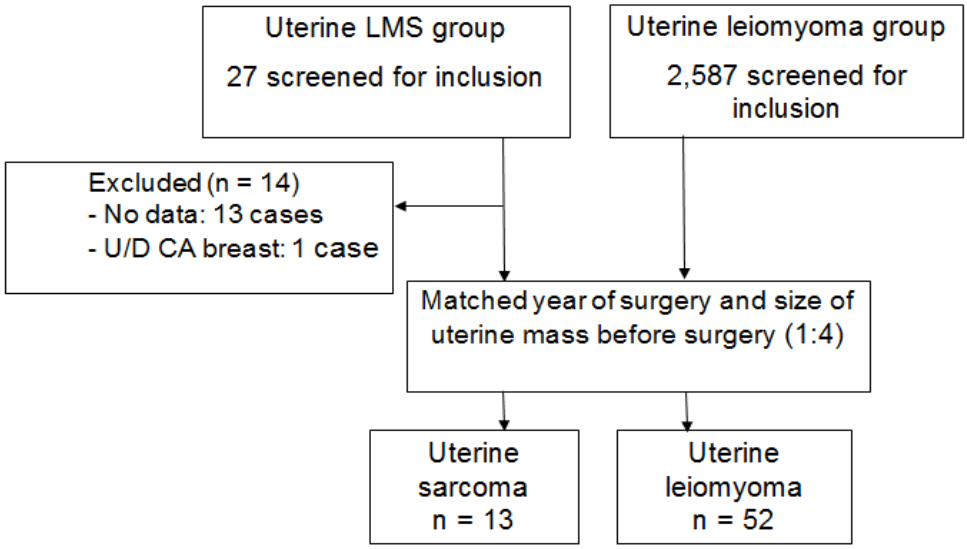


Figure 1. The Receiver Operating Characteristic (ROC) Curves of the Neutrophil-to-Lymphocyte Ratio for the Diagnostic Model



Flow chart 1. Trial Recruitment and Drop Out in Uterine LMS Group and Uterine Leiomyoma Group

Table 1. Baseline Characteristics of the Patients in the Uterine LMS Group and Uterine Leiomyoma Group

Characteristics	Uterine LMS (n = 13)	Uterine leiomyoma (n = 52)	P-value
Age (years) n (%)			0.54*
25–34	0 (0)	8 (15.4)	
35–44	5 (38.5)	16 (30.8)	
45–54	5 (38.5)	22 (42.3)	
55–64	2 (15.4)	5 (9.6)	
>65	1 (7.7)	1 (1.9)	
Marital status n (%)			1.00*
Single	6 (46.2)	26 (50)	
Married	7 (53.8)	26 (50)	
Parity n (%)			0.75*
Nulliparous	7 (53.8)	32 (61.5)	
Multiparous	6 (46.2)	20 (38.5)	
Menopausal status n (%)			0.05*
Pre-menopause	8 (61.5)	45 (86.5)	
Menopause	5 (38.5)	7 (13.5)	
Body mass index (kg/m^2) n (%)			0.73*
<18.5	1 (7.7)	3 (5.8)	
18.5–23	4 (30.8)	24 (46.2)	
23.1–27.5	6 (46.2)	17 (32.7)	
>27.5	2 (15.4)	8 (15.4)	
Underlying disease n (%)			0.32*
None	7 (53.8)	37 (71.2)	
Underlying disease	6 (46.2)	15 (28.8)	
Diabetes	0	1 (1.9)	
Hypertension	3 (23.1)	6 (11.5)	
Dyslipidemia	1 (7.7)	6 (11.5)	
Thyroid disease	1 (7.7)	3 (5.8)	
Others***	3 (23.1)	7 (13.5)	
Size of uterine mass (cm) mean±SD	14.6±7.5	14.6±7.2	0.87**

*, Fisher's exact test; **, Unpaired t-test; ***Others, allergic rhinitis, pulmonary Qtuberculosis, chronic hepatitis B infection, benign breast disease, iron deficiency anemia, thalassemia trait, deep vein thrombosis, major depressive disorder; kg/m^2, kilogram per square meter; cm, centimeter; SD, standard deviation

with uterine LMS had a significant higher NLR than those who were diagnosed with uterine leiomyoma (4.56 ± 2.50 vs. 2.4 ± 1.15; P< 0.0001).

