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Research Paper

The Lymphocyte-Monocyte Ratio Predicts Patient Survival and Aggressiveness of Endometrial Cancer

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Abstract

Objective: We assessed the prognostic implications of preoperative lymphocyte-monocyte ratio (LMR) in patients with endometrial cancer (EC).

Methods: We retrospectively examined the LMR as a prognostic variable in a cohort of 255 patients with EC who underwent surgical resection. Patients were categorized into two groups according to the LMR (LMR-low and LMR-high) using cutoff points determined by receiving operator characteristic (ROC) curve analysis. The primary objective was to correlate the LMR to clinicopathological factors; the secondary objective was to determine the survival significance of the LMR in patients with EC.

Results: Using data from the entire cohort, the most discriminative LMR cutoff value selected on the ROC curve was 3.28 for both disease-free survival (DFS) and overall survival (OS). The LMR-low and LMR-high groups included 33 (12.9%) and 222 patients (87.1%), respectively. The 5-year DFS rates in the LMR-low and LMR-high groups were 64.5 and 93.9% ($P < 0.0001$), respectively, and the 5-year OS rates in the two groups were 76.7 and 96.5% ($P < 0.0001$), respectively. On multivariate analysis, we identified histologic grade, International Federation of Gynecology and Obstetrics (FIGO) stage, and LMR levels as the strongest prognostic factors affecting DFS ($P = 0.0037$, $P < 0.0001$, and $P < 0.0001$, respectively), and FIGO stage and the LMR as the strongest prognostic factors predicting OS ($P < 0.0001$ and $P < 0.0001$, respectively).

Conclusion: The LMR is an independent prognostic factor for both DFS and OS after surgical resection, and it provides additional prognostic value beyond standard clinicopathological parameters.

Key words: Monocytes, Lymphocytes, Endometrial Cancer

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in Europe and North America, and the incidence of this disease and the associated mortality have increased over the past decade

[1]. The majority of ECs present as low-grade tumors that tend to show limited spread to the surface of the endometrium. In addition, most patients with EC present with symptoms of unusual vaginal bleeding, and this enables early diagnosis of malignancy [1]. As the majority of ECs are low-grade tumors detected at an early stage, surgery followed by tailored adjuvant therapy based on the patient's clinicopathological risk profile is the standard initial treatment for this disease. Owing to the favorable tumor characteristics of EC, a long period of remission with a 5-year survival rate of greater than 80% is observed [2], and a cure for the disease is possible in the majority of patients.

However, despite a multidisciplinary treatment approach involving surgery, chemotherapy, and radiotherapy, a significant number of patients suffer from recurrent disease; the risk of recurrence for EC patients is 10–20% for International Federation of Gynecology and Obstetrics (FIGO) stage I–II disease and 50–70% for stage III–IV disease [3]. Therefore, novel approaches to identify tumors that are likely to recur may allow for optimization of treatment in these patients, along with improved survival. Several clinicopathological models have been proposed to identify patients at risk of relapse of EC and subsequent death, and these strategies have the ultimate objective of identifying individuals who would derive the greatest benefit from postoperative therapeutic intervention.

In patients with EC, prognosis is guided by analysis of various cancer-related risk factors: advanced FIGO stage, myometrial invasion [4-6], cervical stromal invasion (CSI) [7], extrauterine disease [6], positive peritoneal cytology [7], lymphovascular space invasion (LVSI) [8], positive pelvic nodes, positive para-aortic nodes [9], grade 3 histology [9], cancer antigen 125 (CA-125) level [10], and completeness of surgical resection. However, it is clear that the ability of these conventional risk factors to predict recurrence and estimate survival is insufficient. Clinical outcomes of patients with EC are influenced not only by cancer-related risk factors, but also by host-related risk factors including white blood cells (WBCs) [11], monocyte counts [12], hemoglobin concentration [13], platelet counts [14], the neutrophil-lymphocyte ratio (NLR) [15-17], and the platelet-lymphocyte ratio (PLR) [15, 17].

