

Are Hematological Inflammatory Markers Useful in the Differential Diagnosis of Endometrial Cancer?

Endometrium Kanserinin Ayırıcı Tanısında Hematolojik İnflamatuvar Belirteçler Yararlı mıdır?

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ABSTRACT

Aim: To evaluate the diagnostic value of clinical characteristics and hematological inflammatory markers, including the systemic immune-inflammation index (SII), in differentiating benign and malignant endometrial pathologies.

Materials and Method: This retrospective cohort study included 395 patients who underwent endometrial sampling between January 2017 and December 2024 at a tertiary referral center. Patients were classified into benign (n=195) and malignant (n=200) groups based on histopathological findings. Clinical variables (age, body mass index [BMI], gravida, comorbidities, and presenting complaints) and hematological parameters were analyzed. Inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SII, were calculated. Statistical analyses were performed using the Mann-Whitney U test and chi-square test. Receiver operating characteristic (ROC) curve analysis was conducted to assess diagnostic performance.

Results: Significant associations were observed between pathological groups and clinical parameters, including age ($p<0.001$), BMI ($p<0.001$), hypertension ($p<0.001$), and gravida ($p=0.004$). Malignancy was more prevalent in patients aged ≥ 54 years (64.5%) and in obese individuals (45.5%). Among hematological parameters, platelet count ($p=0.038$) and PLR ($p=0.001$) were significantly higher in the benign group. However, leukocyte, neutrophil, lymphocyte counts, NLR, and SII showed no statistically significant differences ($p>0.05$). ROC analysis demonstrated poor diagnostic performance for platelet (AUC=0.560) and PLR (AUC=0.593).

Conclusion: Clinical characteristics, particularly age, BMI, hypertension, and reproductive history, are strong predictors of endometrial malignancy. In contrast, hematological inflammatory markers, including SII, have limited diagnostic utility and should not be used as standalone tools. These findings highlight the importance of comprehensive clinical evaluation and suggest that future research should focus on integrated predictive models combining clinical and laboratory parameters.

Keywords: Endometrial cancer; Systemic immune-inflammation index; Platelet-to-lymphocyte ratio; Neutrophil-to-lymphocyte ratio; Inflammatory biomarkers.

ÖZ

Amaç: Bu çalışmanın amacı, sistemik immün-inflamasyon indeksi (SII) başta olmak üzere klinik özellikler ve hematolojik inflamatuvar belirteçlerin benign ve malign endometrial patolojilerin ayırıcı tanısındaki tanılabilirliğini değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif kohort çalışmasına, Ocak 2017 ile Aralık 2024 tarihleri arasında üçüncü basamak bir merkezde endometrial örnekleme yapılan 395 hasta dahil edildi. Hastalar histopatolojik bulgulara göre benign (n=195) ve malign (n=200) gruplara ayrıldı. Yaş, vücut kitle indeksi (VKİ), gravida, komorbiditeler ve başvuru şikayetleri gibi klinik değişkenler ile hematolojik parametreler analiz edildi. Nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) ve SII hesaplandı. İstatistiksel analizlerde Mann-Whitney U testi ve ki-kare testi kullanıldı. Tanılabilir performans alıcısı işletim karakteristiği (ROC) eğrisi analizi ile değerlendirildi.

Bulgular: Patolojik gruplar ile yaş ($p<0.001$), VKİ ($p<0.001$), hipertansiyon ($p<0.001$) ve gravida ($p=0.004$) arasında anlamlı ilişki saptandı. Malignite, 54 yaş ve üzerindeki hastalarda (%64,5) ve obez bireylerde (%45,5) daha sık görüldü. Hematolojik parametreler arasında trombosit sayısı ($p=0.038$) ve PLR ($p=0.001$) benign grupta anlamlı olarak daha yüksekti. Buna karşın lökosit, nötrofil, lenfosit sayıları ile NLR ve SII açısından gruplar arasında anlamlı fark saptanmadı ($p>0.05$). ROC analizinde trombosit (AUC=0,560) ve PLR'nin (AUC=0,593) tanılabilir performansının düşük olduğu gösterildi.

Sonuç: Özellikle yaş, VKİ, hipertansiyon ve reproduktif öykü gibi klinik özellikler endometrial malignitenin güçlü belirleyicileridir. Buna karşılık SII dahil hematolojik inflamatuvar belirteçlerin tanılabilir değeri sınırlıdır ve tek başına tanılabilir araç olarak kullanılmamalıdır. Bu bulgular kapsamlı klinik değerlendirmenin önemini vurgulamakta ve gelecekte klinik ve laboratuvar parametrelerini birleştiren bütünlük prediktif modellerin geliştirilmesi gerektiğini düşündürmektedir.

