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Original Research

The role of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio as a supplemental tool for differential diagnosis of uterine myoma and sarcoma

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Background: The purpose of this study was to investigate whether the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be used as supplemental tools to differentiate between uterine myomas and sarcomas. *Methods*: From January 2000 to May 2020, patients diagnosed with uterine sarcoma or myoma after surgery at the Catholic University Hospital of Daegu were enrolled in the study. The age and preoperative hematologic findings including hemoglobin, white blood cell count, neutrophils, lymphocytes, platelet counts and lactate dehydrogenase were retrospectively investigated. *Results*: A total of 366 patients, including 40 uterine sarcoma patients and 326 uterine myoma patients, were included in the study. Among the hematologic findings, NLR and PLR showed statistically significant differences between uterine sarcoma and myoma. The probability of sarcoma was high when NLR was $\geq$2.6 and PLR was $\geq$150.0. When NLR was $\geq$2.6, the odds ratio of uterine sarcoma risk was 9.761 (95% confidence interval [CI]: 3.950–24.120, $P < 0.001$). When PLR was $\geq$150, the odds ratio of uterine sarcoma risk was 3.502 (95% CI: 1.528–8.027, $P = 0.003$). If NLR was above their cut-offs, the sensitivity of uterine sarcoma diagnosis was 60% and specificity was 83.4%. Identically, PLR was 60% and 73.3%, respectively. *Conclusion*: NLR and PLR are useful supplemental tools for the differential diagnosis of uterine myoma and sarcoma. Therefore, more expensive and accurate imaging studies, such as magnetic resonance imaging, can be more effectively recommended when these hematologic findings are used together with pelvic ultrasonography.

Keywords

Uterine neoplasm; Leiomyoma; Uterine sarcoma; Neutrophil-to-lymphocyte ratio (NLR); Platelet-to-lymphocyte ratio (PLR)

1. Introduction

Uterine sarcoma is a relatively rare tumor originating from the uterine myometrium and endometrial stroma. Uterine sarcoma accounts for approximately 3% of all uterine malignancies. In approximately 0.3% of patients diagnosed with presumed uterine myoma by preoperative evaluation, they are confirmed as sarcomas through postoperative final pathological examination [1, 2].

The differential diagnosis of myomas and sarcomas remains difficult. Several studies on whether clinical symptoms (such as rapid growth in size, abnormal uterine bleeding, and pelvic pain) are helpful for differential diagnosis showed that these clinical symptoms have not been shown to assist in the differentiation between myomas and sarcomas [3, 4].

Pelvic ultrasonography is used as the first imaging test for the differential diagnosis of myomas and sarcomas, taking cost-effective aspects into account. If sarcoma is suspected on ultrasonography, more expensive and accurate imaging tests such as magnetic resonance imaging (MRI) and positron emission tomography computed tomography (PET-CT) are recommended [2]. Therefore, it is important to screen patients suspected of sarcoma requiring expensive imaging utility. However, because the secondary degenerated myoma is very similar to the sonographic findings of uterine sarcoma, it is very difficult to differentiate between uterine myomas and sarcomas by ultrasonography alone [5–8].

Therefore, additional methods are required that can be used as an aid to ultrasonography before performing expensive utility such as MRI and PET-CT. Previous studies have reported that the neutrophil-to-lymphocyte ratio (NLR) is helpful for the differential diagnosis of uterine myoma and sarcoma [9, 10]. However, there have only been few studies on the usefulness of platelet-to-lymphocyte ratio (PLR) in the differential diagnosis of uterine myomas and sarcomas.

The purpose of this study was to investigate whether the NLR and PLR can be used as supplemental tools to differentiate between uterine myomas and sarcomas.

2. Materials and methods

2.1 Patients

From January 2000 to May 2020, patients who were diagnosed with uterine sarcomas including leiomyosarcomas, carcinosarcomas, adenosarcomas, high grade endometrial stromal sarcomas (ESS) were enrolled in this study. Low grade ESS was excluded from this study. In addition, patients with myomas with secondary degeneration or without secondary degeneration at the final pathology after surgery at Daegu Catholic University Hospital were also included. Pa-

Table 1. Univariate analysis of clinical characteristic and hematologic examination between patients with uterine myoma and sarcoma.

