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Original Research

# Lymphocyte-monocyte ratio predicts uterine sarcoma aggressiveness

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**Summary**

*Purpose of Investigation:* The aim of the current study is to assess the prognostic value of the lymphocyte-monocyte ratio (LMR) in patients with uterine sarcoma. *Materials and Methods:* The authors examined the LMR as a prognostic variable in a cohort of 66 patients with uterine sarcoma who underwent surgical resection. Patients were categorized into two groups based on the LMR using cut-off values determined by receiver operating characteristic curve (ROC) analysis. They assessed the effect of the LMR on progression-free survival (PFS) and validated the LMR as independent predictor of survival. *Results:* Using data from the whole cohort, the optimized LMR cut-off value selected using the ROC curve was 5.86 for PFS. The LMR-low and LMR-high groups included 45 (68.2%) and 21 (31.8%) patients, respectively. The five-year PFS rates in the LMR-low and LMR-high groups were 69.0% and 94.4%, respectively ($p = 0.024$). Via multivariate analysis, the authors identified FIGO stage, residual tumor after surgery, and LMR as the most valuable prognostic factors affecting PFS ($p = 0.039$, $p = 0.018$, and $p = 0.043$, respectively). *Conclusion:* The LMR is an independent prognostic factor affecting the PFS of patients with uterine sarcoma.

*Key words:* Lymphocytes; Monocytes; Uterine neoplasms; Uterine sarcoma.

## Introduction

Uterine sarcomas are a rare disease that account for about 3% to 7% of malignant tumors occurring in the uterus [1], but that show an aggressive course unlike other cancers. Their histopathologic diversity makes them difficult to treat and prognosis is also poor. Uterine sarcomas are malignant mesenchymal tumors that include endometrial stromal sarcoma (ESS), undifferentiated uterine sarcoma (UUS), and uterine leiomyosarcoma (uLMS) [2]. Although the incidence rate of uterine sarcomas varies among different reports, a systemic review published in 2012 showed that uLMS, the most common form, has an incidence rate of 63%; ESS has an incidence rate of 21% and UUS is a very uncommon type [3]. Survival rate may differ according to histological classification, but the overall five-year survival rate is 17.5% to 54.7%. The recurrence rate is 45% to 73% [4]. Studies have explored the prognostic parameters of uterine sarcoma due to their rarity, aggressive course, and poor disease prognosis, and indicate that disease clinical stage, patient age, tumor size, and other parameters are independent factors affecting the overall survival rate [5-7], but results have been inconsistent. Recently, there have been several studies of the relationship between inflammation and cancer occurrence. The lymphocyte-monocyte ratio(LMR), in particular, corresponds to patient survival in various types of solid tumors, but its relationship with uterine sarcoma remains unknown. Here, the authors examine the relationship between LMR and other clinicopathological factors with regards to uterine sarcomas, and identify whether LMR is related to the prognosis of uterine sarcoma patients.

## Materials and Methods

The authors retrospectively evaluated 66 women who were diagnosed with uterine sarcoma at university hospitals in Korea between May 2004 and January 2016. Patients who had been treated with radiotherapy or chemotherapy before surgery were excluded from this study. Patients with coexisting cancers or prior malignancies within the previous five years were also excluded.

Those who had a concurrent autoimmune disease, or had evidence of active infection, were ineligible. The Institutional Review Board approved the retrospective review of these records, and this study was conducted in accordance with the detailed enforcement regulations of Korea and the principles of the Declaration of Helsinki. Clinicopathological variables including age, BMI, FIGO stage, histologic type, presence of lymphovascular space invasion (LVSI), residual tumor after surgery, primary tumor size, and adjuvant therapy were obtained retrospectively from patient medical records. All patients underwent hysterectomy as initial therapy. Thirty (45.4%) patients received adjuvant chemotherapy after surgery. Classifications of histologic type were reviewed for consistency by a single pathologist. Laboratory