Recently, the lymphocyte-monocyte ratio (LMR; calculated as the proportional ratio of the absolute count of lymphocytes over the absolute count of monocytes) has been suggested to be associated with survival in patients with malignant lymphomas [18-20] as well as many solid tumors, such as head and neck [21-23], breast [24], lung [25-27], gastrointestinal tract [28-35], and genitourinary system [36, 37] cancers. However, as far as we know, the prognostic value of the LMR in patients with EC has not been reported. The primary objective of the analysis was to assess the correlation between LMR and clinicopathological factors. The secondary objective of the analysis was to determine the survival significance of the LMR in patients with EC.

Methods

This study included 255 newly diagnosed EC patients with histologically confirmed disease who were treated with hysterectomy-based comprehensive surgical staging at university hospitals between January 2005 and December 2014. Excluded cases included those without laboratory results at the time of cancer diagnosis. Patients were also excluded if the blood test including complete blood count (CBC) is not performed within 2 weeks before surgery. In addition, those who had been treated with radiation therapy or neoadjuvant chemotherapy before surgery were also excluded from this study. Patients with prior malignancies within the previous 5 years or concurrent second malignancies were also excluded. Finally, patients were ineligible if they had evidence of active infection, had used recombinant human granulocyte-macrophage colony-stimulating factor or recombinant human granulocyte colony-stimulating factor in the treatment of neutropenia, had a concomitant autoimmune disease, or had been treated with immunosuppressive therapy that may affect WBC count. The Institutional Review Board approved the retrospective review of these records, and this study was performed in accordance with local (Korean regulations) and international (the Declaration of Helsinki) ethical standards.

Clinicopathological variables such as age, histologic type, histologic grade, FIGO stage, lymph node (LN) metastasis, CSI, and presence of LVSI were obtained retrospectively from patient medical records. Staging surgery consisting of total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, and pelvic LN dissection with or without para-aortic LN dissection was performed as the primary treatment for EC [38]. Classification of histologic type was reviewed for consistency by a single pathologist. Subtypes included endometrioid, serous, mucinous, clear cell, mixed cell, and other tumors, and histological diagnosis was determined based on World Health Organization (WHO) histological classification guidelines [39]. Histologic grade was based on the FIGO system, and cancer stage was reclassified based on the 2009 FIGO staging system [38]. Adjuvant treatment was administered depending on risk factors (FIGO stage, histologic type, and histologic grade), patient preference, and physician discretion [40].

Laboratory results for CBCs included WBC count; absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and absolute monocyte count (AMC); hemoglobin levels; mean corpuscular volume (MCV); and platelet counts. In addition, biochemical results for CA-125 and serum albumin levels were abstracted. Laboratory measurements were performed prior to surgery as part of the routine workup. If more than one preoperative CBC results were available, the result from the date closest to the surgical procedure was chosen for analysis [41].

As the optimized cutoff values for the NLR [15-17, 42] and PLR [15, 17] were variable in previous studies, and no prior study examined the influence of the LMR on survival in patients with EC, we used data from the entire cohort to determine best cutoff points for predicting disease-free (DFS) and overall survival (OS) based on receiver operating characteristic (ROC) curve analysis. We determined that the best LMR cutoff value for both DFS and OS was 3.28. Then the patients were grouped based on the results of ROC curve analysis into an LMR-low group (LMR ≤ 3.28) and an LMR-high group (LMR > 3.28). Differences in tumor- and host-related risk factors including age, histologic type, histologic grade, FIGO stage, LN metastasis, CSI, LVSI, and serum CA-125 and serum albumin levels between the LMR-low and LMR-high groups were analyzed. Independent-samples *t*-tests were used to assess continuous variables, whereas independent-samples chi-squared tests were used to assess categorical variables.