	Pathology	Mean standard deviation	*P*-value
Age (yr)	Myoma (n = 326)	44.9 ± 6.6	<0.001
	Sarcoma (n = 40)	57.7 ± 10.4	
Hb (g/dL)	Myoma (n = 326)	11.9 ± 1.9	0.992
	Sarcoma (n = 40)	11.9 ± 1.7	
WBC count (/μL)	Myoma (n = 326)	6482.2 ± 1944.9	0.014
	Sarcoma (n = 40)	8032.5 ± 3775.0	
Neutrophil count (/μL)	Myoma (n = 326)	3793.9 ± 1644.5	0.003
	Sarcoma (n = 40)	5600.1 ± 3592.7	
Lymphocyte count (/μL)	Myoma (n = 326)	2038.9 ± 586.3	0.009
	Sarcoma (n = 40)	1775.5 ± 721.7	
Platelet count (/mm^3)	Myoma (n = 326)	249604.3 ± 63838.8	0.010
	Sarcoma (n = 40)	290825.0 ± 94234.0	
NLR	Myoma (n = 326)	2.0 ± 1.2	0.004
	Sarcoma (n = 40)	3.9 ± 3.8	
PLR	Myoma (n = 326)	131.8 ± 54.2	0.001
	Sarcoma (n = 40)	191.5 ± 106.4	
LDH (U/L)	Myoma (n = 326)	410.6 ± 140.1	0.848
	Sarcoma (n = 40)	403.0 ± 245.9	

Abbreviations: CBC, complete blood count; Hb, hemoglobin; WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LDH, lactate dehydrogenase.

tients with pre-existing infections, medical history of hematologic diseases, preoperative transfusion, other malignant diseases, and thrombolytic drugs were excluded as they could have a confounding effect on the results of this study.

The sample size of sarcoma patients group was 37 to satisfy the following conditions: Predictive positive proportion in uterine myoma (p1) 0.15, predictive positive proportion in uterine sarcoma myoma (p2) 0.35, statistical power (1-β) 80%, and significance level (α) 0.05 (two-sided test).

2.2 Clinical characteristic and preoperative hematologic findings

The patient's age, preoperative hematologic findings, and final biopsy results were reviewed retrospectively by evaluating their medical records. The hematologic findings examined were hemoglobin (Hb), platelet count, white blood cell count, neutrophil count, lymphocyte count, NLR, PLR and lactate dehydrogenase (LDH).

2.3 Statistical analyses

Data were analyzed using IBM SPSS statistics V25.0 (IBM, Armonk, NY, USA) and MedCalc Statistical Software version 19.4.0 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) for receiver operating characteristic (ROC) curve analysis. An independent *t*-test was performed to compare the mean values for continuous variables. ROC curve analysis was performed to establish an appropriate cut-off level. To set the best cut-off level, we obtained a cut-off level that maximized Youden's J statistic (sensitivity + specificity – 1). The sensitivity, specificity, and area under the curve (AUC) were calculated. A binominal logistic regression was used to calculate odds ratios. This study was approved by the ethics committee of the Daegu Catholic University Hospital.

3. Results

This study enrolled a total of 366 patients, including 40 patients diagnosed with uterine sarcomas (20 patients with carcinosarcomas, 13 leiomyosarcomas, two adenosarcomas, two endometrial stromal sarcomas high grade, etc.) and 326 patients diagnosed with myomas (279 patients with myomas without secondary degeneration and 47 patients with myomas with second degeneration).

Table 1 shows the comparison of age and preoperative hematologic findings (complete blood count (CBC) and LDH) between uterine myomas and sarcomas. The age range of each study group was significantly different because uterine sarcomas occur more often in older people. White blood cell (WBC), neutrophil, and platelet counts were higher in patients with uterine sarcomas than in those with myomas. Lymphocyte counts were lower in patients with uterine sarcomas in those with myomas. Both NLR and PLR were higher in patients with uterine sarcomas in those with myomas. Hb and LDH levels did not differ between the two groups.

In the case of carcinosarcoma, it is classified as sarcoma in pathology, however it is commonly thought of as a subtype of endometrial cancer. Therefore, subanalysis is performed exclude for 20 carcinosarcoma patients. In the sarcoma group excluded carcinosarcoma patients, NLR and PLR showed statistically significant differences in each group as well. The detailed results were as follows.

Myoma (n = 326) vs Sarcoma excluded carcinosarcoma (n = 20).

In NLR, 2.0 ± 1.2 vs 4.7 ± 5.0, P = 0.005.

In PLR, 131.8 ± 54.2 vs 198.4 ± 92.7, P = 0.026.

Table 2 shows, the comparison of age and preoperative

Table 2. Univariate analysis of clinical characteristic and hematologic examination between myoma without secondary degeneration and myoma with secondary degeneration.