Anahtar Kelimeler: Endometrium kanseri; sistemik immün-inflamasyon indeksi; trombosit-lenfosit oranı; nötrofil-lenfosit oranı; inflamatuvar biyobelirteçler.

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INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in developed countries, with a steadily increasing incidence attributed to aging populations, obesity, and metabolic disorders (1). Early and accurate differentiation between benign and malignant endometrial pathologies is essential for appropriate clinical management and timely intervention.

In recent years, the role of systemic inflammation in tumor biology has been increasingly recognized. Inflammatory processes contribute to carcinogenesis through multiple mechanisms, including promotion of angiogenesis, inhibition of apoptosis, and modulation of the tumor microenvironment (2). As a result, inflammation-based biomarkers derived from peripheral blood have emerged as potential tools for cancer assessment. Among these inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and particularly the systemic immune-inflammation index (SII) have gained considerable attention in recent years. SII is a marker of systemic inflammatory response derived from complete blood count (CBC) parameters using the formula $\text{platelet count} \times \text{neutrophil count} / \text{lymphocyte count}$ ($P \times N/L$). Owing to its easy accessibility, low cost, and reproducibility, SII has been widely investigated in oncologic and chronic inflammatory diseases (3).

SII was first introduced by Hu et al. in a retrospective study involving 133 patients with hepatocellular carcinoma treated between 2005 and 2006. Its prognostic significance was later validated in a prospective cohort of 123 patients enrolled between 2010 and 2011, where SII was identified as an independent postoperative prognostic marker (4). Since then, the prognostic value of SII has been extensively explored in various malignancies, including gynecologic cancers such as endometrial, cervical, and epithelial ovarian cancers, with multiple studies supporting its clinical relevance (3,5,6). Previous studies have shown that elevated SII levels are associated with poor survival outcomes and unfavorable clinicopathological features in patients with endometrial cancer (7). Furthermore, SII has been identified as an independent prognostic factor and may also play a role in predicting treatment response and disease progression (8). More recently, Doğan et al. demonstrated the diagnostic utility of SII in adnexal torsion, reporting significantly higher SII levels in torsion cases compared to controls. The authors identified an SII cut-off value of 821, with 82% sensitivity and 81% specificity, suggesting that SII may serve as a simple and cost-effective diagnostic inflammatory marker (9). In addition, its utility has also been explored in specific oncologic settings, including ovarian involvement and fertility-preserving treatment strategies (10).

Despite the growing evidence regarding the prognostic importance of inflammatory markers such as SII, NLR, and PLR, their diagnostic

value in differentiating benign from malignant endometrial pathologies remains uncertain. Most available studies have primarily focused on prognostic outcomes and survival analysis rather than preoperative diagnostic discrimination, leaving a clinically important gap in the literature.

Therefore, the aim of the present study was to evaluate the predictive value of clinical characteristics and hematological inflammatory markers, particularly SII, in distinguishing benign from malignant endometrial conditions in a real-world clinical setting.

MATERIALS AND METHOD

Study design and setting

This retrospective cohort study was conducted at Bağcılar Training and Research Hospital, Istanbul, Turkey, a tertiary referral center. The study included patients who underwent endometrial sampling between January 2017 and December 2024. Ethical approval was obtained from the Ethics Committee of Bağcılar Training and Research Hospital, Istanbul, Turkey (Approval No: 2025/02/14/031; Date: 28 February 2025), and the study was conducted in accordance with the Declaration of Helsinki.

Study population

A total of 395 patients were included in the study. Based on histopathological evaluation, patients were divided into two groups:

- Benign group (n = 195)
- Malignant group (n = 200)

Histopathological diagnoses were obtained from endometrial biopsy or curettage specimens. Histopathological diagnoses included normal endometrium, endometrial polyp, endometrial hyperplasia without atypia, atypical endometrial hyperplasia, and endometrial carcinoma. Histological subtypes of endometrial carcinoma included endometrioid adenocarcinoma, serous adenocarcinoma, and mixed-type carcinoma.

Inclusion and exclusion criteria

Inclusion criteria:

- Patients who underwent endometrial sampling
- Availability of complete clinical and laboratory data

Exclusion criteria:

- Presence of acute or chronic infection
- Hematological disorders

- Autoimmune diseases
- Use of immunosuppressive therapy
- Incomplete medical records

Data collection

Demographic and clinical data were obtained from electronic medical records. The collected variables included age, body mass index (BMI), gravida, comorbidities (such as hypertension), and presenting complaints.