We also evaluated the impact of the difference in the LMR between groups on both DFS and OS. DFS was defined as the time interval between hysterectomy-based surgical staging and the date of first recurrence or the date of last follow-up if there was no recurrence. OS was defined as the time interval between the date of hysterectomy-based surgical staging and the date of death due to any cause or last follow-up. 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 analysis of survival curves; survival curves were compared using log-rank tests. We used the univariate Cox proportional hazards model for identifying the contribution of the following variables: age, histologic type, histologic grade, FIGO stage, LVSI, serum CA-125 and serum albumin levels, WBC count, ANC, ALC, AMC, hemoglobin level, MCV, platelet count, NLR, PLR, and LMR. The 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-sided, and statistical significance was declared at $P < 0.05$. Data were analyzed using Statistical Package for the Social Science (SPSS) statistical software, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of the patients are displayed in Table 1. Endometrioid adenocarcinoma was the most common histological subtype (91.8%), and histologic grade 1 was the most frequent grade (50.0%) in our cohort. In total, 190 (74.5%), 25 (9.8%), 35 (13.7%), and 5 (2.0%) patients had stage I, II, III, and IV disease, respectively. LN involvement and CSI were observed in 31 (12.2%) and 45 (17.6%) patients, respectively. Forty-seven (18.4%) patients were found to have LVSI. The median serum level of CA-125 was 19 units/mL, and the median serum albumin level was 4.4 g/dL.

Table 1. Clinicopathological characteristics of 255 patients with endometrial cancer

Variable	*n* (%)
Age (years), median (range)	44 (28–82)
Histology	
Endometrioid	234 (91.8)
Serous	7 (2.7)
Mixed	7 (2.7)
Clear cell	3 (1.2)
Undifferentiated	2 (0.8)
Mucinous	1 (0.4)
Squamous	1 (0.4)
Histologic grade	
G1	127 (50.0)
G2	88 (34.6)
G3	39 (15.4)
FIGO Stage	
I–II	215 (84.3)
III–IV	40 (15.7)
LN metastasis	
Absent	224 (87.8)
Present	31 (12.2)
CSI	
Absent	210 (82.4)
Present	45 (17.6)
LVSI	
Absent	208 (81.6)
Present	47 (18.4)
CA-125 (unit/mL), median (range)	19.0 (5.2–1144.0)
Albumin (g/dL), median (range)	4.4 (2.2–5.3)
WBC (per μL), median (range)	6700 (3080–25900)
ANC (per μL), median (range)	3929.3 (1653.9–21833.7)
ALC (per μL), median (range)	1979.3 (366.6–4498.5)
AMC (per μL), median (range)	357.3 (72.4–2201.5)
Hemoglobin (g/dL), median (range)	12.7 (6.2–15.7)
MCV (fL), median (range)	89.3 (63.7–98.5)
Platelet ($\times 10^3$/μL), median (range)	264.0 (73.0–571.0)

FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; CSI, cervical stromal invasion; LVSI, lymphovascular space invasion; CA-125, cancer antigen 125; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; MCV, mean corpuscular volume

When patients were stratified according to the LMR, the LMR-low and LMR-high groups included 33 (12.9%) and 222 (87.1%) patients, respectively. To evaluate the relevance of the LMR, we assessed differences in the baseline characteristics of the patients according to the different LMR categories. Significant mean differences between the LMR-low and LMR-high groups were demonstrated for the following continuous variables: serum albumin levels (P < 0.0001), WBC count (P < 0.0001), ANC (P < 0.0001), ALC (P < 0.0001), AMC (P < 0.0001), hemoglobin concentration (P = 0.0016), NLR (P < 0.0001), and PLR (P < 0.0001). In addition, significant differences in categorical variables included histologic type (P = 0.0259), FIGO stage (P = 0.0133), and LVSI (P = 0.0180) (Table 2).

