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ORIGINAL RESEARCH

Preoperative Haematologic Markers for the Differentiation of Endometrial Cancer from Benign Endometrial Lesions in Postmenopausal Patients with Endometrial Masses

Yong Jung Song[1,2], Hwi Gon Kim[1,2], Hyung Joon Yoon[1], Kyung Un Choi[3], Dong Soo Suh[1,*], Ki Hyung Kim[1,*]

[1]Department of Obstetrics and Gynecology, Pusan National University School of Medicine, Busan, South Korea; [2]Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, South Korea; [3]Department of Pathology, Pusan National University School of Medicine, Busan, South Korea

*These authors contributed equally to this work

Correspondence: Ki Hyung Kim, Department of Obstetrics and Gynecology, Pusan National University School of Medicine, Busan, 49241, South Korea, Tel +82-51-240-7287, Fax +82-51-248-2384, Email ghkim@pusan.ac.kr

Purpose: The diagnostic value of preoperative hematological changes in endometrial cancer (EC) remains unclear. This study aimed to assess the role of preoperative hematologic parameters in differentiating EC from benign endometrial lesions in postmenopausal women with endometrial masses.

Methods: Preoperative laboratory variables were retrospectively reviewed in patients with malignant or benign endometrial lesions, and the significance of intergroup differences was assessed. Receiver operating characteristic curves were used to analyze the optimal cut-off values for each variable. Logistic regression analysis was used to identify the variables predicting the presence of endometrial malignancy.

Results: Preoperative laboratory variables of 176 patients (84 EC and 92 benign lesions) with endometrial masses were analyzed. Significant differences were observed between malignant and benign lesions in terms of WBC count, ANC, MCV, MPV, PDW, CA125, NLR, PMR, LMR, and SII ($P < 0.05$). Multivariate analyses showed that a high WBC count, high ANC, low MCV, low MPV, low PDW, high CA125, high NLR, high PMR, high LMR, and high SII independently predicted the presence of endometrial malignancy.

Conclusion: The combination markers, MPV+PDW+NLR, had good discriminatory power for the presence of malignancy (AUC 0.797). Our results suggest that hematologic markers could be useful for the differentiation of malignant and benign endometrial lesions.

Keywords: endometrial cancer, differentiation, hematologic parameters, combination markers

Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries and usually affects postmenopausal women.[1] In Korea, the incidence of EC has increased rapidly in recent years; in 2018, the age-standardized incidence rate was 7.7 cases per 100,000 women, and the number of newly diagnosed EC cases and deaths attributed to EC was 3182 and 327, respectively.[2,3]

Endometrial polyps are frequently encountered in daily practice and are more common in postmenopausal women (11.8%) than in premenopausal women (5.8%).[4] Recent meta-analyses showed that the prevalence of premalignant or malignant lesions in patients diagnosed with endometrial polyps was 3.4 to 4.93% in postmenopausal women and 1.12% in premenopausal women,[5,6] and concluded that a postmenopausal status with endometrial polyps was associated with an increased risk of malignancy. Transvaginal ultrasonography (TVUS) could be used as a first-line, cost-effective, and more acceptable imaging modality for patients. The sensitivity, specificity, and accuracy of ultrasonography in the

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diagnosis of endometrial polyps and submucosal myomas were 90.0%, 66.7%, and 87.9%, vs 88.9%, 50.0%, and 81.8%, respectively.[7] MRI is considered as the most accurate imaging technique for the preoperative assessment of endometrial cancer due to its excellent soft tissue contrast resolution. Routine MR protocols combined with diffusion-weighted imaging (DWI) sequences or apparent diffusion coefficient (ADC) measurements may provide supplementary information for the evaluation of benign and malignant lesions. The combined sensitivity and specificity of the mean ADC values for differentiating EC from benign lesions were 93% and 94%, respectively.[8] However, key sonographic findings are nonspecific and overlap between benign and malignant disorders[9] and MRI is expensive, time consuming and not always easily accepted by patients.

Invasive histological evaluation is the only standard diagnostic method to differentiate benign endometrial polyps from neoplastic lesions. Expectant management is not recommended for patients with symptoms, especially for postmenopausal women. The balance between surgery and expectant management for endometrial polyps continues to remain a clinical issue.[5] Although based on patient preference, the presence of medical comorbidities, or failed hysteroscopy, 22% of postmenopausal women with endometrial polyps are managed expectantly.[10] In these situations, the early noninvasive preoperative differentiation of EC is an important issue. Moreover, more effective noninvasive methods are needed to prevent the high healthcare costs and psychological distress associated with overtreatment of endometrial polyps.

