RESEARCH ARTICLE

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Prognostic Value of Systemic Inflammatory and Nutritional Indices for Lymphovascular Space Invasion and Lymph Node Metastasis in Endometrioid Endometrial Cancer

Endometrioid Endometrium Kanserinde Lenfovasküler İnvazyon ve Lenf Nodu Metastazı İçin Sistemik İnflamatuvar ve Nutrisyonel İndekslerin Prognostik Değeri

ABSTRACT

Objective

This study aimed to evaluate the relationship between preoperative inflammatory parameters including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), and C-reactive protein (CRP), as well as nutritional markers such as prognostic nutritional index (PNI) and albumin, with lymphovascular space invasion (LVSI) and lymph node metastasis (LNM) in patients with endometrioid endometrial cancer.

Materials and Methods

A total of 186 patients with endometrioid endometrial cancer who underwent surgery between November 2023 and May 2025 were retrospectively analyzed. Preoperative blood parameters were used to calculate NLR, PLR, MLR, SII, and PNI. Patients were stratified according to the presence of LVSI and LNM, and compared accordingly. Receiver operating characteristic (ROC) analysis was performed to assess the discriminatory ability of each parameter.

Results

In 39 patients with LVSI, PNI was significantly lower, whereas NLR, PLR, MLR, SII, and CRP were significantly higher (all $p<0.05$). ROC analysis showed that NLR had the highest AUC for predicting LVSI (0.778), indicating moderate discrimination. Among 24 patients with LNM, NLR and SII were significantly higher, and lymphocyte count was significantly lower (all $p<0.05$). PNI showed no significant association with LNM.

Conclusion

Preoperative inflammatory indices, particularly NLR and SII, appear to be valuable biomarkers for predicting the risk of LVSI and LNM. Although PNI was significantly lower in patients with LVSI, ROC analysis demonstrated limited predictive performance. Therefore, the prognostic utility of PNI may be more meaningful when assessed in conjunction with other inflammatory indices, contributing more effectively to preoperative risk stratification.

Key Words

Endometrioid Endometrial Cancer, Lymphovascular Space Invasion, Lymph Node Metastasis, Neutrophil-To-Lymphocyte Ratio, Systemic Immune-Inflammation Index, Prognostic Nutritional Index, Preoperative Biomarkers

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ÖZ

Amaç

Bu çalışma, endometrioid tip endometrium kanserli hastalarda preoperatif dönemde değerlendirilen inflamatuvar parametreler olan nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), monosit-lenfosit oranı (MLR), sistemik immün-inflamasyon indeksi (SII) ve C-reaktif protein (CRP) ile nutrisyonel göstergeler olan prognostik nutrisyonel indeks (PNI) ve albüminin, lenfovasküler invazyon (LVSI) ve lenf nodu metastazı (LNM) ile ilişkisini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler

Kasım 2023 ile Mayıs 2025 tarihleri arasında cerrahi uygulanan toplam 186 endometrioid endometrium kanserli hasta retrospektif olarak analiz edildi. Preoperatif kan parametreleri kullanılarak NLR, PLR, MLR, SII ve PNI hesaplandı. Hastalar LVSI ve LNM varlığına göre gruplandırıldı ve karşılaştırıldı. Her bir parametrenin ayırt edici gücünü değerlendirmek için alıcı işletim karakteristik (ROC) analizi yapıldı.

Bulgular

LVSI saptanan 39 hastada PNI anlamlı derecede düşük, NLR, PLR, MLR, SII ve CRP ise anlamlı derecede yüksekti (tümü $p<0,05$). ROC analizinde, LVSI'yi öngörmede en yüksek AUC değeri NLR için bulundu (0,778). LNM saptanan 24 hastada NLR ve SII anlamlı derecede yüksek, lenfosit sayısı ise anlamlı derecede düşüktü (tümü $p<0,05$). PNI'nin LNM ile anlamlı bir ilişkisi bulunmadı. Sonuç: Preoperatif inflamatuvar indeksler, özellikle NLR ve SII, LVSI ve LNM riskinin öngörülmesinde klinik açıdan değerli biyobelirteçlerdir. PNI, LVSI pozitif hastalarda anlamlı derecede düşük bulunmasına rağmen ROC analizi prediktif performansının sınırlı olduğunu ortaya koymuştur. Bu nedenle PNI'nin, tek başına kullanıldığında zayıf kalan öngörü gücünün, diğer inflamatuvar indekslerle birlikte değerlendirildiğinde preoperatif risk sınıflamasına daha anlamlı katkı sağlayabileceği düşünülmektedir.