Complete blood count (CBC) parameters obtained at the patients' initial hospital admission, prior to any surgical intervention, were recorded for analysis.

Patients were categorized according to age groups, BMI categories, and clinical characteristics for comparative analysis.

Laboratory parameters

The evaluated parameters included leukocyte, neutrophil, lymphocyte, and platelet counts.

Inflammatory indices were calculated as follows:

- Neutrophil-to-lymphocyte ratio (NLR) = neutrophil count / lymphocyte count
- Platelet-to-lymphocyte ratio (PLR) = platelet count / lymphocyte count
- Systemic immune-inflammation index (SII) = platelet count $\times$ neutrophil count / lymphocyte count

Statistical analysis

Statistical analyses were performed using SPSS software (version 27; IBM Corp., Armonk, NY, USA). Age was categorized as <54 and $\geq$ 54 years based on the optimal cut-off obtained from ROC

curve analysis. Continuous variables were expressed as median (interquartile range) and analyzed using the Mann–Whitney U test. Categorical variables were expressed as frequencies and percentages and analyzed using the chi-square test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of hematological parameters. The area under the curve (AUC) was calculated for each parameter. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 395 patients were included in the analysis, comprising 195 benign and 200 malignant cases. The clinical and demographic characteristics of the patients are summarized in Table 1.

There was a statistically significant association between pathological groups and age distribution ($p<0.01$). The proportion of benign cases was markedly higher among individuals younger than 54 years (74.9%), whereas the proportion of malignant cases increased in patients aged 54 years and older (64.5%). A significant relationship was also observed between BMI categories and pathological groups ($p<0.01$). Benign cases were more common in the normal BMI group, whereas the frequency of malignancy increased in obese and morbidly obese patients. Hypertension was significantly associated with pathological groups ($p<0.01$). Benign cases were more frequent among patients without hypertension, while hypertension was more prevalent in the malignant group (45.5%). A statistically significant relationship was found between metabolic and thyroid disorders and pathological groups ($p<0.01$). Hyperthyroidism was observed only in the malignant group (6.5%), whereas hypothyroidism was present in both groups but was more common in the benign group. Gravida was also significantly

Table 1. Clinical and demographic characteristics of the study population

Variable	Benign (n=195)	Malignant (n=200)	p-value
Age <54 years, n (%)	146 (74.9%)	71 (35.5%)	<0.001
Age $\geq$ 54 years, n (%)	49 (25.1%)	129 (64.5%)	
BMI - Normal	22 (11.3%)	9 (4.5%)	<0.001
BMI - Overweight	117 (60.0%)	70 (35.0%)	
BMI - Obese	40 (20.5%)	91 (45.5%)	
BMI - Morbid obese	16 (8.2%)	30 (15.0%)	<0.001
Hypertension (+), n (%)	51 (26.2%)	91 (45.5%)	
Hypertension (-), n (%)	144 (73.8%)	109 (54.5%)	
Gravida 0	6 (3.1%)	23 (11.5%)	0.004
Gravida 1-3	130 (66.7%)	106 (53.0%)	
Gravida 4-6	45 (23.1%)	53 (26.5%)	
Gravida $\geq$ 7	14 (7.2%)	18 (9.0%)	
Menorrhagia	77 (39.5%)	41 (20.5%)	<0.001
USG finding	54 (27.7%)	70 (35.0%)	
Other complaints	64 (32.8%)	82 (41.0%)	

associated with pathological groups ($p<0.01$). The proportion of malignancy was higher among nulligravid patients (11.5%), whereas benign cases were more frequent in patients with 1–3 pregnancies. Although the distribution was more balanced in higher gravida groups, lower gravida appeared to be associated with malignancy. Presenting complaints differed significantly between groups ($p<0.01$). Menorrhagia was more common in the benign group (39.5%), whereas ultrasonographic findings and other complaints were more frequent in the malignant group. Notably, asymptomatic patients were observed only in the malignant group. Among hematological parameters, platelet count and PLR were significantly different between the benign and malignant groups

($p<0.05$). However, leukocyte, neutrophil, lymphocyte counts, NLR, and SII did not show statistically significant differences. The ROC curves for platelet and PLR are presented in Figures 1 and 2, respectively. ROC analysis demonstrated that platelet and PLR had limited diagnostic value. The AUC values were 0.560 for platelet and 0.593 for PLR, indicating poor discriminative performance. Platelet and PLR values were significantly higher in the benign group. In contrast, leukocyte, neutrophil, lymphocyte counts, NLR, and SII did not show statistically significant differences between the groups ($p>0.05$). These findings are consistent with the results of the ROC analysis, which demonstrated limited diagnostic performance of hematological parameters (Table 2).