Haematological parameters are readily accessible, routinely measured, and inexpensive inflammatory biomarkers.[11] Several studies have evaluated the relationship between inflammation and EC, but few have evaluated the diagnostic value of systemic inflammatory markers in different cancers. In a previous study, we reported the usefulness of preoperative hematologic parameters as diagnostic markers of the presence of epithelial ovarian cancer (EOC) or uterine leiomyosarcoma.[12,13] Recent studies have shown that several serum markers could be used to differentiate EC from benign endometrial pathologies.[14,15]

The conclusions reached in studies investigating the diagnostic values of inflammatory markers in EC are controversial. In a study that analyzed the relationship between hematological markers and cancer, age was found to be an important confounding factor because age-related changes in the hematopoietic system affected overall results in the elderly.[11] However, few studies have addressed hematological marker changes in postmenopausal patients with endometrial malignancy. Thus, the current study aimed to evaluate the diagnostic value of preoperative haematological parameters in postmenopausal women with endometrial masses.

Materials and Methods

Subjects

We retrospectively reviewed the clinical records of 176 patients who underwent surgical resection of endometrial masses between January 2018 and September 2021. Most women presented with postmenopausal spotting/bleeding, brownish vaginal discharge, or thickened endometrium on ultrasonography. TVUS was performed before surgery for both benign and malignant diseases. Endometrial cancer, endometrial polyps, and submucosal myomas were diagnosed after hysteroscopic resection or D&C, respectively. In cases of endometrial cancer after hysteroscopic resection or D&C, MRI was performed for further treatment. The 176 patients were categorized into two groups: an endometrial cancer group (n=84) and a benign group (n=92). The benign group included women with endometrial polyps (n=69) or submucosal myomas (n=23). Submucosal myomas appear as polypoid masses protruding into the uterine cavity. The exclusion criteria were as follows: (1) current receipt of tamoxifen for breast cancer or a previous history of endometrial hyperplasia or malignancy; (2) an infectious, inflammatory, hepatorenal, or hematological disease; (3) high-grade endometrioid type or nonendometrioid type carcinoma; and (4) an endometrial lesion highly suspected to be malignant based on ultrasound findings. Clinical and preoperative laboratory variables were subjected to statistical analyses. All microscope slides were reviewed by a single gynecologic pathologist (KU Choi) to ensure consistency. The study was performed in accordance with the ethical standards described in the Declaration of Helsinki and was approved beforehand by the Institutional Review Board (IRB) of Pusan National University Hospital (IRB #2210-019-120), which waived the requirement for written informed consent because of the retrospective nature of the study. All participants' identities remained anonymous and confidential.

Data Extraction

Patient ages, body weights, and body mass index (BMIs) at the time of surgery were retrieved from medical records. Laboratory data such as white blood cell (WBC) count, platelet count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), hemoglobin (Hb) concentrations, mean corpuscular volumes (MCVs), red cell distribution widths (RDWs), mean platelet volumes (MPVs), platelet distribution widths (PDWs), and cancer antigen 125 (CA125) levels were assessed. Laboratory tests were performed within 1–2 weeks prior to surgery. The NLR, platelet-to-lymphocyte ratio (PLR), platelet-to-monocyte ratio (PMR), and lymphocyte-to-monocyte ratio (LMR) were calculated by dividing ANC by ALC, platelet count by ALC, platelet count by AMC, and ALC by AMC. The systemic immune-inflammatory index (SII) was defined as SII = P × N/L, where P, N, and L are pretreatment peripheral blood platelet, neutrophil, and lymphocyte counts (cells/L), respectively. ROC curve analysis was used to determine the discriminatory power for the presence of endometrial malignancy.

Statistical Analysis

Categorical variables were presented as frequencies and percentages. Continuous variables with a normal distribution are presented as the mean and standard deviation (SD); skewed variables are reported as median and interquartile range (IQR). The normality of the data distribution was checked using the Kolmogorov–Smirnov test. The two groups were compared using a two-sample *t*-test or Mann–Whitney *U*-test for continuous data and Fisher's exact test for categorical data. Receiver operating characteristic (ROC) curves were drawn by plotting sensitivity against 1-specificity, and areas under the ROC curves (AUCs) were used to evaluate diagnostic performance. Statistical analysis of the characteristics of endometrial cancer patients was performed using R (http://cran.r-project.org) version 4.0.5, and additional packages (pROC, plotROC). In all analyses, a p-value <0.05 was considered statistically significant.