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measurements, including complete blood cell counts (CBC) and biochemical profiles, were conducted prior to surgery as part of the routine evaluation. If numerous prior CBCs were available, the results from the date closest to the surgical procedure were selected for analysis. The authors determined optimized LMR cutoff values for predicting progression-free survival (PFS) using receiver operating characteristic (ROC) curve analysis. The best LMR cutoff value for PFS was 5.86. The patients were grouped based on the results of the ROC curve analysis into LMR-low (LMR ≤ 5.86) and LMR-high groups (LMR > 5.86). Differences in tumor- and host-related risk factors including age, histologic type, FIGO stage, tumor size, LVSI, and residual tumor after surgery between LMR-low and LMR-high groups were analyzed. Mann- Whitney U test was used to assess continuous variables, whereas independent-samples chi-square tests were used to assess categorical variables. The authors also evaluated the impact of the difference in the LMR between groups on PFS. PFS was defined as the time interval between hysterectomy-based surgery and the date of first recurrence or the date of last follow-up if there was no recurrence. Patients who did not experience cancer recurrence or death were censored at the time of last known contact date. The Kaplan-Meier method was used for descriptive analyses of survival curves, and survival curves were compared using log-rank tests. The authors used the univariate Cox proportional hazards model for identifying the contributions of the following variables: age, BMI, histologic type, histologic grade, FIGO stage, tumor size, LVSI, residual tumor after surgery, WBC count, hemoglobin level, platelet count, and LMR. Multivariate Cox proportional hazards models were used to determine adjusted hazard ratios for survival. Variables with *p*-values < 0.1 were selected for the multivariate analysis. All presented *p*-values are two-tailed, and statistical significance was defined as $p < 0.05$. Data were analyzed using SPSS software, version 18.0.

Table 1. — *Epidemiological, clinicopathological, and laboratory characteristics of uterine sarcoma.*

| Variable | Median (range) |
|---|---|
| Age (years) | 50.5 (32.0-74.0) |
| BMI (kg/m$^2$) | 23.0 (16.9-31.6) |
| Histology, *n* (%) | |
| ESS | 29 (43.9%) |
| LMS | 37 (56.1%) |
| FIGO Stage, *n* (%) | |
| I-II | 52 (78.8%) |
| III-IV | 14 (21.2%) |
| Tumor size (cm) | 8.0 (1-27) |
| LVS invasion, n (%) | |
| Negative | 52 (78.8%) |
| Positive | 14 (21.2%) |
| Residual tumor after surgery, n (%) | |
| Negative | 62 (93.9%) |
| Positive | 3 (4.6%) |
| WBC (per μL) | 6950 (3,050-25,000) |
| ANC (per μL) | 4429.6 (1,596.0-20,394.0) |
| ALC (per μL) | 1788.5 (608.0-6,214.1) |
| AMC (per μL) | 368.4 (103.7-2,602.3) |
| Hemoglobin (g/dL) | 12.1 (6.5-14.8) |
| Platelet (× 10$^3$/μL) | 303 (113-501) |
| LMR | 4.5 (1.5-11.9) |

*BMI: body mass index; ESS: endometrial stromal sarcomas; LMS: leiomyosarcoma; LVS: lymphovascular space; WBC: white blood cell; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; AMC: absolute monocyte count; LMR: lymphocyte-monocyte ratio.*

## Results

The baseline characteristics of patients are listed in Table 1. All patients underwent hysterectomy (Table 2). Of the 66 patients, 37 (56%) and 29 (44%) had histopathologically diagnosed uLMS and ESS, respectively. In total, 50 (75.8%), 2 (3.0 %), 5 (7.6%), and 9 (13.6%) patients had Stage I, II, III, and IV disease, respectively. LVSI and residual tumor after surgery were observed in 14 (21.2%) and 3 (4.6%) patients, respectively. The mean tumor size was 8.0 cm. The LMR-low and LMR-high groups included 45 (68.2%) and 21 (31.8%) patients, respectively. To evaluate the relevance of the LMR, the authors assessed differences in the baseline characteristics of the patients according to LMR. Significant mean differences between the LMR-low and LMR-high groups were demonstrated for the following continuous variables: WBC count ($p = 0.003$), ANC ($p < 0.023$), ALC ($p < 0.001$), and AMC ($p = 0.004$) (Table 3).