	Pathology	Mean standard deviation	*P*-value
Age (yr)	Without degeneration (n = 279)	44.9 ± 6.5	0.760
	With degeneration (n = 47)	45.2 ± 7.3	
Hb (g/dL)	Without degeneration (n = 279)	11.9 ± 1.9	0.857
	With degeneration (n = 47)	11.9 ± 1.9	
WBC count (/μL)	Without degeneration (n = 279)	6383.2 ± 1869.1	0.025
	With degeneration (n = 47)	7070.2 ± 2280.3	
Neutrophil count (/μL)	Without degeneration (n = 279)	3703.5 ± 1529.4	0.015
	With degeneration (n = 47)	4330.3 ± 2151.4	
Lymphocyte count (/μL)	Without degeneration (n = 279)	2041.9 ± 592.6	0.823
	With degeneration (n = 47)	2021.2 ± 553.3	
Platelet count (/mm^3)	Without degeneration (n = 279)	245741.9 ± 63755.7	0.008
	With degeneration (n = 47)	272531.9 ± 60003.9	
NLR	Without degeneration (n = 279)	2.0 ± 1.2	0.073
	With degeneration (n = 47)	3.9 ± 3.8	
PLR	Without degeneration (n = 279)	129.6 ± 54.5	0.080
	With degeneration (n = 47)	144.6 ± 51.0	

Abbreviations: CBC, complete blood count; Hb, hemoglobin; WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LDH, lactate dehydrogenase.

Table 3. The diagnostic values of NLR and PLR.

	Cut-off	Sensitivity (%)	Specificity (%)
NLR	2.6	60.0	83.4
PLR	150.0	60.0	73.3

Abbreviations: ROC, Receiver operating characteristic; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio.

hematologic findings between myomas with secondary degeneration and myomas without secondary degeneration. WBC, neutrophil, and platelet counts were higher in patients with secondary degeneration than in those without secondary degeneration. Age, Hb, lymphocyte count, NLR, and PLR did not differ between the two groups.

Patients with uterine sarcoma were evaluated using ROC curve analysis (Table 3, Figs. 1,2). The diagnostic cut-off value, sensitivity, and specificity for NLR and PLR were calculated. The diagnostic cut-off value that maximized Youden's J statistic for NLR and PLR was used for differentiation. The diagnostic cut-off value for NLR (AUC = 0.755, $P < 0.001$) for differentiating between uterine myomas and sarcomas was 2.6, with a sensitivity of 60.0% and specificity of 83.4% (Fig. 1). The diagnostic cut-off value of PLR (AUC = 0.679, $P < 0.001$) for differentiating between uterine myomas and sarcomas was 150.0 with a sensitivity of 60.0% and specificity of 73.3% (Fig. 2).

According to the results in Table 4, include confounding factor like age, when NLR was ≥2.6 and PLR was ≥150, the odds ratio of uterine sarcoma risk was 9.761 (95% confidence interval CI: 3.950–24.120, $P < 0.001$) and 3.502 (95% CI: 1.528–8.027, $P = 0.003$), respectively.

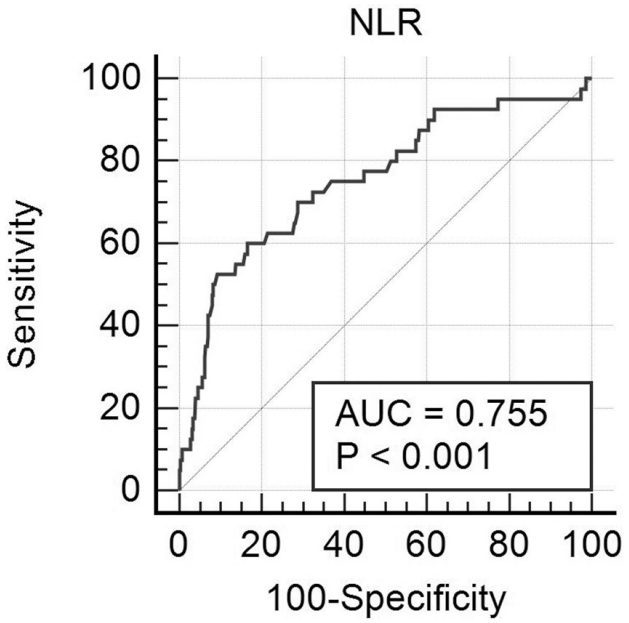

Fig. 1. The diagnostic values of neutrophil-to-lymphocyte ratio (NLR) determined by receiver operating characteristic curve. Abbreviations: NLR, neutrophil-to-lymphocyte ratio; AUC, area under curve.