Results

Patient Characteristics

Eighty-four patients had EC and 92 patients had benign lesions (endometrial polyps or submucosal myomas). Hysteroscopic resection was performed in 89 cases and D&C in 87 cases. Patients with EC were matched to patients with benign lesions who underwent hysteroscopic resection, D&C, or hysterectomy during the same period. The patient characteristics are summarized in Table 1. The median ages of the EC patients and benign group were 58 (51–75) and 61.5 (51–86) years, respectively, and the median BMIs were 24.4 (range, 18.4–32.5) and 22.9 (range, 15.7–34.4), respectively. A significant difference was observed between the EC patients and the benign group in the presence of AUB (78.6% vs 29.3%).

Laboratory Values Between Endometrial Cancer and Benign Lesions

The laboratory results for both the groups are shown in Table 2. The following variables were significantly different between the two groups: WBC count, ANC, MCV, MPV, PDW, CA125, NLR, PMR, LMR, and SII ($P < 0.05$). In the EC group, the median WBC count, ANC, MCV, MPV, PDW, and CA125 were 6560/μL (3700–13,590/μL), 3969.7/μL (1997.9–12,434.9/μL), 89.8 fL (67.7–96.2 fL), 9.95 fL (8.00–11.30), 10.95 fL (8.40–15.20 fL), and 19.5 U/mL (5.23–290.8), respectively, and the corresponding values in the benign group were 5590/μL (3090–14,060/μL), 3182.3/μL

Table 1 Patient Characteristics of Malignant and Benign Lesions

	Malignant Lesions, Median (IQR) (n=84)	Benign Lesions, Median (IQR) (n=92)	*P* value
Age (years)	58.0 (51–74)	61.5 (51–86)	0.002
BMI (kg/m^2)	24.4 (18.4–32.5)	22.9 (15.7–34.4)	0.001
Nulliparity (n, %)	7 (8.3)	19 (20.7)	0.032
AUB (n, %)	66 (78.6)	27 (29.3)	0.000
Hypertension (n, %)	31 (36.9)	15 (16.3)	0.002
Diabetes mellitus (n, %)	12 (14.3)	7 (6.4)	0.024

Table 2 Laboratory Values Between Endometrial Malignancy and Benign Lesions

	Malignant Lesions, Median (IQR) (n=84)	Benign Lesions, Median (IQR) (n=92)	*P*-value
WBC (per μL)	6560.0 (3700–13,590)	5590.0 (3090–14,060)	0.000
ANC (per μL)	3969.7 (1997.9–12,434.8)	3182.3 (1192.7–8478.2)	0.000
MCV (fL)	89.8 (67.7–96.2)	91.7 (72.0–103.2)	0.000
MPV (fL)	9.95 (8.0–11.3)	10.20 (8.6–13.0)	0.000
PDW (fL)	10.95 (8.4–15.2)	11.70 (8.2–51.0)	0.015
CA125 (U/mL)	19.5 (5.2–290.8)	13.7 (4.5–71.4)	0.000
NLR	1.99 (0.81–17.94)	1.78 (0.03–4.02)	0.016
PMR	702.0 (214.5–2512.7)	632.0 (81.0–1370.8)	0.011
LMR	5.6 (0.85–11.97)	5.0 (0.65–408.47)	0.028
SII	514.1 (171.7–4449.7)	418.8 (8.6–1632.1)	0.009

Note: P-values for comparisons of medians were obtained using Wilcoxon rank-sum test.
Abbreviations: IQR, interquartile range; BMI, body mass index; WBC, white blood cell; ANC, absolute neutrophil count; MCV, mean corpuscular volume; MPV, mean platelet volume; PDW, platelet distribution width; NLR, neutrophil-lymphocyte ratio; PMR, platelet-to- monocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammatory index.

(1192.7–8478.2/μL), 91.7 fL (72.0–103.2), 10.20 fL (8.60–13.00 fL), 11.70 fL (8.20–51.00), and 13.7 U/mL (4.53–71.40), respectively. In addition, the NLR, PMR, LMR, and SII in the EC group were 1.99 (0.81–17.94), 702.0 (214.5–2512.7), 5.64 (0.85–11.97), and 514.1 (171.7–4449.7), respectively, and the corresponding values in the benign group were 1.78 (0.03–4.02), 632.0 (81.02–1370.84), 5.03 (0.65–408.47), and 418.8 (8.63–1632.11), respectively. Hb, RDW, lymphocyte, monocyte, and platelet counts did not differ significantly between the two groups ($P > 0.05$).