According to Kaplan-Meier analysis, the five-year PFS rates in the LMR-low and LMR-high groups were 69.0 and 94.4% ($p = 0.024$), respectively. In addition, the five-year PFS rates in patients with Stages I/II and III/IV disease were 86.7 and 44.6% ($p = 0.002$), respectively. Lastly, the five-year PFS rates in the smaller (≤ 8 cm) and larger (> 8 cm) tumor size groups were 87.9 and 64.9% ($p = 0.015$), respectively (Table 4). The median duration of follow-up was 34.4 (range, 1.0-125.0) months. Univariate analysis for PFS identified significant differences in several variables, including FIGO staging ($p = 0.005$), tumor size ($p = 0.024$), and LMR ($p = 0.053$). Multivariate analysis showed FIGO stage ($p = 0.039$), residual tumor after surgery ($p = 0.018$), and LMR ($p = 0.043$) were significant prognostic factors for PFS (Table 5).

Table 2. — *Surgical methods.*

| | |
|---|---|
| TAH | 18 |
| TLH | 13 |
| Vaginal hysterectomy | 3 |
| TLH, BSO | 5 |
| TAH, BSO | 18 |
| TAH, BSO, PLND | 9 |
| Total patients | 66 |

*TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy, BSO: bilateral salpingo-oophorectomy, PLND: pelvic lymph node dissection.*

## Discussion

Uterine sarcomas are rare malignancies of the uterus, but are more aggressive and less likely to respond to treatment than other uterine cancers. Among patients with FIGO Stages III-IV, the five-year survival rate is 25% to 33% and

Table 3. — *Epidemiological, clinicopathological, and laboratory characteristics according to the lymphocyte-monocyte ratio (LMR) in patients with uterine sarcoma.*

| Variable | LMR-low (≤ 5.86) | | LMR-high (> 5.86) | | *p*-value |
|---|---|---|---|---|---|
| | *n* | Median (IQR) | *n* | Median (IQR) | |
| Age (years) | 45 | 51 (46-57) | 21 | 50 (43-56) | 0.639 |
| BMI (kg/m$^2$) | 45 | 23.0 (21.5-25.2) | 21 | 22.7 (21.5-26.0) | 0.758 |
| Histology | | | | | |
| ESS | 21 (46.7%) | | 8 (38.1%) | | |
| LMS | 24 (53.3%) | | 13 (61.9%) | | 0.783 |
| FIGO Stage | | | | | |
| I-II | 32 (71.1%) | | 20 (95.2%) | | 0.056 |
| III-IV | 13 (28.9%) | | 1 (4.8%) | | |
| Tumor size (cm) | 45 | 9.0 (5.7-26.5) | 21 | 7.0 (5.2-8.4) | 0.124 |
| LVS invasion | | | | | |
| Negative | 34 (75.6%) | | 18 (85.7%) | | 0.537 |
| Positive | 11 (24.4%) | | 3 (14.3%) | | |
| Residual tumor after surgery | | | | | |
| Negative | 44 (97.8%) | | 18 (90.0%) | | 0.460 |
| Positive | 1 (2.2%) | | 2 (10.0%) | | |
| WBC (per μL) | 45 | 7,280 (6,330-10,340) | 21 | 6,200 (5,040-6,670) | 0.003 |
| ANC (per μL) | 45 | 4,971 (4,025-7,993) | 21 | 3,469 (3,035-3,833) | 0.023 |
| ALC (per μL) | 45 | 1,580 (1,307-1,871) | 21 | 2,058 (1,876-2,482) | <0.001 |
| AMC (per μL) | 45 | 453 (351-568) | 21 | 254 (240-321) | 0.004 |
| Hemoglobin (g/dL) | 45 | 12.0 (10.3-13.2) | 21 | 12.3 (10.1-13.3) | 1.000 |
| Platelet (× 10$^3$/μL) | 45 | 293 (237-352) | 21 | 315 (259-404) | 0.382 |

*P-values for comparisons of mean differences in continuous variables were obtained using a t-test. P-values for comparisons of categorical variables were obtained using the chi-squared test. LMR: lymphocyte-monocyte ratio; IQR: interquartile range; BMI: body mass index; ESS: endometrial stromal sarcomas; LMS: leiomyosarcoma; LVS: lymphovascular space; WBC: white blood cell; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; AMC: absolute monocyte count.*

the prognosis is poor [7]. Total hysterectomy is the standard treatment for uterine sarcoma. However, additional surgery may be required if uterine sarcoma was originally misdiagnosed as uterine myoma and histological verification was completed after myomectomy. However, as there are also reports suggesting that subsequent surgery does not improve survival, individualized treatment is required [2]. In this study, all patients were treated with a total hysterectomy and received no additional surgery. Whether bilateral salpingo-oophorectomy should be performed in conjunction with total hysterectomy is also controversial. Moreover, for uLMS cases diagnosed at an early stage, the ovary can be preserved in premenopausal women [8].