Anahtar Kelimeler

Endometrioid Endometrium Kanseri, Lenfovasküler Alan İnvazyonu, Lenf Nodu Metastazı, Nötrofil/Lenfosit Oranı, Sistemik İmmün-İnflamasyon İndeksi, Prognostik Nutrisyonel İndeks, Preoperatif Biyobelirteçler

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in developed countries, and its global incidence is steadily increasing. According to GLOBOCAN data, 417,000 new cases and 97,000 disease-related deaths are reported annually worldwide (1). The main pathological factors determining the prognosis of the disease include FIGO stage, histologic type and grade, depth of myometrial invasion, cervical stromal involvement, lymph node metastasis (LNM), and lymphovascular space invasion (LVSI) (2, 3). LVSI is recognized as an independent prognostic indicator reflecting the potential for tumor dissemination via the lymphatic system and is associated with an increased risk of recurrence (3,4). LNM is strongly correlated with advanced-stage disease and poor survival outcomes (4).

In recent years, there has been growing interest in the role of systemic inflammation in cancer progression. Hematological indices derived from complete blood count, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII), are considered indirect markers of immune response and inflammatory activity within the tumor microenvironment (5, 6). Systematic reviews and meta-analyses have demonstrated significant associations between these indices and adverse prognostic features in endometrial cancer, including advanced stage, deep myometrial invasion, LVSI, and LNM (7).

A large-scale retrospective study by Cong et al. reported that preoperative NLR, PLR, and MLR had independent prognostic value in endometrial cancer. Moreover, the combined use of these three parameters yielded greater predictive accuracy for survival compared to their individual use, achieving high prognostic performance in a nomogram model (Harrell's C-index: 0.847) (9).

Among composite indices, the systemic immune-inflammation index (SII), derived from neutrophil, platelet, and lymphocyte counts, and the systemic inflammation response index (SIRI), calculated from neutrophil, monocyte, and lymphocyte counts, have been proposed as novel markers reflecting tumor-associated inflammation (10). However, their prognostic performance may vary and warrants disease-specific evaluation. In a broader meta-analysis, Zhou et al. found that elevated preoperative SIRI levels were associated with significantly worse overall and disease-free survival across various cancer types (11).

Nutritional status is also an important determinant of prognosis in gynecologic malignancies. The prognostic nutritional index (PNI), calculated from serum albumin concentration and lymphocyte count, reflects both metabolic reserve and immune competence. Kim et al. reported that higher preoperative PNI values were independently associated with cancer-specific survival in endometrial

cancer patients (8). Additionally, PNI has been linked to a lower risk of postoperative complications in both endometrial and cervical cancers (12).

This study aims to evaluate the relationship between preoperative hematologic and biochemical parameters, including derived indices such as NLR, PLR, MLR, SII, and PNI, and adverse pathological features such as LVSI, deep myometrial invasion, and LNM in patients with endometrioid endometrial cancer. Our hypothesis is that these easily accessible and low-cost parameters may have significant prognostic value in predicting high-risk pathological features prior to surgery.

MATERIALS and METHODS

Study Design and Patient Selection

This retrospective observational study was conducted between November 2023 and May 2025 at the Gynecologic Oncology Center of İzmir City Hospital. Patients were eligible if they had a histopathologically confirmed diagnosis of endometrioid-type endometrial cancer, had undergone total hysterectomy, bilateral salpingo-oophorectomy, and pelvic ± para-aortic lymphadenectomy as part of complete surgical staging, and had complete preoperative blood count parameters available. Patients with non-endometrioid histological subtypes, concomitant malignancies, a history of chronic inflammatory or autoimmune diseases, or incomplete clinical or laboratory data were excluded.
The study was approved by the Ethics Committee of İzmir City Hospital (Date: 04/06/2025, Decision No: 2025/276) and conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