Predictive Efficacy of Laboratory Data

ROC curve analysis determined that the optimal thresholds for WBC count, ANC, MCV, MPV, PDW, and CA125 were 6230, 2841, 92.1, 10.0, 11.3, and 13.5, respectively (Table 3). The variable AUCs, sensitivities, specificities, and P-values are shown in Table 4. ROC curve analyses determined that the optimal cut-off points for NLR, PMR, LMR, and SII were; 1.96 (AUC=0.605; sensitivity, 0.524; specificity, 0.685), 883.3 (AUC=0.611; sensitivity, 0.369; specificity, 0.826), 6.85 (AUC=0.596; sensitivity, 0.357; specificity, 0.826), and 508.4 (AUC=0.615; sensitivity, 0.524; specificity, 0.663), respectively (Table 4). The following variables were significantly associated with the presence of EC in univariate

Table 3 Univariate and Multivariate Analyses for the Discrimination of Variables That Predict Endometrial Adenocarcinoma

Optimal Cut-off		Univariate		Multivariate Adjusted for Age and BMI	
		OR (95% CI)	P value	OR (95% CI)	P value
WBC (per μL)	≥6230	3.047 [1.648, 5.635]	0.000	3.131 [1.621, 6.049]	0.001
ANC (per μL)	≥2841	3.864 [1.933, 7.726]	0.000	3.958 [1.884, 8.313]	0.000
MCV (fL)	≤92.1	3.511 [1.810, 6.808]	0.000	3.103 [1.541, 6.248]	0.002
MPV (fL)	≤10.0	3.980 [2.080, 7.617]	0.000	4.048 [2.032, 8.064]	0.000
PDW (fL)	≤11.3	2.517 [1.371, 4.620]	0.003	3.079 [1.582, 5.990]	0.001
CA125 (U/mL)	≥13.5	3.706 [1.855, 7.404]	0.000	5.552 [2.533, 12.166]	0.000
NLR	≥1.96	2.390 [1.293, 4.415]	0.005	2.523 [1.305, 4.878]	0.006
PMR	≥883.3	2.778 [1.383, 5.583]	0.004	2.692 [1.272, 5.699]	0.010
LMR	≥6.85	2.639 [1.311, 5.313]	0.007	2.468 [1.184, 5.147]	0.016
SII	≥508.4	2.165 [1.178, 3.978]	0.013	2.336 [1.210, 4.096]	0.011

Notes: Results of multiple logistic regression with variables show a P-value less than 0.05 in univariate regression. Multivariate model is adjusted for BMI.
Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; WBC, white blood cell; ANC, absolute neutrophil count; MCV, mean corpuscular volume; MPV, mean platelet volume; PDW, platelet distribution width; NLR, neutrophil-lymphocyte ratio; PMR, platelet-to- monocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammatory index.

Table 4 Predictive Efficacy of Clinical Characteristics and Laboratory Data

	AUC	95% CI	Sensitivity	Specificity	LR+	LR-	PPV	NPV	*P*-value
BMI	0.641	0.559–0.723	0.571	0.685	1.813	0.626	0.623	0.636	0.001
WBC (per μL)	0.658	0.578–0.738	0.619	0.652	1.780	0.584	0.619	0.652	0.000
ANC (per μL)	0.666	0.586–0.745	0.821	0.457	1.511	0.391	0.580	0.737	0.000
MCV (fL)	0.661	0.581–0.742	0.786	0.489	1.538	0.438	0.584	0.714	0.000
MPV (fL)	0.659	0.579–0.740	0.762	0.554	1.710	0.430	0.610	0.718	0.000
PDW (fL)	0.606	0.522–0.690	0.607	0.620	1.596	0.634	0.593	0.633	0.014
CA125 (U/mL)	0.684	0.602–0.766	0.788	0.600	1.575	0.425	0.612	0.702	0.000
NLR	0.605	0.522–0.689	0.524	0.685	1.662	0.695	0.603	0.612	0.015
PMR	0.611	0.528–0.695	0.369	0.826	2.122	0.764	0.660	0.589	0.010
LMR	0.596	0.511–0.680	0.357	0.826	2.054	0.778	0.652	0.585	0.027
SII	0.615	0.532–0.698	0.524	0.663	1.555	0.718	0.587	0.604	0.007
Model 1	0.797	0.732–0.862	0.810	0.674	2.483	0.283	0.694	0.795	0.000

Note: Model 1= MPV+PDW+NLR.