In the case that surgery is required, additional chemotherapy or radiotherapy should be performed according to the clinical stage or histologic grade of disease. Patients with incompletely resected or metastatic diseases are recommended to undergo chemotherapy with or without palliative radiation therapy [2]. After complete surgical resection, chemotherapy has been reported to increase overall PFS time [9] . Although adjuvant pelvic radiation can lower the local recurrence rate, however, whether adjuvant therapy significantly improves survival is still controversial [5] .

The symptoms of uterine sarcomas include abnormal bleeding, abdominal pain, and palpable mass. These symptoms are similar to those of benign diseases, such as adenomyosis or uterine myoma. Also, as there are no effective

Table 4. — *Kaplan-Meier analysis of five-year progression-free survival according to epidemiological, clinicopathological, and laboratory variables.*

| Characteristics | Categories five-year | PFS (%) | *p*-value |
|---|---|---|---|
| Age (years) | ≤ 65 | 63.1 | 0.352 |
| | > 65 | 66.7 | |
| BMI (kg/m$^2$) | ≤ 25 | 80.1 | 0.305 |
| | > 25 | 73.7 | |
| Histology, *n* (%) | ESS | 77.8 | 0.878 |
| | LMS | 77.4 | |
| FIGO Stage | I-II | 86.7 | 0.002 |
| | III-IV | 44.6 | |
| Tumor size (cm) | ≤ 8 | 87.9 | 0.015 |
| | > 8 | 64.9 | |
| LVS invasion | Negative | 82.9 | 0.324 |
| | Positive | 54.4 | |
| Residual tumor after surgery | Negative | 79.8 | 0.112 |
| | Positive | 33.3 | |
| WBC (per μL) | ≤ 11,000 | 77.2 | 0.947 |
| | > 11,000 | 80.0 | |
| Hemoglobin (g/dL) | < 12 | 75.1 | 0.685 |
| | ≥ 12 | 80.3 | |
| Platelet count (x 10$^3$ per μL) | ≤ 400 | 80.5 | 0.308 |
| | > 400 | 68.6 | |
| LMR | ≤ 5.86 | 69.0 | 0.024 |
| | > 5.86 | 94.4 | |

*PFS: progression-free survival; BMI: body mass index; ESS: endometrial stromal sarcomas; LMS: leiomyosarcoma; FIGO: The International Federation of Gynecology and Obstetrics; LVS: lymphovascular space; WBC: white blood cell; LMR: lymphocyte-monocyte ratio.*

Table 5. — *Relationship of epidemiological, clinicopathological, and laboratory variables with progression-free survival in patients with uterine sarcoma.*

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Age (years) (≤65 *vs*. >65) | 2.03 (0.44, 9.23) | 0.362 | | |
| BMI (≤25 *vs*. >25) | 1.79 (0.58, 5.49) | 0.312 | | |
| Histology (ESS *vs*. LMS) | 1.09 (0.35, 3.38) | 0.878 | | |
| FIGO stage (I-II *vs*. III-IV) | 4.86 (1.63, 14.49) | 0.005 | 3.32 (1.06, 3.32) | 0.039 |
| Tumor size (g/dL) (≤8 *vs*. >8) | 3.99 (1.20, 13.27) | 0.024 | | |
| LVS invasion (negative *vs*. positive) | 1.82 (0.55, 6.04) | 0.331 | | |
| Residual tumor after surgery (negative *vs*. positive) | 3.26 (0.70, 15.20) | 0.132 | 8.96 (1.45, 8.96) | 0.018 |
| WBC (per μL) (≤11000 *vs*. >11000) | 1.05 (0.23, 4.81) | 0.947 | | |
| Hemoglobin (g/dL) (≤12.0 *vs*. >12.0) | 0.80 (0.27, 2.39) | 0.686 | | |
| Platelet (x $10^3$/μL) (≤400 *vs*. >400) | 1.78 (0.58, 5.44) | 0.315 | | |
| LMR (≤5.86 *vs*. >5.86) | 0.13 (0.02 ,1.03) | 0.053 | 0.09 (0.01, 0.93) | 0.043 |