Demographic and clinical data, including age, body mass index (BMI), menopausal status, and comorbidities, were recorded. Complete blood count and serum albumin levels measured within 7 days prior to surgery were assessed. Based on these values, the following systemic inflammatory and nutritional indices were calculated:
Neutrophil-to-Lymphocyte Ratio (NLR) = Neutrophil count / Lymphocyte count
Platelet-to-Lymphocyte Ratio (PLR) = Platelet count / Lymphocyte count
Monocyte-to-Lymphocyte Ratio (MLR) = Monocyte count / Lymphocyte count
Systemic Immune-Inflammation Index (SII) = (Platelet × Neutrophil) / Lymphocyte
Prognostic Nutritional Index (PNI) = [10 × serum albumin (g/dL)] + [0.005 × total lymphocyte count (/mm³)]

Histopathological Evaluation

Postoperative pathology reports were reviewed to record prognostic features, including the presence of deep myometrial invasion (<50% or ≥50%), lymphovascular space invasion (LVSI), and lymph node metastasis (LNM). All pathological assessments were performed by experienced gynecologic pathologists who were blinded to the blood parameter results.

Statistical Analysis

Cases with missing data were excluded from the analysis; no data imputation was performed. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as frequency and percentage. Between-group comparisons were performed using the Student's t-test or Mann–Whitney U test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables. The diagnostic performance of each parameter in predicting LVSI, deep myometrial invasion, and LNM was evaluated using receiver operating characteristic (ROC) curve analysis. Cut-off values were determined using the Youden index; area under the curve (AUC) values were interpreted as low (<0.7), moderate (0.7–0.8), or high (≥0.8) discriminative ability.
To identify independent prognostic factors, parameters with $p<0.1$ in univariate analyses were included in multivariate logistic regression models. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 186 patients with endometrioid-type endometrial cancer were included in the study. The mean age was 60.7 ± 9.2 years (range, 35–82). Histopathological evaluation revealed Grade 1 tumors in 118 patients (63.4%), Grade 2 tumors in 56 patients (30.1%), and Grade 3 tumors in 12 patients (6.5%). Deep myometrial invasion (≥50%) was present in 71 patients (38.2%). Lymphovascular space invasion (LVSI) was positive in 39 patients (21.0%). Lymph node metastasis (LNM) was detected in 24 patients (12.9%); of these, 14 had pelvic-only involvement, 3 had isolated para-aortic involvement, and 7 had both pelvic and para-aortic involvement.

Laboratory assessment showed a mean hemoglobin level of 12.41 ± 0.99 g/dL, neutrophil count of 4.29 ± 0.80 ×10□/L, lymphocyte count of 1.81 ± 0.40 ×10□/L, monocyte count of 0.41 ± 0.11 ×10□/L, platelet count of 280.1 ± 55.0 ×10□/L, C-reactive protein (CRP) level of 6.43 ± 1.44 mg/L, albumin level of 4.15 ± 0.28 g/dL, and CA 125 level of 27.27 ± 13.24 U/mL. The mean values of the calculated indices were: NLR, 2.53 ± 0.93; PLR, 163.84 ± 56.50; MLR, 0.24 ± 0.09; SII, 708.30 ± 306.21; and PNI, 50.54 ± 3.66 (Table I).

Table I. Descriptive Statistics of Patient Demographics and Laboratory Parameters

Variable	Mean ± SD or n (%)
Age (Years)	60.7 ± 9.2
Tumor Grade	
Grade 1	118 (63.4%)
Grade 2	56 (30.1%)
Grade 3	12 (6.5%)
Deep Myometrial İnvasion (≥50%)	71 (38.2%)
LVSI Positivity	39 (21.0%)
Lymph Node Metastasis	24 (12.9%)
Pelvic Positive	14
Isolated Para-Aortic Positive	3
Both Pelvic and Para-Aortic Positive	7
Hemoglobin (g/dL)	12.41 ± 0.99
Neutrophil (×10³/μL)	4.29 ± 0.80
Lymphocyte (×10³/μL)	1.81 ± 0.40
Monocyte (×10³/μL)	0.41 ± 0.11
Platelet (×10³/μL)	280.1 ± 55.0
CRP (mg/L)	6.43 ± 1.44
Albumin (g/dL)	4.15 ± 0.28
CA 125 (U/mL)	27.27 ± 13.24
NLR	2.53 ± 0.93
PLR	163.84 ± 56.50
MLR	0.24 ± 0.09
SII	708.30 ± 306.21
PNI	50.54 ± 3.66