Abbreviations: AUC, area under curve; CI, confidence interval; WBC, white blood cell; ANC, absolute neutrophil count; MCV, mean corpuscular volume; MPV, mean platelet volume; PDW, platelet distribution width; NLR, neutrophil-lymphocyte ratio; PMR, platelet-to-monocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammatory index; LR+, Positive likelihood ratio; LR-, Negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

logistic regression analyses: BMI, WBC count, ANC, MCV, MPV, PDW, CA125, NLR, PMR, LMR, and SII (all $P < 0.05$). Multivariate logistic regression analyses showed that high WBC count (OR=3.13, 95% CI=1.62–6.05, P=0.001), high ANC (OR=3.96, 95% CI=1.88–8.31, P=0.00), low MCV (OR=3.10, 95% CI=1.54–6.25, P=0.002), low MPV (OR=4.05, 95% CI=2.03–8.06, P=0.000), low PDW (OR=3.08, 95% CI=1.58–5.99, P=0.001), high CA125 (OR=5.55, 95% CI=2.53–12.17, P=0.000), high NLR (OR=2.52, 95% CI=1.31–4.88, P=0.006), high PMR (OR=2.69, 95% CI=1.25–5.70, P=0.010), high LMR (OR=2.47, 95% CI=1.18–5.15, P=0.016), and high SII (OR=2.34, 95% CI=1.21–4.10, P=0.011) independently predicted the presence of endometrial cancer (Table 3). Model 1, based on a combination of hematologic markers (MPV+PDW+NLR), had an AUC of 0.797, a sensitivity of 0.810, and a specificity of 0.674 (Figure 1).

Discussion

Although previous studies have reported the diagnostic efficiency of EC as determined using sonographic (postmenopausal endometrial thickness) or clinical (postmenopausal bleeding) criteria, few have attempted to identify easily accessible hematological markers for the differentiation of EC and benign endometrial lesions. Furthermore, studies on the associations between hematologic parameters and the preoperative differentiation of EC in postmenopausal patients are lacking. Accordingly, we aimed to determine the predictive values of preoperative hematological parameters in postmenopausal patients with endometrial masses. In this study, univariate and multivariate logistic regression analyses showed that WBC ≥ 6230 (/μL), ANC ≥ 2842 (/μL), MCV ≤ 92.1 fL, MPV ≤ 10.0 fL, PDW ≤ 92.1 fL, CA125 ≥ 13.5 (U/mL), NLR ≥ 1.96, PMR ≥ 883.3, LMR ≥ 6.85, and SII ≥ 508.4 significantly predicted the presence of EC. Furthermore, a combination of hematologic markers (MPV+PDW+NLR) improved the differential diagnosis of malignant and benign endometrial lesions, with an AUC of 0.797, a sensitivity of 81.0%, and a specificity of 67.4%. No significant intergroup differences were observed in Hb, RDW, or lymphocyte, monocyte, or platelet counts.

Whether the endometrial masses included in this study were endometrial polyps or submucosal myomas remains undetermined. In addition to endometrial polyps, submucosal myomas appear as polypoid masses protruding into the uterine cavity. Submucosal myomas are among the main reasons for postmenopausal uterine bleeding and are included in the differential diagnosis of endometrial polyps and malignant lesions.[16] The uterine myomas included in this study appeared to be endometrial polyps on preoperative ultrasonography, and after surgery, they were finally confirmed as uterine myomas.

Cancer development and inflammation are closely associated, and increasing evidence suggests that chronic inflammation plays a crucial role in tumor initiation, progression, and host antitumor immunity. This suggests that systemic

