Am J Cancer Res 2025;15(8):3471-3485
www.ajcr.us /ISSN:2156-6976/ajcr0165423

Original Article

Systemic immune-inflammation index and lymphocyte-to-monocyte ratio predict recurrence after radical surgery for stage I/II endometrial cancer

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Received April 17, 2025; Accepted August 4, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Early-stage endometrial cancer (stage I/II) is often treated successfully with radical surgery, but recurrence remains a concern in some patients. Identifying reliable biomarkers for recurrence risk is essential for improving post-surgical management. This study investigated the prognostic significance of systemic immune-inflammation index (SII) and lymphocyte-to-monocyte ratio (LMR) in predicting recurrence after radical surgery for stage I/II endometrial cancer. This retrospective cohort study analyzed 950 patients who underwent radical surgery for stage I/II endometrial cancer between March 2015 and October 2024. Patients were classified into recurrence (n=95) and non-recurrence (n=855) groups. The predictive value of LMR and SII was assessed using logistic regression. Predictive accuracies were evaluated using the area under the curve (AUC). Additionally, an external validation cohort consisting of 495 patients, who met the same inclusion criteria, was used to further validate the predictive model. LMR and SII were significantly associated with cancer recurrence. High SII and low LMR were predominantly observed in the recurrence group, demonstrating substantial predictive power. Multivariate logistic regression revealed that LMR was the strongest independent predictor of recurrence (OR=1.795, 95% CI, 1.417-2.274). The combined model of LMR and SII achieved an AUC of 0.876, highlighting its excellent predictive performance. SII and LMR are valuable systemic immune-inflammation indices for predicting recurrence in stage I/II endometrial cancer patients after radical surgery.

Keywords: Endometrial cancer, recurrence prediction, systemic immune-inflammation index, lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, radical surgery outcomes

Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries, with an increasing incidence that parallels the rising prevalence of obesity and an aging population [1]. Early-stage (stage I/II) endometrial cancer, confined to the uterus, is typically treated with radical hysterectomy and bilateral salpingo-oophorectomy, offering a potentially curative approach [2]. Despite favorable prognoses in early-stage cases, a percentage of patients experience recurrence, significantly compromising overall survival and quality of life [3]. Identifying reliable prognostic biomarkers for recurrence risk is crucial for tailoring postoperative management, allowing for better stratification of patients who may benefit from adjuvant therapies and closer surveillance [4, 5].

Recent studies have highlighted the potential of systemic inflammation markers as predictive tools for cancer prognosis. The systemic immune-inflammation index (SII), which integrates platelet count (PLT), neutrophil count (NC), and lymphocyte count (LC), has been studied across multiple cancer types, demonstrating associations with survival outcomes owing to its reflection of host inflammatory status and immune response [6, 7]. Similarly, the lymphocyte-to-monocyte ratio (LMR) serves as a potential marker that reflects the balance between immune surveillance (lymphocytes) and tumor-promoting inflammation (monocytes) [8, 9]. These markers are of particular inter-

https://doi.org/10.62347/ZWXU9375

est due to their accessibility, cost-effectiveness, and ease of incorporation into routine clinical practice.

The role of inflammation in cancer progression is well documented, with evidence suggesting that an inflammatory tumor microenvironment can promote tumor growth, invasion, and metastasis [10]. Tumor-infiltrating lymphocytes are essential for orchestrating an effective anti-tumor immune response, while monocytes can be recruited into the tumor microenvironment and differentiate into tumor-associated macrophages (TAMs), which support tumor progression through angiogenesis and immunosuppression [11, 12]. In this context, a high SII may indicate a heightened systemic inflammation state, promoting tumor aggressiveness and recurrence, while a low LMR could be indicative of relative immunosuppression, allowing for tumor progression and recurrence [13, 14].

Although several studies have suggested potential prognostic roles for SII and LMR in various cancer types, their specific prognostic significance in patients with early-stage endometrial cancer remains uncertain [15, 16]. Given this background, the current study aims to investigate the potential of SII and LMR as predictors of recurrence in patients with stage I/II endometrial cancer following radical surgery.

Materials and methods

Case selection

This retrospective cohort study was conducted in strict accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [17]. A total of 950 patients diagnosed with stage I/II endometrial cancer who underwent radical surgery at the Second Affiliated Hospital of Fujian Medical University between March 2015 and October 2024 were included. Patients were categorized into two cohorts based on their postoperative recurrence: the non-recurrence group (n=855), and the recurrence group (n=95). Since the study utilized de-identified patient data, informed consent was waived, and the study was approved by the ethics review committee of The Second Affiliated Hospital of Fujian Medical University, adhering to relevant regulations. Furthermore, an external cohort of 495 patients, who met the same inclusion and exclusion criteria, was included for external validation. Based on postoperative recurrence status, these patients were also divided into a recurrence group (n=45) and a non-recurrence group (n=450).