The median duration of follow-up was 51.3 months (range, 1.0–130.0 months). Univariate analysis for DFS identified a significant difference in several variables: age (P = 0.0085), histologic type (P < 0.0001), histologic grade (P = 0.0014), FIGO stage (P < 0.0001), LVSI (P < 0.0848), CA-125 levels (P < 0.0001), serum albumin levels (P = 0.0138), WBC count (P = 0.0075), ANC (P = 0.0478), ALC (P = 0.0019), AMC (P < 0.0001), hemoglobin concentration (P = 0.0079), MCV (P = 0.0139), platelet count (P = 0.0282), NLR (P = 0.0032), PLR (P = 0.0108), and LMR (P < 0.0001). Using the multivariate Cox proportional hazards model, we identified histologic grade (hazard ratio [HR] = 9.57, 95% confidence interval [CI] = 2.08–44.01, P = 0.0037), FIGO stage (HR = 8.14, 95% CI = 3.14–21.11, P < 0.0001), and LMR (HR = 0.10, 95% CI = 0.03–0.22, P < 0.0001) as the strongest prognostic factors (Table 3).

Using univariate analysis for OS, significant differences for variables were obtained for several variables: histologic type (P < 0.0001), FIGO stage (P < 0.0001), LVSI (P < 0.0001), CA-125 levels (P < 0.0001), serum albumin levels (P = 0.0460), ALC (P = 0.0117), AMC (P = 0.0042), hemoglobin concentration (P < 0.0001), NLR (P = 0.0217), PLR (P = 0.0497), and LMR (P < 0.0001). In multivariate analyses using Cox proportional hazards model for OS, FIGO stage (HR = 18.67, 95% CI = 4.08–85.50, P < 0.0001), and LMR (HR = 0.07, 95% CI = 0.02–0.24, P < 0.0001) were identified as significant prognostic factors (Table 4).

According to Kaplan-Meier analysis, the 5-year DFS rates for patients with histologic grade 1 and grade 2–3 disease were 98.3 and 81.5% (P = 0.0001), respectively, and the 5-year OS rates in these groups were 100.0 and 88.4%, respectively (P = 0.0001). In addition, the 5-year DFS rates for patients with stage I–II and III–IV disease were 95.9 and 53.2% (P < 0.0001), respectively, and the 5-year OS rates in these two patient groups were 99.4 and 64.3%, respectively (P < 0.0001). Finally, the 5-year DFS rates in the LMR-low and LMR-high groups were 64.5 and 93.9% (P < 0.0001), respectively, and the 5-year OS rates in these two groups were 76.7 and 96.5%, respectively (P < 0.0001) (Fig. 1).

Table 2. Clinical and pathological characteristics according to the LMR in 255 patients with endometrial cancer

Variable		LMR-low (≤ 3.28)		LMR-high (> 3.28)		*P*-value
		n (%)	Mean ± SD	*n* (%)	Mean ± SD	
Age (years)		33	56.1 ± 11.3	222	54.8 ± 9.5	0.5017
Histology	Endometrioid	27		207		0.0259
	Non-endometrioid	6		15		
Histologic grade	G1	16		111		1.0000
	G2–G3	16		111		
FIGO stage	I–II	23		192		0.0133
	III–IV	10		30		
LN metastasis	Absent	26		198		0.0880
	Present	7		24		
CSI	Absent	24		186		0.1201
	Present	9		36		
LVSI	Absent	22		186		0.0180
	Present	11		36		
CA-125 (unit/mL)		31	74.3 ± 210.9	217	39.0 ± 73.9	0.0705
Albumin (g/dL)		33	3.9 ± 0.7	222	4.4 ± 0.4	< 0.0001
WBC (per μL)		33	9200.0 ± 4624.2	222	6931.7 ± 1990.0	< 0.0001
ANC (per μL)		33	6986.8 ± 4326.1	222	4228.5 ± 1757.2	< 0.0001
ALC (per μL)		33	1397.5 ± 484.3	222	2137.7 ± 654.8	< 0.0001
AMC (per μL)		33	637.3 ± 335.4	222	364.7 ± 132.0	< 0.0001
Hemoglobin (g/dL)		33	11.6 ± 2.1	222	12.6 ± 1.5	0.0016
MCV (fL)		33	86.8 ± 7.6	222	87.9 ± 6.4	0.3507
Platelet (×10³/μL)		33	267.7 ± 92.9	222	276.6 ± 74.3	0.5336
NLR		33	5.8 ± 4.6	222	2.2 ± 1.8	< 0.0001
PLR		33	205.3 ± 76.4	222	142.1 ± 64.4	< 0.0001