4. Discussion

To differentiate between sarcoma and myoma before surgery is very challenging for most of clinician. Preoperative differential diagnosis of myoma and sarcoma is difficult, many patients are diagnosed through final pathological biopsy after surgery. If a presumed leiomyoma is confirmed as a uterine sarcoma after surgery, the morcellation used during surgery results in a poor prognosis. For this reason, motorized morcellation is controversial during laparoscopic or

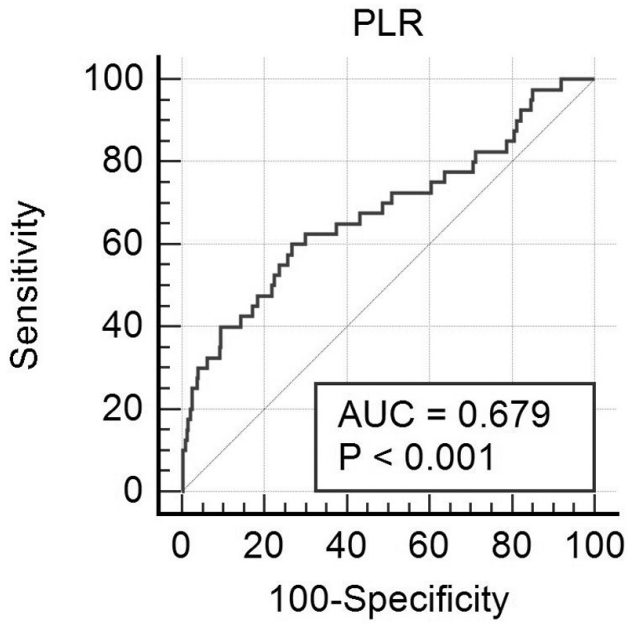

Fig. 2. The diagnostic values of platelet-to-lymphocyte ratio (PLR) determined by receiver operating characteristic curve. Abbreviations: PLR, platelet-to-lymphocyte ratio; AUC, area under curve.

Table 4. Odds ratio to each range of NLR and PLR for differential diagnosis of uterine myoma and sarcoma.

	Odds ratio	95% CI	*P*-value
NLR (≥2.6)	9.761	3.950–24.120	<0.001
Age	1.243	1.165–1.327	<0.001
PLR (≥150)	3.502	1.528–8.027	0.003
Age	1.227	1.154–1.305	<0.001

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CI, confidence interval.

robotic myomectomy [11, 12]. If myomectomy is planned for minimally invasive surgery, differentiating between uterine myoma and sarcoma before surgery is even more important. Therefore, various imaging studies have attempted to differentiate between myomas and sarcomas prior to surgery, such as pelvic ultrasonography, MRI, and PET-CT.

Pelvic ultrasonography findings used the differentiate sarcomas from myomas include recurrent refractory shadow of the tumor, calcification shadow, echogenicity, cystic degeneration, margin demarcation between the tumor and adjacent myometrium, and increased doppler flow [6–8]. However, these findings are usually insufficient in differentiating between uterine myomas and sarcomas.

Conversely, MRI can accurately describe pelvic soft tissue lesions anatomically without the use of contrast agents and achieves 66.7%–100% accuracy in differentiating myomas and leiomyosarcomas using apparent diffusion coefficient cut-off values [13]. A study by Li *et al.* [14] showed that the sensitivity and specificity of differentiation between degenerated myomas and sarcomas using MRI were 100% and 90%, respectively. Therefore, MRI is currently the most useful preoperative imaging test. However, performing MRI in all patients with presumed myoma can be cost-ineffective. Therefore, pelvic ultrasonography should be performed preferentially because of its simplicity, and MRI should be performed when sarcomas are suspected as a result of ultrasonographic findings.

There is a need for additional methods that can be used to aid in ultrasonography examinations before performing expensive tests such as MRI and PET-CT. In addition, in cases where sarcoma is suspected after ultrasonography, it may be helpful if there are supplemental measures that can assist in differential diagnosis prior to expensive imaging.

The CBC with differential counts has the advantage of being the most basic, fast, and easy way to obtain results, and is usually performed preoperatively in almost all patients. Therefore, we used CBC with differential counts in our study. A study by Cho Hy *et al.* [9] showed that patients with an NLR of >2.1, were more likely to have sarcomas. In our study, a significant increase in neutrophil counts was observed, and an increased NLR was observed in patients with sarcomas (NLR cut-off was ≥2.6, AUC = 0.755, $P < 0.001$, sensitivity 60%, specificity 83.4%). These results are thought to be due to hematologic changes related to a systemic inflammatory response in the patient's body [15, 16].