Inclusion and exclusion criteria

Inclusion criteria: (1) Histopathologically confirmed stage I/II endometrial cancer (Federation of Gynecology and Obstetrics [FIGO] 2023) [18]; (2) Underwent standardized radical surgery (total hysterectomy + bilateral adnexectomy); (3) Complete medical records accessible; (4) Age 18-75 years; (5) Minimum 24-month postoperative follow-up with documented recurrence or death events; (6) Preoperative blood tests (within 7 days) without transfusion or leukocyte-enhancing treatment.

Exclusion criteria: (1) Incomplete clinical or pathological data; (2) Received neoadjuvant chemotherapy, radiotherapy, or immunotherapy before surgery; (3) Incomplete treatment regimens (surgery, postoperative chemotherapy, or radiotherapy); (4) A history of malignant tumors or symptoms indicative of malignant tumors (excluding non-melanoma skin cancer); (5) Severe heart disease, liver or kidney dysfunction, hematologic disorders, or other serious comorbidities that might influence study outcomes; (6) Autoimmune diseases or current immunosuppressive therapy; (7) Active infectious diseases, such as HIV or active tuberculosis; (8) Use of immunomodulatory medication (e.g., long-term steroids); (9) Pregnancy or lactation (**Figure 1**).

Data collection

Data were collected from the medical record system, encompassing demographic details such as age, sex, and body mass index (BMI). Clinical features were also recorded, including disease stage, tumor location, differentiation grade, TNM stage, and type of surgery performed. Additional data from preoperative laboratory tests included red blood cell (RBC) count, white blood cell (WBC) count and its subsets, PLT, C-reactive protein (CRP) levels, and lipid profiles. Moreover, the SII and lymphocyte-monocyte ratio (LMR) were calculated. Follow-up information, including the duration of follow-up, postoperative recurrence status, and survival status, was meticulously recorded. To

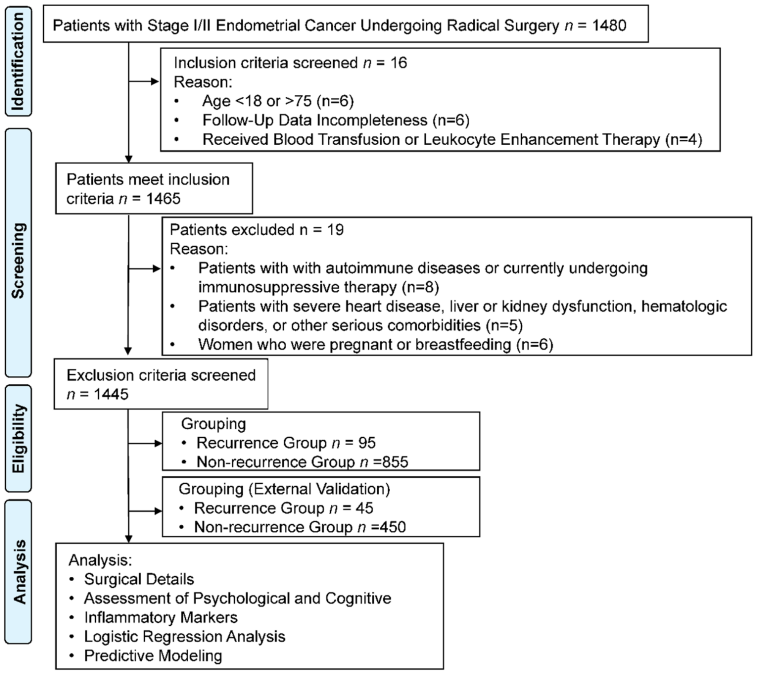

Figure 1. Schematic diagram of the patient selection.

ensure data accuracy and completeness, two independent researchers reviewed all information, employing a double-data entry method.

The primary endpoint of this study was to evaluate the predictive value of SII and LMR for postoperative recurrence. Secondary endpoints included other clinical parameters such as BMI, disease stage, differentiation grade, and surgical type.