P-values for comparison of mean differences in continuous variables were obtained by *t*-test; *P*-values for independent tests of categorical variables were obtained by chi-square test.
LMR, lymphocyte monocyte ratio; SD, standard deviation; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; CSI, cervical stromal invasion; LVSI, lymphovascular space invasion; CA-125, cancer antigen 125; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; MCV, mean corpuscular volume; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio

Table 3. Relationship between tumor- and host-related characteristics and disease-free survival in 255 patients with endometrial cancer

Variable	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years) (≤ 56 vs. > 56)	3.59 (1.39, 9.29)	0.0085		
Histology (endometrioid vs. others)	7.81 (3.05, 19.97)	< 0.0001		
Histologic grade (G1 vs. G2–G3)	10.81 (2.52, 46.41)	0.0014	9.57 (2.08, 44.01)	0.0037
FIGO stage (I–II vs. III–IV)	15.09 (6.03, 37.78)	< 0.0001	8.14 (3.14, 21.11)	< 0.0001
LVSI (absent vs. present)	8.29 (3.43, 20.03)	< 0.0001		
CA-125 (unit/mL) (≤ 48.1 vs. > 48.1)	5.54 (2.20, 13.97)	< 0.0001		
Albumin (g/dL) (≤ 4.4 vs. > 4.4)	0.21 (0.06, 0.73)	0.0138		
WBC (per μL) (≤ 5410 vs. > 5410)	5.86 (0.79, 43.31)	0.0848		
ANC (per μL) (≤ 3665.1 vs. > 3665.1)	3.01 (1.01, 8.94)	0.0478		
ALC (per μL) (≤1526.9 vs. >1526.9)	0.25 (0.10, 0.60)	0.0019		
AMC (per μL) (≤ 528.4 vs. > 528.4)	4.83 (2.01, 11.64)	< 0.0001		
Hemoglobin (g/dL) (≤11.7 vs. >11.7)	0.31 (0.13, 0.74)	0.0079		
MCV (fL) (≤ 90 vs. > 90)	3.16 (1.26, 7.91)	0.0139		
Platelet (x 10^3/μL) (≤204 vs. >204)	0.34 (0.13, 0.89)	0.0282		
NLR (≤ 2.44 vs. > 2.44)	3.68 (1.55, 8.76)	0.0032		
PLR (≤ 190.78 vs. > 190.78)	3.08 (1.30, 7.32)	0.0108		
LMR (≤ 3.28 vs. > 3.28)	0.10 (0.04, 0.25)	< 0.0001	0.10 (0.03, 0.32)	< 0.0001

HRs were obtained from Cox's proportional hazard model.

HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion;CA-125, cancer antigen 125; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; MCV, mean corpuscular volume; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio