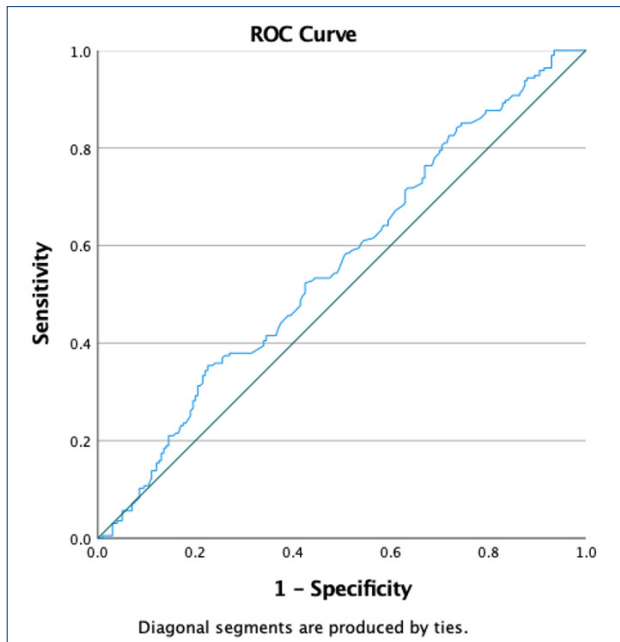


Figure 1. Receiver operating characteristic (ROC) curve of platelet count for distinguishing benign and malignant endometrial pathologies.

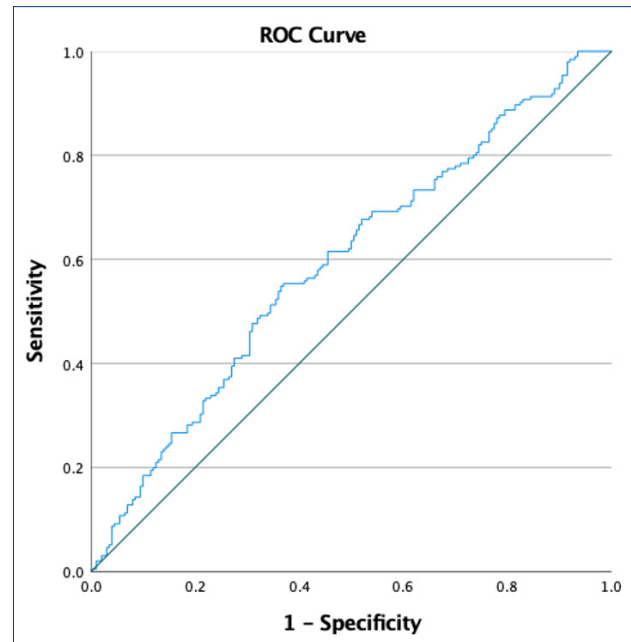


Figure 2. Receiver operating characteristic (ROC) curve of platelet-to-lymphocyte ratio (PLR) for distinguishing benign and malignant endometrial pathologies.

Table 2. Comparison of hematological parameters between benign and malignant groups

Parameter		N	Min-Max (Median)	P
Leukocyte	Benign	195	1001-21320 (7530)	0.053
	Malignant	200	1281-19500 (7945)	
Neutrophil	Benign	195	1940-20400 (4630)	0.119
	Malignant	200	1190-17680 (4910)	
Lymphocyte	Benign	195	460-7700 (2160)	0.267
	Malignant	200	270-53702 (2270)	
Platelet	Benign	195	92000-575000 (273000)	0.038*
	Malignant	200	212-657000 (264000)	
SII	Benign	195	93870.13-18837446.81 (601484.02)	0.206
	Malignant	200	392.93-6445481 (560487)	
NLR	Benign	195	0.39-8.55 (0.62)	0.574
	Malignant	200	0.08-8.52 (0.62)	
PLR	Benign	195	15.02-240.76 (38.05)	0.001**
	Malignant	200	0.01-202.97 (34.2)	

Mann Whitney U Test; * $p<0.05$; ** $p<0.01$

DISCUSSION

The present study evaluated the diagnostic value of clinical characteristics and hematological inflammatory markers in distinguishing benign from malignant endometrial pathologies. Our findings demonstrate that clinical parameters, particularly age, body mass index (BMI), hypertension, and reproductive history, are strongly associated with endometrial malignancy, whereas hematological inflammatory markers have limited diagnostic utility.