Treatment approach

All patients underwent radical surgery for endometrial cancer, with the choice between laparoscopic and open surgery based on clinical characteristics and surgeon judgment. Laparoscopic surgery was preferred for early-stage disease (Stage I/II), while open surgery was reserved for larger tumors or extensive lymphadenectomy. For laparoscopic surgery, patients were placed in lithotomy position and a uterine manipulator was inserted. A 1 cm incision above the umbilicus was made to establish CO_2 pneumoperitoneum (12-14 mmHg). A laparoscope (1288HD, Stryker Endoscopy, USA) and a 10 mm trocar were inserted, with additional 5 mm trocars placed at strategic points. The abdominal cavity was thoroughly explored, and pelvic lavage fluid was collected for cytological examination. Following procedures included extraperitoneal total hysterectomy, pelvic lymphadenectomy, bilateral adnexectomy, and para-aortic lymph node sampling. Hemostasis was meticulously achieved, a vaginal drainage tube was inserted, and the incisions were sutured. In cases of uncontrollable bleeding, severe adhesions, or unclear anatomy, the procedure was converted to laparotomy. For laparotomy, a 15-20 cm midline incision was made in the lower abdomen. The intraoperative procedures mirrored those of the laparoscopic group, including pathological biopsies and routine postoperative anti-infection treatments. Drainage tube was removed if the drainage volume was less than 50 mL within 24 hours and patient recovery was satisfactory. Postoperative adjuvant therapy was customized based on high-risk factors, including tumor differentiation, depth of myometrial invasion, and lymph node metastasis. High-risk patients were treated with adjuvant chemotherapy (cisplatin, carboplatin, and paclitaxel) along with adjuvant radiotherapy, hormone therapy, or other targeted therapies as appropriate.

Preoperative blood collection and laboratory analysis

Fasting venous blood samples were collected from all patients within seven days prior to surgery using BD Vacutainer® EDTA tubes (Becton Dickinson, USA) to prevent coagulation. The samples were promptly dispatched to the laboratory for analysis. Hematological status and inflammatory response were assessed through RBC, WBC and its subsets - LC, MC, and NC - as well as PLT, using an automated hematology analyzer (Sysmex XN-1000, Sysmex Corporation, Japan). The acute-phase inflammatory response was evaluated by measuring CRP levels, using an immunonephelometric method on an immunology analyzer (BN ProSpec, Siemens Healthineers, Germany). Lipid metabolism status was evaluated through lipid profile parameters, including total cholesterol (TC), triglycer-

ides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), using an automated biochemical analyzer (Hitachi 7600, Hitachi High-Technologies Corporation, Japan). These indicators were integral to the study, serving as potential predictors of postoperative recurrence.

Systemic immune-inflammation markers

Several systemic immune-inflammation markers (SIIMs) were evaluated to determine their predictive value for postoperative recurrence in patients with stage I/II endometrial cancer. The markers examined included:

SII: This index was derived from the peripheral blood PLT, NC, and LC using the formula $SII = \frac{PLT \times NC}{LC}$.

LMR: The LMR was calculated by dividing the peripheral blood LC by the monocyte count (MC), expressed as $LMR = \frac{LC}{MC}$.

Blood samples for calculating these indices were collected within seven days before surgery to ensure consistent and reliable results.

Statistical method

Statistical analyses were conducted using SPSS 29.0 (SPSS Inc.). Categorical variables were expressed as n (%), and chi-square tests were used for comparisons, as all expected cell frequencies were greater than 5 and the total sample size was greater than 40. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed data were presented as mean ± standard deviation (SD) and compared using the independent samples t-test. Statistical significance was set at $P<0.05$.

Lasso regression was utilized for feature selection to identify key prognostic factors prior to logistic regression analysis. Univariate and multivariate logistic regression analyses were performed to evaluate the associations between potential predictors and recurrence risk, with results presented as odds ratios (ORs) and 95% confidence intervals (CIs). The predictive performance of systemic immune-inflammatory indices and other significant clinical factors was evaluated by calculating the area under the curve (AUC) of receiver operating characteristic (ROC) curves. An integrated predictive model incorporating these indices was developed and validated externally.

Results

Comparison of baseline demographic characteristics between the recurrence and non-recurrence groups

Comparison of the demographic characteristics between the recurrence group and the non-recurrence group revealed no significant differences in terms of mean age, ethnicity distribution, smoking history, alcohol consumption history, prevalence of diabetes, hypertension, heart disease, other chronic diseases, gynecological conditions (e.g., endometriosis, uterine fibroids, polycystic ovary syndrome, and cervical dysplasia), marital status, educational level, or monthly household income per person between the two groups (all $P>0.05$) (**Table 1**). However, BMI was significantly higher in the recurrence group ($P=0.004$). Overall, among the demographic factors examined, only BMI was significantly associated with recurrence, suggesting that higher BMI may be a potential risk factor for recurrence in this cohort.