In patients with LVSI positivity, neutrophil count (4.63 ± 0.99 vs. 4.19 ± 0.72 ×10³/μL, p = 0.013), CRP (7.35 ± 1.46

Table II. Comparison of Laboratory Parameters Between LVSI-Positive and LVSI-Negative Patients (n=186)

Parameter	LVSI (+) (n=39) Mean ± SD	LVSI (−) (n=147) Mean ± SD	p-value
Hemoglobin (g/dL)	12.53 ± 0.97	12.38 ± 0.99	0.398
Neutrophil (×10³/μL)	4.63 ± 0.99	4.19 ± 0.72	0.013
Lymphocyte (×10³/μL)	1.50 ± 0.36	1.89 ± 0.37	<0.001
Monocyte (×10³/μL)	0.41 ± 0.11	0.41 ± 0.11	0.835
Platelet (×10³/μL)	276.27 ± 53.93	281.05 ± 55.37	0.626
CRP (mg/L)	7.35 ± 1.46	6.19 ± 1.33	<0.001
Albumin (g/dL)	3.96 ± 0.30	4.20 ± 0.25	<0.001
CA 125 (U/mL)	30.43 ± 12.73	26.51 ± 13.30	0.170
NLR	3.30 ± 1.25	2.32 ± 0.70	<0.001
PLR	199.55 ± 78.50	154.37 ± 44.84	0.001
MLR	0.29 ± 0.11	0.23 ± 0.08	0.002
SII	923.98 ± 415.66	651.08 ± 241.08	<0.001
PNI	47.08 ± 3.34	51.46 ± 3.17	<0.001

Data are presented as mean ± standard deviation. p<0.05 was considered statistically significant.

Table III. Comparison of Preoperative Parameters According to Lymph Node Positivity

Parameter	Lymph Node (+) (n=24) Mean ± SD	Lymph Node (−) (n=162) Mean ± SD	p-value
Neutrophil (×10³/μL)	4.90 ± 0.82	4.19 ± 0.76	<0.001
Lymphocyte (×10³/μL)	1.65 ± 0.37	1.83 ± 0.40	0.035
CRP (mg/L)	7.05 ± 1.27	6.34 ± 1.44	0.017
NLR	3.11 ± 0.88	2.44 ± 0.91	<0.001
SII	882.04 ± 397.96	682.56 ± 282.75	0.015
Hemoglobin (g/dL)	12.47 ± 0.88	12.40 ± 1.00	0.727
Monocyte (×10³/μL)	0.41 ± 0.10	0.41 ± 0.11	0.881
Platelet (×10³/μL)	275.82 ± 67.18	280.68 ± 53.14	0.737
Albumin (g/dL)	4.13 ± 0.24	4.15 ± 0.28	0.628