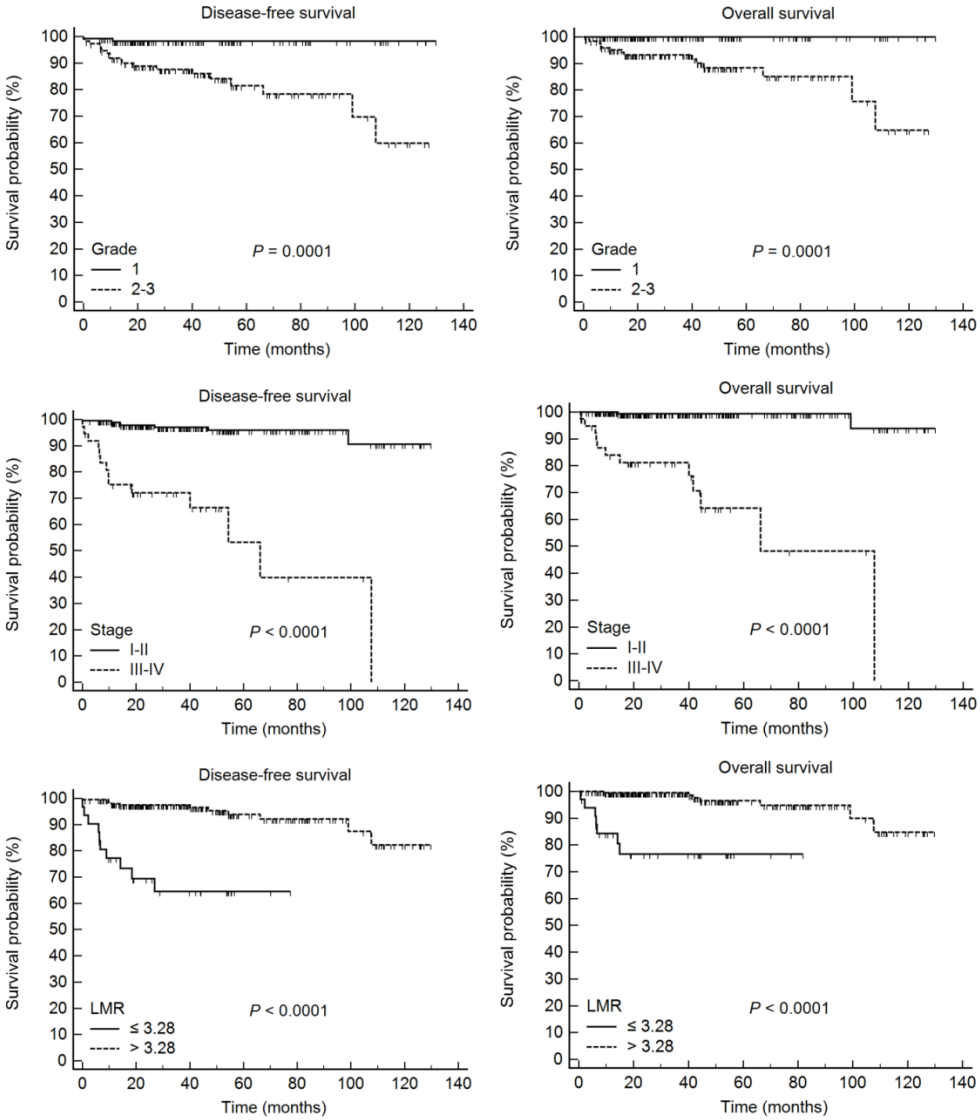

Figure 1. Disease-free survival and overall survival according to the histological grade, FIGO stage, and lymphocyte-monocyte ratio in 255 patients with endometrial cancer.

Table 4. Relationship between tumor- and host-related characteristics and overall survival in 255 patients with endometrial cancer