Comparison of clinical disease characteristics between the recurrence and non-recurrence groups

Further, we compared disease characteristics between the two groups. Disease stage showed a significant difference, with more advanced stages observed in the recurrence group ($P=0.008$) (**Table 2**). Tumor differentiation also exhibited a significant trend towards more poorly differentiated tumors in the recurrence group ($P=0.002$). However, no significant differences were found in TNM staging or myometrial invasion depth (all $P>0.05$). These findings indicate that disease stage and tumor differentiation are significantly associated with recurrence risk, whereas TNM stage, myometrial invasion depth, and postoperative adjuvant therapy do not show statistically significant associations. Advanced disease stage and poorer tumor differentiation may be critical factors influencing recurrence following treatment for endometrial cancer.

Table 1. Comparison of demographic characteristics between the recurrence and non-recurrence groups

Parameters	Recurrence Group (n=95)	Non-recurrence Group (n=855)	t/χ^2	P
Age (years)	61.34 ± 9.87	59.23 ± 10.45	1.875	0.061
BMI (kg/m^2)	27.12 ± 5.12	25.68 ± 4.56	2.879	0.004
Ethnicity (Han/Other) [n (%)]	89 (93.68%)/6 (6.32%)	800 (93.57%)/55 (6.43%)	0.198	0.965
Smoking history [n (%)]	26 (27.37%)	183 (21.40%)	1.773	0.183
Drinking history [n (%)]	38 (40.00%)	264 (30.88%)	3.282	0.070
Medical History [n (%)]			6.960	0.138
Diabetes	15 (15.79%)	91 (10.64%)		
Hypertension	29 (30.52%)	225 (26.32%)		
Heart Disease	6 (6.31%)	40 (4.68%)		
Other Chronic Diseases	11 (11.59%)	77 (9.00%)		
None	34 (35.79%)	422 (49.36%)		
Gynecological Diseases [n (%)]			7.600	0.107
Endometriosis	9 (9.47%)	52 (6.08%)		
Uterine Fibroids	8 (8.42%)	48 (5.61%)		
Polycystic Ovary Syndrome	6 (6.32%)	28 (3.27%)		
Cervical Dysplasia	4 (4.21%)	19 (2.24%)		
None	68 (71.58%)	708 (82.80%)		
Marital Status [n (%)]			0.421	0.516
Married	82 (86.32%)	716 (83.74%)		
Unmarried or Divorced	13 (13.68%)	139 (16.26%)		
Educational level [n (%)]			0.682	0.409
High school or below	63 (66.31%)	602 (70.41%)		
Junior college or above	32 (33.68%)	253 (29.59%)		
Monthly household income/person [n (%)]			0.999	0.607
<5000	17 (17.89%)	136 (15.91%)		
5000-10000	54 (56.84%)	462 (54.03%)		
>10000	24 (25.27%)	257 (30.06%)		

BMI: body mass index.

Table 2. Comparison of disease characteristics between the recurrence and non-recurrence groups

Parameters	Recurrence Group (n=95)	Non-recurrence Group (n=855)	χ^2	P
Disease Stage [n (%)]			7.088	0.008
Stage I	56 (58.95%)	616 (72.05%)		
Stage II	39 (41.05%)	239 (27.95%)		
Differentiation [n (%)]			12.304	0.002
Well-differentiated	13 (13.69%)	257 (30.06%)		
Moderately-differentiated	50 (52.63%)	396 (46.32%)		
Poorly-differentiated	32 (33.68%)	202 (23.62%)		
TNM Stage [n (%)]			3.316	0.069
T1	59 (62.11%)	608 (71.11%)		
T2	36 (37.89%)	247 (28.89%)		
Myometrial Invasion Depth [n (%)]			2.642	0.104
≤50%	43 (45.26%)	462 (54.04%)		
>50%	52 (54.74%)	393 (45.96%)		

LVSI: Lymphovascular Space Invasion.

Table 3. Comparison of laboratory test results between the recurrence and non-recurrence groups

Parameters	Recurrence Group (n=95)	Non-recurrence Group (n=855)	t	P
RBC (×10^12/L)	4.22 ± 0.52	4.32 ± 0.44	1.925	0.057
CRP (mg/L)	4.20 ± 1.27	3.89 ± 1.49	1.942	0.052
WBC (×10^9/L)	7.22 ± 1.99	6.88 ± 1.82	1.693	0.091
LC (×10^9/L)	1.97 ± 0.52	2.02 ± 0.55	0.835	0.404
MC (×10^9/L)	0.50 ± 0.22	0.46 ± 0.19	1.696	0.093
NC (×10^9/L)	5.10 ± 1.68	4.78 ± 1.52	1.906	0.057
PLT (×10^9/L)	252.05 ± 49.58	244.32 ± 45.15	1.568	0.117
TC (mmol/L)	5.05 ± 1.78	4.85 ± 1.67	1.093	0.274
TG (mmol/L)	1.44 ± 0.42	1.37 ± 0.41	1.605	0.109
HDL-C (mmol/L)	1.26 ± 0.30	1.32 ± 0.42	1.887	0.061
LDL-C (mmol/L)	3.03 ± 0.71	2.91 ± 0.63	1.654	0.099