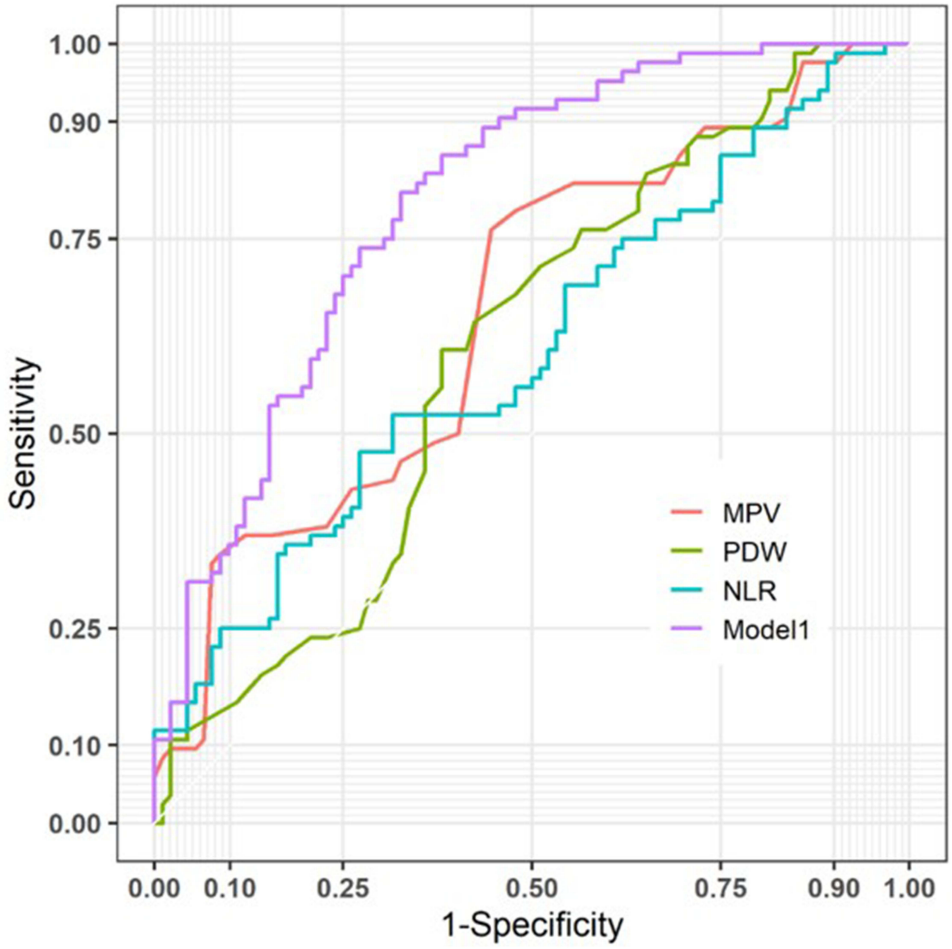

Figure 1 Receiver operating characteristic (ROC) curves for the differentiation between endometrial malignant and benign lesions. Model 1, a combination of hematologic markers (MPV+PDW+NLR).
Abbreviations: MPV, mean platelet volume; PDW, platelet distribution width; NLR, neutrophil-lymphocyte ratio.

inflammatory blood markers might provide useful information regarding the presence of malignancy. Inflammation and EC have been reported to be closely associated, and the inflammatory responses to malignant and benign endometrial pathologies vary, which concurs with our findings. Although the mechanism has not been elucidated, neutrophils, lymphocytes, and platelets, which are the main components of inflammation, are known to contribute to tumor development.[17] A list of recent studies that used hematologic parameters as a preoperative diagnostic marker is provided in Table 5. Notably, the reported results are inconsistent.

Risk factors for EC include advanced age, obesity, diabetes mellitus, hypertension, and nulliparity. In particular, the association between age and malignancy risk has been well studied. Bel et al reported the prevalence of malignant lesions in menopausal patients with endometrial polyps. Subgroup analysis showed that the risk of malignancy was highest in postmenopausal women > 59 years with abnormal uterine bleeding who presented with an endometrial polyp (12%).[6] Additionally, age-related changes in the immune system include low-grade inflammation and the immune response, which increase susceptibility to various diseases, including malignancies.[27] In the present study, patients presenting a malignant lesion were significantly older. Based on age at presentation, the median age of patients with EC was lower than that of the benign group, probably due to earlier symptom occurrence and earlier hospital visits in the EC group. Diabetes mellitus and hypertension have been considered to be positively associated with the risk of EC, and we found that the prevalence of both was higher in patients with EC than in the benign group. Furthermore, BMI is a well-known independent risk factor for EC and is also significantly associated with endometrial polyps in postmenopausal women.[28] As has been reported in previous studies, women with a malignant lesion had a higher mean BMI in this study.

Table 5 Summary of Recent Studies Using Hematologic Parameters as a Preoperative Diagnostic Marker

Author (Year)	WBC	ANC	Hb	MCV	RDW	PLT	MPV	PDW	NLR	LMR	PMR	PLR	SII	CA125
Acmaz et al (2014)[18]	◉					◉			◉			◉		
Kurtoglu et al (2015)[17]							◉	◉						
Karateke et al (2015)[19]							◉	◉						
Kemal et al (2015)[20]					◉									
Ural et al (2015)[21]								◉	◉					
Abide et al (2018)[22]				◉	◉		◉							
Pergialiotis et al (2018)[23]									◉					
Bacanakgil et al (2018)[24]									◉					
Zhang et al (2020)[15]			◉		◉		◉	◉						◉
Alper et al (2021)[25]									◉					
Ilgen et al (2022)[26]									◉					
Our study (2023)	◉	◉		◉			◉	◉	◉	◉	◉		◉	◉

Note: The colored parameters are a part that has been reported to be significant in common in several previous studies.
Abbreviations: WBC, white blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; MCV, mean corpuscular volume; RDW, red cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PMR, platelet-to- monocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index.