Variable	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years) (≤ 56 vs. > 56)	2.55 (0.85, 7.67)	0.0960		
Histology (endometrioid vs. others)	12.868 (4.13, 40.02)	< 0.0001		
Histologic grade (G1 vs. G2–G3)	69.88 (0.94, 5173.32)	0.0531		
FIGO stage (I–II vs. III–IV)	45.27 (10.00, 204.82)	<0.0001	18.67 (4.08, 85.50)	< 0.0001
LVSI (absent vs. present)	16.86 (4.70, 60.49)	< 0.0001		
CA-125 (unit/mL) (≤ 48.1 vs. > 48.1)	6.76 (2.23, 20.51)	< 0.0001		
Albumin (g/dL) (≤ 4.4 vs. > 4.4)	0.22 (0.05, 0.97)	0.0460		
WBC (per μL) (≤ 5410 vs. > 5410)	3.52 (0.46, 27.04)	0.2260		
ANC (per μL) (≤ 3665.1 vs. > 3665.1)	2.47(0.69, 8.85)	0.1663		
ALC (per μL) (≤1526.9 vs. >1526.9)	0.26 (0.09,0.74)	0.0117		
AMC (per μL) (≤ 528.4 vs. > 528.4)	4.86 (1.65, 13.32)	0.0042		
Hemoglobin (g/dL) (≤11.7 vs. >11.7)	0.14 (0.04, 0.44)	< 0.0001		
MCV (fL) (≤ 90 vs. > 90)	3.01 (0.99, 9.13)	0.0513		
Platelet (x 10^3/μL) (≤204 vs. >204)	0.32 (0.09, 1.07)	0.0638		
NLR (≤ 2.44 vs. > 2.44)	3.47 (1.20, 10.05)	0.0217		
PLR (≤ 190.78 vs. > 190.78)	2.89 (1.00, 8.38)	0.0497		
LMR (≤ 3.28 vs. > 3.28)	0.02 (0.01, 0.55)	< 0.0001	0.07 (0.02, 0.24)	< 0.0001

HRs were obtained from Cox's proportional hazard model.

HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion;CA-125, cancer antigen 125; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio

Discussion

Cancer of the endometrium is now the most frequently diagnosed gynecologic cancer in the developed world [1]. The majority of ECs present as low-grade tumors with a low risk for extrauterine spread and favorable survival outcomes. In addition, abnormal bleeding from the vagina is an early sign of EC, and thus the majority of patients are diagnosed with stage I disease [1]. Because of the favorable tumor characteristics in EC, with frequent low-grade tumors and early-stage disease at the time of presentation, long periods of remission and even cure are possible in the majority of patients. However, despite a multidisciplinary treatment approach with surgery, chemotherapy, and radiotherapy, certain patients with EC do develop disease recurrence, and cure in these cases can be quite challenging. Therefore, novel approaches for identifying tumors that are likely to recur may allow for optimization of treatment in these patients, along with improved survival.

The association between inflammation and cancer was first described by Virchow in 1863 [43], and emerging evidence has highlighted the importance of chronic inflammation in the malignant transformation, promotion, and metastasis of cancer [44, 45]. In previous clinical studies, pretreatment numbers of peripheral blood cells, including neutrophils, lymphocytes, and monocytes, have been found to be significantly associated with the progression and survival in several different kinds of cancers [24, 37, 46]. Furthermore, in recent years, several prognostic indicators derived from peripheral blood, such as the NLR, PLR, and LMR, have been widely investigated as potentially useful prognostic markers in cancers. Despite inconsistent results from several clinical trials, these markers allegedly have significant diagnostic and prognostic value in a wide variety of cancer conditions. The NLR has been demonstrated to be a prognostic parameter for various cancer types. In EC, an elevated NLR was found to predict poor OS [15, 16] on multivariate analysis. In addition, elevated PLR was found to significantly affect the OS of women with EC on multivariate analysis [15]. In the present study, the prognostic impact of the NLR and PLR on DFS and OS was demonstrated on univariate analysis, but the significance of the associations was lost on multivariate analysis (Tables 3 and 4), as has been reported by Li et al. [47]. The possible reasons for the discrepant findings for the NLR and PLR may relate to the fact that optimized cutoffs were quite different between studies.