Using the NLR cut-off value at 2.1 from the study of Kim et al., (2010), the univariable logistic regression analysis did not define NLR as a significant independent risk factor for uterine LMS. However, using NLR cut off value at 2.8 and 2.9 the showed a significant as an independent risk factor for uterine LMS in univariable logistic regression analysis (OR = 3.24; 95% CI 1.01–10.43 and OR = 3.70; 95% CI 1.16–11.80 for 2.8 and 2.9 cut-off values, respectively). We did not find significant differences in other factors including age, marital status, parity, and BMI between the case group and control group.

As described above, the menopausal status was different between the patients in both groups. We used multivariable logistic regression to adjust for menopausal status and found that the NLR cut-off value of 2.9 was still a statistically significant risk factor for uterine LMS (OR = 3.61; 95% CI 1.08–12.06).

The sensitivity and specificity of NLR to detect uterine LMS in this study are shown in table 3 and plotted in ROC curve (Figure 1). The area under the curve was 0.76 (95% CI 0.59–0.93). The best cut-off value was then evaluated. The NLR cut-off value of 2.1 had a high sensitivity but poor specificity (84.6% sensitivity and 44.2% specificity) to detect uterine LMS. When 2.8 was used as the NLR cut-off value, it had a 61.5% sensitivity and 73.1% specificity. The most suitable NLR cut-off value was calculated using the results from the ROC curve, which showed that an NLR of 4.1 was the most suitable cut-off level, with 61.5% sensitivity and 89% specificity.

Discussion

Uterine LMS is a rare and aggressive malignant uterine neoplasm. It is a disease characterized as having either no

Table 2. Comparison of Factors between the Uterine LMS Group and Uterine Leiomyoma Group

	Uterine LMS (n=13)	Uterine leiomyoma (n=52)	Odds ratio (95% CI)	P-value	Adjusted Odds ratio (95% CI)*	P-value
Age (years), n (%)						
<60	12 (92.3)	50 (96.2)	Reference		-	-
≥60	1 (7.7)	2 (3.8)	2.00 (0.18–22.06)	0.57		
Marriage status, n (%)						
Single	6 (46.2)	26 (50)	Reference		-	-
Married	7 (53.8)	26 (50)	1.22 (0.30–4.91)	0.78		
Parity, n (%)						
Nulliparous	7 (53.8)	32 (61.5)	0.67 (0.17–2.68)	0.57	-	-
Multiparous	6 (46.2)	20 (38.5)	Reference			
Menopausal status, n (%)						
Pre-menopause	8 (61.5)	45 (86.5)	Reference	0.06		
Menopause	5 (38.5)	7 (13.5)	3.31 (0.94–11.70)			
BMI (kg/m^2), n (%)						
≤23	5 (38.5)	26 (50)	Reference		-	-
>23	8 (61.5)	26 (50)	1.56 (0.47–5.18)	0.47		
NLR, n (%)						
<2.1	2 (15.4)	22 (42.3)	Reference			
≥2.1	11 (84.6)	30 (57.7)	3.53 (0.75–16.53)	0.11	4.09 (0.79–21.20)	0.09
<2.8	5 (38.5)	37 (71.2)	Reference			
≥2.8	8 (61.5)	15 (28.8)	3.24 (1.01–10.43)	0.04	3.17 (0.95–10.58)	0.06
<2.9	5 (38.5)	39 (75)	Reference			
≥2.9	8 (61.5)	13 (25)	3.70 (1.16–11.80)	0.03	3.61 (1.08–12.06)	0.04
<4.1	5 (38.5)	46 (88.5)	Reference			
≥4.1	8 (61.5)	6 (11.5)	8.54 (2.22–32.82)	< 0.01	7.66 (1.94–30.33)	<0.01
Complete blood count						
(Mean±SD)						
Hemoglobin	10.8±2.5	12.2±2.2	0.79 (0.61–1.03)	0.09	-	-
Total white blood cell count	9,957.7±3,367.9	6,997.5± 2,490.10	1.00 (1.00–1.00)	0.01	1.00 (1.00–1.00)	0.02
Neutrophil	71.4±12.5	62.1±9.8	1.07 (1.01–1.14)	0.02	1.06 (1.01–1.13)	0.03
Lymphocyte	20.4±10.6	29.6±8.7	0.91 (0.84–0.98)	0.01	0.91 (0.84–0.98)	0.02
Monocyte	4.8±2.6	4.8±1.9	1.00 (0.75–1.34)	0.99	-	-
Eosinophil	2.1±1.8	2.1±1.9	0.99 (0.72-1.38)	0.97	-	-
Basophil	0.7±0.5	0.4±0.3	7.17 (1.21– 42.62)	0.03	16.9 (1.99–143.31)	0.01
Platelet count	373,307.7±129,064.2	292,461.5±70,736.9	1.00 (1.00–1.00)	0.02	1.00 (1.00–1.00)	0.02