Several studies have evaluated the potential use of CA125 as a diagnostic biomarker for EC.[29,30] Knific et al reported that serum CA125 levels were significantly higher in patients with EC than in the benign group; median CA125 levels were 19.58 U/mL (range, 5.46–880.10) and 13.07 U/mL (range, 6.70–35.82), respectively.[29] Similarly, in our study, median CA125 levels were 19.45 U/mL (range, 5.23–290.8) and 13.65 U/mL (range, 4.53–71.40), respectively. In contrast, Abdalla et al reported that this marker alone did not reliably differentiate between malignant and benign endometrial pathologies.[31] Others evaluated the diagnostic value of CA125 alone or in combination with other tumor markers, and combinations including CA125 and other serum markers showed better diagnostic discriminatory potential than serum CA125 alone.[29,30] Optimal diagnostic performance was reported for a model including BMI and serum CA125 and HE4 levels,[29] and a combination of CA125 and multiplication of neutrophils and monocytes (MNM) had significantly higher diagnostic efficacy than CA125.[30]

Furthermore, in line with previous reports,[18] we found that the WBC counts were significantly higher in the EC group than in the benign group. Neutrophils are the most predominant leukocyte subset and are involved in the activation, regulation, and effector functions of immune cells,[32] and in the presence of systemic inflammation, increases in neutrophil numbers have been related to the presence of malignancies, although the mechanism remains unclear.[33] Neutrophils may release several mediators and related chemokines that promote tumor development and progression. In the present study, the median neutrophil count in the EC group was higher than that in the benign group, which is consistent with previous studies.[11] However, the median lymphocyte and platelet counts were similar in the two study groups. Unlike neutrophils, lymphocytes are involved in the regulation of tumor immunity; thus, lymphopenia indicates a diminished antitumor immune ability. Studies on lymphocyte counts in EC patients are limited. Nonetheless, reports indicate that relative lymphopenia secondary to an increased neutrophil count occurs in response to systemic inflammation. However, studies have also reported that lymphocyte count is associated or not associated with the prognosis of EC.[34,35] In our study, median lymphocyte counts were not significantly different between the two groups.

Furthermore, studies have reported that an elevated preoperative NLR (an index of systemic inflammation) significantly predicts the presence of EC,[18,21,23–25] and a meta-analysis showed that NLR values were significantly higher in patients with EC than in controls. However, the NLR cannot be used alone to diagnose malignant lesions in postmenopausal women

because of its low diagnostic accuracy.[23] However, other researchers failed to find any meaningful difference between NLR values in benign and malignant endometrial groups.[15,22,36] In the present study, the NLR was higher in the EC group than in the benign group (p=0.016), which is in line with prior studies. Bacanakgil et al reported that an NLR of ≥ 4 significantly differentiated endometrial pathologies before intervention in patients with abnormal uterine bleeding.[24] Ural et al reported that the NLR was significantly higher in EC patients than in controls.[21] However, the cut-off values reported by these investigators were higher than those determined in our study (Table 3). Furthermore, we previously reported that LMR predicts the presence of EOC,[13] and in this study, a high LMR (≥ 6.85) was also associated with the presence of EC.

Inflammatory cells in the tumor microenvironment release cytokines, and excessive production of these cytokines stimulates the release of young and large platelets from the bone marrow to the peripheral blood and changes hematological parameters.[22] Platelets are thought to be associated with the immune system and tumor development, and an elevated platelet count is an inflammatory marker associated with the response to cancer.[37] However, no significant intergroup difference was observed in the present study, which is consistent with previous studies.[19,22] MPV and PDW are considered to reflect platelet activation. MPV is the main indicator of platelet activation and plays an important role in cancer progression.[38] Furthermore, a systematic review and meta-analysis found that MPV is significantly higher in individuals with various malignancies than in healthy individuals,[39] and others have shown that MPV values are higher in EC than in benign cases.[15,19,22] Zhang et al reported that an increase in MPV may be related to cancer occurrence and progression in EC,[15] and Abide et al found MPV was significantly higher in EC patients than in healthy controls and that an AUC for MPV of 58.7% for the presence of EC.[22] In contrast, Vural et al recently reported that geriatric (≥ 65 years old) and nongeriatric EC patients had significantly lower MPV values than healthy controls.[11] Similarly, in our study, MPV was significantly lower in EC patients than in the benign group (Table 2). Studies on PDW in EC are limited. Cytokines released from cancer cells lead to increased thrombopoiesis and changes in platelet size, which are expected to increase the PDW values. One study reported that PDW was significantly higher in patients with EC than in controls,[19] but recent studies have reported lower PDW values in patients with EC than in controls,[15,21,40] which concurs with our observations. Further investigations are required to resolve this issue.