Consistent with previous reports, advanced age and obesity were significantly associated with malignancy in our cohort. Endometrial cancer is closely linked to metabolic and hormonal factors, particularly in postmenopausal women. Obesity contributes to increased peripheral estrogen production through aromatization, resulting in prolonged endometrial stimulation and increased carcinogenic risk. Furthermore, components of metabolic syndrome, including hypertension, have been widely associated with the development of endometrial cancer (11,12).

In recent years, systemic inflammation has been recognized as a key factor in cancer biology. Inflammatory cells and mediators within the tumor microenvironment promote tumor growth, angiogenesis, and metastasis (13). Consequently, inflammation-based biomarkers such as NLR and PLR have been widely investigated across multiple malignancies and have shown variable diagnostic and prognostic value (14).

SII, which integrates platelet, neutrophil, and lymphocyte counts, has been proposed as a comprehensive indicator of the balance between host immune response and tumor-promoting inflammation. Several studies have demonstrated that elevated SII is associated with poor survival outcomes and advanced disease stages in endometrial cancer patients (3,7). Moreover, SII has been reported as an independent prognostic factor and a predictor of treatment response (8).

However, in contrast to these findings, our study did not demonstrate a significant association between SII and endometrial malignancy. This discrepancy may be explained by differences in study design and endpoints. Most previous studies have focused on prognostic outcomes, such as survival and recurrence, rather than diagnostic discrimination between benign and malignant conditions. Additionally, differences in patient selection, sample size, and timing of laboratory measurements may have contributed to the variability in results.

Importantly, the biological behavior of endometrial cancer differs from that of acute inflammatory conditions. While acute gynecological conditions are typically associated with a pronounced

systemic inflammatory response, malignancies—particularly in early stages—may not elicit a comparable degree of systemic inflammation. This may limit the sensitivity of inflammation-based indices such as SII in detecting malignancy.

Although platelet count and PLR showed statistically significant differences between groups, their diagnostic performance was poor, as reflected by low AUC values. This finding highlights an important distinction between statistical significance and clinical applicability. While group-level differences may exist, their ability to accurately classify individual patients remains insufficient for routine clinical use.

From a biological perspective, systemic inflammatory markers are influenced by various non-malignant factors, including subclinical inflammation, obesity, and metabolic disorders. This lack of specificity may further explain their limited performance in distinguishing benign from malignant endometrial pathology. Similarly, previous proteomic studies have demonstrated that endometrial carcinogenesis involves complex molecular and protein expression alterations beyond systemic inflammatory pathways, suggesting that single hematological markers may be insufficient to fully reflect the biological heterogeneity of endometrial cancer (15).

Taken together, our findings suggest that inflammatory markers should not be used as standalone diagnostic tools. Instead, they may provide complementary information when interpreted alongside clinical risk factors.

Strengths and limitations

The strengths of this study include a relatively large sample size and the comprehensive evaluation of both clinical and hematological parameters in a real-world population. The inclusion of a well-defined control group enhances the validity of comparisons. However, several limitations should be acknowledged. First, the retrospective design introduces potential selection bias. Second, this is a single-center study, which may limit generalizability. Third, inflammatory markers were evaluated at a single time point and may not reflect dynamic changes in systemic inflammation. Finally, menopausal status was not recorded as a separate variable in the study dataset and therefore could not be included in the analysis.

Clinical implications and future directions

Our results emphasize that clinical parameters remain the cornerstone in the evaluation of endometrial pathology. Future studies should focus on developing combined predictive models integrating clinical and laboratory parameters to improve diagnostic accuracy. Prospective, multicenter studies are warranted to validate these findings.

CONCLUSION

Clinical characteristics, particularly age, obesity, hypertension, and reproductive history, were more strongly associated with endometrial malignancy than hematological inflammatory markers. Although platelet count and PLR differed significantly between benign and malignant groups, their diagnostic performance was poor, while SII showed no significant diagnostic value. Therefore, these inflammatory markers should not be used as standalone diagnostic tools but may provide complementary information alongside established clinical risk factors.

Conflict of Interest Statement: The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Author Contributions: Y.C: Study conception and design, statistical analysis, interpretation of data, manuscript drafting, and critical revision.

Ö. Y. A.: Data collection, literature review, manuscript drafting, and final approval of the manuscript.

Ö. A.: Data interpretation, methodological support, and critical revision of the manuscript.

E. Y.: Statistical supervision, analysis support, and manuscript review.

H. G.: Study supervision, study design, critical revision, and final approval of the manuscript.

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