OR, odds ratio; CI, confidence interval; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; kg/m^2, kilogram per square meter; SD, standard deviation; * Adjusted OR, variables that were significantly associated with NLR in the conditional logistic regression model were further examined by multivariable regression analysis; adjusted for menopause

symptoms or nonspecific symptoms. This makes diagnosis difficult; thus, it is often confused with uterine leiomyoma. For the early initiation of treatment and management of uterine LMS, efforts have been undertaken into finding various methods to help identify the correct diagnosis before surgery, such as using ultrasonography, CT, MRI, or even conducting biological tumor marker tests. However, there are currently no available methods that are accurate enough to confirm the diagnosis of uterine LMS (Mallmann, 2018). Hence, the only method to confirm the diagnosis is by pathologic examination following excision.

Table 3. Sensitivity and Specificity of the Neutrophil to Lymphocyte Ratio (NLR) for Detecting LeiomyosarComa from Leiomyoma

NLR	Sensitivity (%)	Specificity (%)
2.1	84.6	44.2
2.8	61.5	73.1
2.9	61.5	75.0
4.1	61.5	89.0

Results from previous studies have demonstrated the correlation between the size of the uterine mass and uterine LMS. Hence, our study aimed to determine the correlation between other factors and the diagnosis of uterine LMS while matching the size of the uterine masses and the year of surgery between both groups to control the associated factors, such as physician experience and the type of laboratory machines that were not the same technology in the past. This study had one pathologist that

conditions of age, year of surgery, and surgeon. Their results showed that an NLR of ≥2.1, tumor size of >8 cm, and BMI of <20 kg/m^2 were independent risk factors for uterine sarcoma.

However, our findings show that an NLR of ≥2.1 had a sensitivity and specificity of 84.6% and 44.2%, respectively. Moreover, from the analysis of statistical data, this cut-off value was not an independent predictor for uterine LMS. The difference in our study results from those of others could be due to differences in terms of the matching condition.

In our study, we found that the NLR cut-off value of 2.8 was a significant risk factor for the presence of uterine LMS. Additionally, after adjusting for the menopausal status, the results from conditional logistic regression were marginally significant. The reason that the cut-off value of 2.8 had an effect of being marginally significant may be due to the small number of patients in our study. However, we believe that the cut-off value of 2.8 was in lieu with the results of a previous study by Zhang et al., (2020), which studied the preoperative clinical characteristics scoring system for differentiating uterine sarcoma from uterine leiomyoma. Although this study was conducted only for LMS. For this reason, our study supported Zhang et al., (2020)'s results. Therefore, an NLR of ≥2.8, which had a sensitivity and specificity of 61.5% and 73.1%, respectively, was a suitable cut-off value for predicting the occurrence of LMS. At a cut-off value of 2.9, the sensitivity was 61.5% and the specificity was 75%, which was not much different from our cut-off value of 2.8. This study still has limitations, which were the small number of patients. Accompany, no study has been conducted to determine the best cut-off value for NLR. Further studies with a larger sample size are recommended to confirm the present findings such as cut-off value of 2.9.

The ROC curve was created to identify the most appropriate cut-off value for the NLR, which showed that the most suitable cut-off value was 4.1. The mentioned value had a sensitivity of 61.5% and a specificity of 89%. An NLR cut-off value of 4.1 will help predict the occurrence of LMS much more accurately.

To our knowledge, there have only been a few published studies that evaluated the NLR as a diagnostic marker for uterine sarcoma. Moreover, this study was conducted not only to compare the NLR between uterine leiomyoma and uterine sarcoma but also to evaluate the appropriate cut-off value when using the NLR. Our findings suggest that the NLR may be a feasible marker that is efficacious and cost-effective when used for the preoperative differentiation of uterine LMS from uterine leiomyomas in clinical settings.

However, this study still has limitations, which were the small number of patients with uterine LMS and this being a single center-based retrospective study. The small in sample size may bring to low statistical power in this study. Further multicenter studies with a larger sample size are recommended to confirm the present findings and conclusions. We suggest further studies to evaluate other factors that will be used as a new model for uterine LMS prediction.

In conclusion, patients who were pathologically diagnosed with uterine LMS had a significantly higher NLR than those who were pathologically diagnosed with uterine leiomyoma. The NLR is a simple and effective method for predicting the presence of a uterine LMS in patients who are pre-operatively diagnosed with a uterine mass.

Author Contribution Statement

All authors contributed equally in this study.

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Data availability

The data related to the current study will be available for interested person by emailing to corresponding author.

Conflict of the interest

All authors declare no conflicts of interest.

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