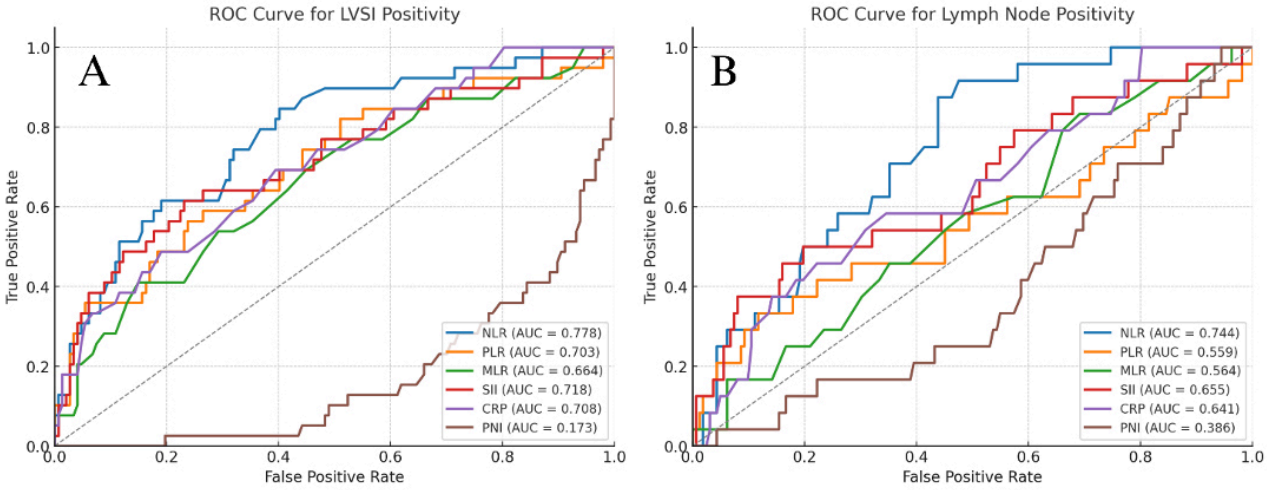


Figure 1.
Receiver operating characteristic (ROC) curves for inflammatory and nutritional markers in predicting:
(A) Lymphovascular space invasion (LVSI): NLR showed the highest predictive performance (AUC = 0.778; moderate discrimination), followed by SII (AUC = 0.718) and CRP (AUC = 0.708).
(B) Lymph node metastasis: NLR achieved the highest AUC (0.744; moderate discrimination), with SII (AUC = 0.655) ranking second. PNI demonstrated poor predictive ability in both analyses.
Data are presented as mean ± standard deviation. p<0.05 was considered statistically significant.

vs. 6.19 ± 1.33 mg/L, p < 0.001), NLR (3.30 ± 1.25 vs. 2.32 ± 0.70, p < 0.001), PLR (199.55 ± 78.50 vs. 154.37 ± 44.84, p = 0.001), MLR (0.29 ± 0.11 vs. 0.23 ± 0.08, p = 0.002), and SII (923.98 ± 415.66 vs. 651.08 ± 241.08, p < 0.001) were significantly higher; whereas lymphocyte count (1.50 ± 0.36 vs. 1.89 ± 0.37 ×10³/μL, p < 0.001), albumin (3.96 ± 0.30 vs. 4.20 ± 0.25 g/dL, p < 0.001), and PNI (47.08 ± 3.34 vs. 51.46 ± 3.17, p < 0.001) were significantly lower. No significant differences were observed in hemoglobin, monocyte, platelet, or CA 125 levels (p > 0.05) (Table II).

When patients with LNM (n = 24, 12.9%) were compared to those without, the metastasis-positive group had higher neutrophil counts (4.90 ± 0.82 vs. 4.19 ± 0.76 ×10³/μL, p < 0.001), CRP (7.05 ± 1.27 vs. 6.34 ± 1.44 mg/L, p = 0.017), NLR (3.11 ± 0.88 vs. 2.44 ± 0.91, p < 0.001), and SII (882.04 ± 397.96 vs. 682.56 ± 282.75, p = 0.015), along with lower lymphocyte counts (1.65 ± 0.37 vs. 1.83 ± 0.40 ×10³/μL, p = 0.035). No significant differences were noted in hemoglobin, monocyte, platelet, albumin, CA 125, PLR, MLR, or PNI values (p > 0.05) (Table III).

Receiver operating characteristic (ROC) analysis demonstrated that NLR had the highest area under the curve (AUC) for predicting LVSI (AUC = 0.778), followed by SII (AUC = 0.718), CRP (AUC = 0.708), PLR (AUC = 0.703), and MLR (AUC = 0.664). PNI showed no significant predictive performance, with a low AUC value (AUC = 0.173). For predicting LNM, NLR again had the highest AUC (AUC = 0.744), followed by SII (AUC = 0.655), CRP (AUC = 0.641), MLR (AUC = 0.564), and PLR (AUC = 0.559), while PNI remained a poor predictor (AUC = 0.386) (Figure 1).

DISCUSSION

This study is among the limited number of investigations examining the association between preoperative inflammatory (NLR, PLR, MLR, SII, CRP) and nutritional (PNI, albumin) parameters and prognostically critical pathological findings such as lymphovascular space invasion (LVSI) and lymph node metastasis (LNM) in endometrioid-type endometrial cancer. Our findings suggest that the systemic inflammatory response may exert significant effects on both local invasion and metastatic dissemination potential.