The LMR has been suggested to be associated with survival in patients with malignant lymphomas [18-20] and many solid tumors, such as head and neck [21-23], breast [24], lung [25-27], esophageal [28, 29], gastric [30, 31], colorectal [32, 33], pancreatic [34, 35], bladder [36], and cervical cancers [37]. The cutoff values for the LMR were determined by ROC curve analysis in most studies, and these values ranged from 2.6 to 5.1. A low LMR was found to be associated with poor OS in previous studies [18, 19, 21, 23, 25-29, 32-37], and the LMR can be considered a potential surrogate biomarker in various cancers. The findings of the present study demonstrate that the LMR is a surrogate marker for both DFS and OS on multivariate analysis (Tables 3 and 4). Moreover, although circulating ALC could predict survival outcomes, the LMR was shown to outperform ALC. In a similar study by Cummings et al., the monocyte-lymphocyte

ratio, the reciprocal of the LMR, was not an independent prognostic factor for OS [15].

Although the precise mechanisms of the association between lower LMR and poor outcome have not been clarified, LMR is thought to reflect the balance between the favorable prognostic effect of lymphocytes and the unfavorable role of monocytes with respect to cancer progression [23]. Lymphocytes play important roles in defense against cancer cells by inducing apoptosis and suppressing proliferation and migration of cancer cells [44, 48]. The CD3+ T cells and natural killer (NK) cells exhibit potent anti-cancer activities by inhibiting growth and metastasis of cancer cells [49]. Prognostic significance of peripheral lymphocyte count in various kinds of cancers has been reported [21, 50]. In the present study, ALC was a prognostic factor for both DFS and OS on univariate analysis, although not on multivariate analysis. Monocytes are another important component of peripheral blood. Inflammation can trigger the mobilization of monocytes from the bone marrow to the peripheral blood [51]. After recruitment into tumor tissue, monocytes can differentiate into tumor-associated macrophages (TAMs) [52, 53]. Circulating monocytes in the blood may reflect the presence of TAMs [25]. In a study by Matsuo et al., elevated monocyte counts were an independent prognostic factor for DFS and OS in patients with EC [12]. In the current study, the AMC was a prognostic variable for both DFS and OS, but the significance was lost on multivariate analysis (Tables 3 and 4).

Histologic grade is one of the important factors associated with extrauterine spread and survival. Fortunately, the majority of ECs are present as low-grade tumors that tend to limit their spread to the surface of the endometrium, with a low likelihood of metastatic extension or need for adjuvant therapy [54]. Histologic grade was reported to be an independent prognostic factor for both DFS [12, 55-57] and OS [12, 55-60] in EC. In the present study, we also found histologic grade to be a predictor of DFS on multivariate analysis, as reported in previous studies [12, 55-57]. However, histologic grade was not a predictor of OS in the present study, as found in previous reports [14, 61].

The strength of the current study is that it represents the first attempt to evaluate the prognostic value of the LMR in patients with EC. It is worth noting that the optimum cutoff point for LMR determined in the current study delineates a relatively small subset of patients as high risk, although this subset was associated with predominantly poor outcomes. Moreover, the value of the LMR was evaluated together with previously validated biomarkers, namely the NLR and PLR. In addition, our study was conducted at multiple institutions. Finally, by performing simple and low-cost peripheral blood examinations, it might be possible to identify patients who are at high risk of experiencing relapse or death after the standard treatment.

This study had some limitations that should be addressed, including its retrospective nature and the inclusion of a relatively small number of patients. Potential confounding biases may have negatively affected the accuracy of the results. Moreover, the median follow-up duration was rather short. In addition, the tumor types and stages included in this study were heterogeneous. Another limitation was that the LMR may be a non-specific marker of inflammation, and the results may have been affected by the presence of other systemic diseases [62]. To better understand the prognostic role of the LMR and to apply this convenient, simple, and inexpensive prognostic factor for risk stratification, additional large-scale investigations should be conducted.

In conclusion, we found that an elevated LMR was an independent prognostic factor for DFS and OS, as determined by multivariate analysis using the Cox model. Therefore, the LMR may be clinically reliable, and thus useful for the accurate prediction of prognosis in EC.

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Competing Interests

The authors have declared that no competing interest exists.

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