Results showed that patients with uterine sarcomas had significantly higher mean platelet counts than those with myomas. In addition, an increased PLR was significantly observed in patients with sarcomas (PLR cut-off was ≥150.0, AUC = 0.679, $P < 0.001$, sensitivity 60%, specificity 73.3%). Several studies have reported an association between thrombocytosis and cancer [17, 18]. Levin *et al.* [18] found occult cancer in nearly 40% of 140,000 patients with platelet counts >400,000/mm^3. In addition, patients with thrombocytosis cancer in the ovary, lung, stomach, colorectal and breast have poor prognosis and have been reportedly have resistance to chemotherapeutic agents [19–22].

Regarding the association between cancer and platelet counts, various studies on the mechanism of interaction have also been reported, and it is known that the interaction between cancer and platelets may promote carcinogenesis and cancer metastasis in addition to thrombocytosis. Regarding tumor cells that promote thrombopoiesis, thrombopoietic cytokines and interleukin-1, 3, 6, and 11 are produced from tumor cells and host tissues, which induce hepatic thrombopoietin generation and lead to thrombocytosis [22, 23]. Tumor-derived platelet factor 4 is also known to be involved in platelet production [24]. In addition, cancer directly changes platelet behavior by inducing the formation of tumor-platelet aggregates and platelet granules, and altering platelet phenotypes. However, these processes can be caused by phenotype transitions of tumor cells to promote tumor survival in circulation and to promote extravasation. This mechanism increases cancer invasion and metastasis. As a result, cancer-platelet interactions cause poor prognosis in cancer patients [25].

Some studies on the relationship between the diagnosis and prognosis of uterine sarcoma and NLR have been conducted, but studies on the relationship between PLR and uterine sarcoma are relatively insufficient [26, 27]. Kim *et al.* [10] reported that NLR may be more useful than serum CA-125 levels as a cost-effective tool for preoperative diagnosis in patients with uterine sarcomas. Jeong *et al.* [26] suggested that a high NLR was significantly associated with lower disease-free survival rate (DFS) ($P = 0.007$) and overall survival rate (OS) ($P = 0.039$) in uterine sarcoma patients. PLR has been studied for its association with diagnosis and prognosis in malignancies other than uterine sarcoma. For example, one meta-analysis study suggested that elevated PLR was significantly correlated with poor OS (hazard ratio (HR): 1.56, 95% CI: 1.32–1.85, $P < 0.001$) and DFS/PFS (HR = 1.56; 95% CI: 1.26–1.94; $P < 0.001$) in a total of 12 studies comprising 3668 patients with cervical cancer [28]. Backacak *et al.* [29] reported that the cut-off value for PLR was 161.13 in, distinguishing malignant from benign ovarian tumors ($P < 0.001$).

It has also been shown that increased LDH levels are more common in patients with sarcomas than in those with myomas, which may be helpful in differential diagnosis [30]. However, there was no statistically significant difference in LDH between myoma and uterine sarcoma groups in this study.

There are some limitations to this study. First, the study was a retrospective based on chart reviews. In addition, as this was a single-center study, our sample size was small.

Our study showed that the CBC count can be used as a noninvasive, cost-effective test to help diagnose uterine sarcomas that are difficult to differentiate from myomas by pelvic ultrasonography alone. Therefore, using hematologic findings together with ultrasonography, can better aid in the recommendation of more expensive and accurate imaging studies, such as MRI. In conclusion, we suggest the usefulness of NLR and PLR calculated using the CBC count as supplemental tools for the preoperative diagnosis of uterine sarcomas.

Abbreviations

MRI, Magnetic resonance imaging; PET-CT, Positron emission tomography computed tomography; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; ESS, Endometrial stromal sarcomas; Hb, Hemoglobin; LDH, Lactate dehydrogenase; ROC, Receiver operating characteristic; AUC, Area under the curve; CBC, Complete blood count; WBC, White blood cell; CI, Confidence interval; DFS, Disease-free survival rate; OS, Overall survival rate.

Author contributions

YYJ conducted data collection, analysis and manuscript writing. EJL and EBC are both conducted data collection and analysis. JMR and YSC conducted project development, analysis and manuscript writing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Ethics Committee of Daegu Catholic University Hospital (CR-20-043-L). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study was conducted based on gynecologic oncology database managed by the Department of Obstetrics and Gynecology at our medical center. Therefore, patient consent could not obtained from each patient.

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Conflict of interest

The authors declare no conflict of interest.

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