In our cohort, patients with LVSI positivity exhibited significantly higher neutrophil counts, CRP, NLR, PLR, MLR, and SII values, while lymphocyte counts, albumin, and PNI were markedly lower. Similarly, in patients with LNM, neutrophil counts, CRP, NLR, and SII were elevated, with concomitant reductions in lymphocyte counts; however, PNI was not significantly associated with LNM. In ROC analysis, NLR demonstrated the highest discriminatory ability for predicting LVSI (AUC = 0.778) and LNM (AUC = 0.744), both indicating moderate discriminative performance according to our predefined thresholds. SII provided moderate discrimination for both outcomes (AUC = 0.718 for LVSI; 0.655 for LNM), whereas CRP, PLR, and MLR showed lower accuracy.

These results are consistent with existing evidence in the literature. One of the earliest studies highlighting the prognostic significance of NLR clearly demonstrated its relationship with tumor progression and metastasis (5). Meta-analyses focusing on endometrial cancer have reported that elevated NLR, PLR, and MLR values are associated with adverse histopathological features and poorer survival outcomes (7, 9).

SII integrates neutrophil, lymphocyte, and platelet counts into a single formula, thereby providing a comprehensive reflection of tumor-associated inflammation (6). Matsubara et al. reported that SII is an independent prognostic factor in endometrial cancer, with higher values significantly associated with advanced stage and deep invasion. Our data support these findings, indicating that SII has meaningful predictive capacity, particularly in the presence of LVSI and LNM (6).

Consistent with these findings, other studies have also demonstrated that elevated SII represents an independent risk factor for lymph node metastasis, deep myometrial invasion, and higher pathological grade in endometrial cancer patients (10).

Among nutritional indicators, PNI combines serum albumin levels and lymphocyte counts to reflect both nutritional and immune status (8, 12, 15). Previous studies have reported that low PNI values may be associated with poor prognosis (8, 16, 17). Although PNI was significantly lower in LVSI-positive patients, its standalone predictive performance for LVSI and LNM was limited in ROC analysis. These findings suggest that PNI may be more informative when interpreted alongside inflammatory indices rather than as a single predictor.

From a clinical perspective, the ability to predict LVSI and LNM in the preoperative period is critical for determining surgical strategy and planning adjuvant therapy (3, 4, 13, 14). Our findings suggest that inflammatory indices may serve as complementary tools in preoperative risk stratification, while nutritional parameters, though limited in value when assessed alone, may contribute to clinical decision-making when interpreted alongside inflammatory markers.

Strengths and Limitations

Strengths of our study include the use of a homogeneous histological subtype, the measurement of biomarkers using standardized laboratory protocols, and the determination of clinically relevant cut-off values via ROC analysis. Nonetheless, the retrospective, single-center design and the absence of long-term survival data represent notable limitations. The relatively small sample size may have reduced statistical power, particularly in subgroup analyses. Inflammatory parameters can be influenced by tumor-unrelated causes such as infections or subclinical inflammation, and advanced biomarker analyses to exclude these effects were not performed. Furthermore, the cross-sectional design precludes conclusions regarding the direction of causality between inflammatory/nutritional status and LVSI or LNM. Validation of these findings in prospective, multicenter studies is required before they can be generalized to broader populations. Future prospective studies should systematically ascertain and control for non–tumor-related inflammatory confounders (e.g., intercurrent infections, inflammatory comorbidities, and medications) to delineate the independent prognostic contribution of these indices.

CONCLUSION

In conclusion, this study demonstrates that preoperative inflammatory (NLR, PLR, MLR, SII, CRP) and nutritional (PNI, albumin) parameters are significantly associated with prognostic features such as LVSI and LNM in patients with endometrioid-type endometrial cancer. The combined evaluation of systemic inflammation and nutritional status may enhance prognostic accuracy in the preoperative setting. In particular, NLR and SII exhibited moderate discriminatory ability for predicting LVSI and LNM, supporting their role as complementary biomarkers in surgical planning and adjuvant therapy decision-making. Although PNI was significantly lower in LVSI-posi-

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