*Hazard ratios were obtained using Cox's proportional hazard model. HR: hazard ratio; CI: confidence interval; BMI: body mass index; ESS: endometrial stromal sarcomas; LMS: leiomyosarcoma; LVS: lymphovascular space; WBC: white blood cell; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; AMC: absolute monocyte count; LMR: lymphocyte-monocyte ratio.*

tools that can detect uterine sarcoma prior to surgery, in most cases, uterine sarcoma is confirmed after removing the tumor with misdiagnosis as a benign disease. Morcellation during laparoscopic surgery for benign uterine neoplasms is especially prohibited in uterine sarcoma due to increases in intra-abdominal metastasis and recurrence rate as well as short recurrence-free survival [10, 11]. Such characteristics of uterine sarcoma have led researchers to perform many studies of prognosis-related factors, including clinical characteristics. In most studies, whether the tumor is characterized by residual cancer cells, patient age, stage, tumor size, and other variables have been identified as independent factors [12-14]. However, there have been few studies to date examining the relationship between prognosis and hematologic or imaging tests of uterine sarcoma, and the results of these studies are inconsistent [15-17]. The correlation between inflammation and cancer was first noted by Virchow in 1863 [18]. Since then, studies have indicated that malignant transformation, progression, and metastasis of cancers are correlated with chronic inflammation. Local immune response and systemic inflammation are related to the progression of cancers and patient survival [19]. A large number of studies have suggested correlations between cancers and C-reactive protein (CRP), known as a major acute-phase plasma protein among systemic inflammation mediators. In a systemic review of several studies of colorectal, breast, and lung cancer patients, CRP in particular was proposed to show potential for the early diagnosis of cancers and the prognostic marker [20-22]. With respect to uterine sarcoma, the higher the serum CRP prior to treatment is related with the lower the overall survival [16]. One analysis found that the number of pretreatment peripheral blood cells in various cancers was correlated with progression and survival of the disease. Several papers that were recently published proposed that the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), LMR, and other factors can be used as prognostic markers of cancers. Moreover, according to a systemic review, NLR was increased in patients with advanced, aggressive disease, suggesting that NLR alone is a viable independent prognostic factor [23].

Studies of thrombocytosis and PLR have found that while the cutoff range for thrombocytosis varies, it can be a useful prognostic marker in colorectal cancer. In particular, pre-surgery PLR is an independent predictor of poor outcomes in pancreatic and colorectal cancers [24].

The monocytes in peripheral blood become macrophages in tissues. The increase of monocytes observed in colorectal cancer is correlated with clinical stage and poor survival rates [25]. Although many cancers have not yet been studied, this correlation may exist, not only in inflammatory disease, but also in the pathogenesis of cancer, as the circulation of monocytes is essential for infection control [26, 27]. Lymphocytes are known to play an important role in defense against cancer cells through the inducement of cytotoxic cell death, the inhibition of tumor cell proliferation, and other mechanisms. In addition, the reduction of blood lymphocytes has been reported as an independent prognostic factor for overall survival in various cancers, though the exact mechanism is not yet known [26, 27]. Many studies have been conducted to confirm the relationship between LMR and cancer prognosis. There is a correlation between LMR and patient survival rate when patients have solid tumors such as colorectal, lung, breast, bladder, and cervical cancer. In most studies, the cutoff value of LMR was determined using the ROC curve, and low LMR was associated with poor overall survival rate. In the present study, the LMR cutoff value was 5.86, and if the value was lower, the PFS rate was low.

The significance of this study is that it is the first attempt to confirm the prognostic value of LMR in uterine sarcoma patients. Moreover, the potential of LMR as a non-invasive marker of uterine sarcoma was evaluated together with previously validated factors, likely as FIGO staging, residual

tumor after surgery, and tumor size. However, the sample size included in this study is not large, because of the low prevalence of uterine sarcomas. Potential confounding factors may have affected the accuracy of the results due to the limitations of the retrospective design.

In the present chart review, patients with inflammatory systemic diseases that may have affected LMR were excluded, but there may remain some bias regarding unrecorded systemic diseases. Therefore, it is necessary to confirm the potential of LMR as a prognostic marker in uterine sarcomas through larger well-designed prospective studies.

In conclusion, in this study, the authors showed for the first time that LMR is an independent marker of PFS in uterine sarcomas. If LMR is clinically available, LMR may be used to accurately predict prognosis for patients with aggressive uterine sarcoma with poor prognoses.

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