The SII (systemic immune-inflammatory index) is based on lymphocyte, neutrophil, and platelet counts and has been reported to be a better index of systemic inflammation.[41] In a previous study on the predictive value of preoperative SII in EC, an elevated SII was found to be significantly associated with prognostic factors, including age, menopause, FIGO stage, and lymph node metastasis.[41] In another study, SII better-predicted prognosis than NLR or PLR in EC.[42] The combined status of neutrophils, platelets, and lymphocytes may comprehensively unveil associations between cancer cells and systematic inflammatory environments.[43] However, the ability of this strategy to predict the presence of EC remains unclear. In the present study, the SII was higher in patients with EC than in the benign group (Table 2), indicating that an elevated SII reflects elevated neutrophil or platelet counts. In addition, univariate and multivariate logistic regression analyses showed that the SII was significantly associated with the presence of EC (Table 3). However, this finding has not been reported previously.

Recently, studies on combinations of markers, rather than single markers, have reported improved diagnostic efficiencies.[15,29] In our study, the AUC of several significant single markers ranged from 0.596 to 0.684 (Table 4). A diagnostic model based on several hematologic markers differentiated between EC and benign endometrial lesions more accurately. ROC analysis was used to analyze the diagnostic values of MPV, PDW, NLR, and their combinations (Figure 1). The AUC values of MPV, PDW, and NLR were 0.659 (0.579–0.740), 0.606 (0.522–0.690), and 0.605 (0.522–0.689), respectively, and that of the combination for the diagnosis of EC was 0.797 (Table 4). Model 1 was made using a combination of factors that have been studied and are commonly known to be significant in previous studies (Table 5). Similar findings have not reported previously.

We previously reported on the usefulness of preoperative hematological parameters as diagnostic markers of the presence of gynecological cancers such as EOC and uterine leiomyosarcoma.[12,13] In these studies, the inflammatory markers LMR, NLR, and PLR were found to predict the presence of EOC. Furthermore, we suggest that inflammatory markers in elderly or postmenopausal patients should be considered independent biomarkers of uterine leiomyosarcoma and leiomyoma differentiation.

Recent evidence shows that non-coding RNAs (ncRNAs) play a fundamental role in various biological processes associated with the pathogenesis, risk stratification, prognosis prediction, and therapeutic strategy of EC patients.[44–46] Recent studies have reported the use of circulating micro RNAs as diagnostic biomarkers in EC. It has been reported that hundreds of ncRNAs are potentially deregulated in EC and ncRNAs can be detected in the blood circulation; therefore, circulating ncRNAs can be fast, accurate, and minimally invasive diagnostic tools.[44,47] Circulating micro RNAs of EC patients as diagnostic, prognostic and therapeutic markers could be potentially applicable for personalized medicine in the future.[44]

One strength of the current study is that it focused on postmenopausal women with endometrial masses, and the differentiation of endometrial cancer from benign endometrial masses in postmenopausal women is an important clinical issue that has not been addressed previously. However, this study had several limitations. First, the single-center, retrospective design of the present study is the main limitation. Second, the serum markers examined were nonspecific with respect to inflammation, and the laboratory results may have been affected by other clinically covert systemic inflammatory conditions, although known inflammatory diseases were excluded. Third, the sample sizes were too small to resolve differences between reported cut-off values of serum markers for the presence of EC, because cut-off values of markers vary in different studies. Further larger-scale multicenter investigations are required.

In conclusion, we compared the hematological parameters of postmenopausal women with malignant or benign endometrial lesions. Our findings showed that a combination model based on preoperative serum MPV, PDW, and NLR and patient clinical characteristics had satisfactory diagnostic accuracy for the differentiation of EC and benign endometrial lesions. Transvaginal ultrasonography has a high overall accuracy rate and excellent pathologic correlation. Our findings do not mean that hematological markers are superior to conventional ultrasonography and MRI, or that they can replace them. Our question is whether this easy and inexpensive means of predicting the presence of EC in postmenopausal patients can be an ancillary method to traditional methods. Although this topic needs further investigation, the use of these hematological markers would provide a straightforward and inexpensive means of predicting the presence of EC in postmenopausal patients with an endometrial mass. Clinically, this study would be useful during discussions of management options with patients and for selecting patients for hysteroscopic resection of endometrial polyps. Further prospective studies are necessary to identify a reliable combination of diagnostic hematological markers for patients with EC and validate the clinical application of our findings. We propose a multicenter, prospective study with a larger sample size, strict inclusion and exclusion criteria, and homogenous control group to draw firm conclusions.

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Disclosure

The authors declare that they have no competing interests in this work.

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