RBC: Red Blood Cell count; CRP: C-reactive Protein; WBC: White Blood Cell Count; CRP: C-reactive protein; LC: Lymphocyte Count; MC: Monocyte Count; NC: Absolute Neutrophil Count; PLT: Platelet count; TC: Total cholesterol; TG: Triglyceride; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol.

Comparison of preoperative laboratory parameters between the recurrence and non-recurrence groups

Various laboratory parameters were compared between the recurrence and the non-recurrence groups (**Table 3**). The mean RBC counts, CRP levels, WBC counts, and NC were slightly higher in the recurrence group, but these differences were not statistically significant (all P>0.05). Similarly, no significant differences were observed in LC, MC, PLT, TC, TG, HDL-C, or LDL-C levels between the groups (all P>0.05). These findings indicate that, while certain parameters showed trends towards higher levels in the recurrence group, they did not significantly correlate with recurrence risk in this cohort.

Comparison of surgical procedure and outcomes between the recurrence and non-recurrence groups

The distribution of surgical types differed significantly between the two groups, with open surgery being more common in the recurrence group (P=0.018) (**Table 4**). However, no significant differences were found in mean surgical time, intraoperative blood loss, incidence of intraoperative complications, or provision of postoperative adjuvant therapy (chemotherapy, radiotherapy, or none) between the two groups (all P>0.05). These findings suggest that while there is a significant association between surgical type and recurrence risk, surgical duration, intraoperative blood loss, complication rates, and postoperative adjuvant therapy do not significantly influence recurrence following radical surgery for endometrial cancer.

Comparison of systemic immune-inflammatory indices (SII and LMR) between the recurrence and non-recurrence groups

The predictive performance of SII and LMR for postoperative recurrence in stage I/II endometrial cancer patients was evaluated. SII was significantly elevated in the recurrence group (P=0.036), while LMR was notably decreased in the recurrence group (P<0.001) (**Figure 2**). These findings indicate that both SII and LMR are significantly associated with recurrence risk following radical surgery for stage I/II endometrial cancer.

Variable selection using LASSO regression

Feature selection was performed using Lasso regression, with variable coefficient trajectories visualized in **Figure 3**. LASSO regression with 10-fold cross-validation was used to select optimal variables (λ=0.01). The tuning parameter was chosen to minimize the mean squared error. Variables with non-zero coefficients were selected as key predictors for subsequent logistic regression modeling. These variables included LMR, SII, BMI, disease stage (I/II), differentiation grade, and surgical type.

Univariate logistic regression analysis of factors associated with recurrence

In the univariate logistic regression analysis, we evaluated several variables for their association with postoperative recurrence in stage I/II endometrial cancer patients. The variables included in the analysis were systemic immune-inflammatory indices (LMR, SII), BMI (kg/m^2), disease stage (I/II), differentiation grade (well/moderately/poorly), and surgical type (open vs. laparoscopic surgery) (**Table 5**). LMR showed a negative association with recurrence (coeffi-

Table 4. Comparison of surgical findings between the recurrence and non-recurrence groups

Parameters	Recurrence Group (n=95)	Non-recurrence Group (n=855)	t/χ^2	P
Surgical Type [n (%)]			5.631	0.018
Open Surgery	53 (55.79%)	368 (43.04%)		
Laparoscopic Surgery	42 (44.21%)	487 (56.96%)		
Surgical Time (min)	200.24 ± 45.03	193.36 ± 44.15	1.824	0.068
Intraoperative Blood Loss (mL)	281.06 ± 90.12	262.13 ± 90.09	1.921	0.055
Intraoperative Complications [n (%)]	14 (14.74%)	89 (10.41%)	1.656	0.198
Postoperative Adjuvant Therapy [n (%)]			1.019	0.601
Chemotherapy	21 (22.11%)	162 (18.95%)		
Radiotherapy	22 (23.16%)	180 (21.05%)		
None	52 (54.73%)	513 (60.00%)		

LMR: Lymphocyte-to-Monocyte Ratio; SII: Systemic Immune-Inflammation Index.

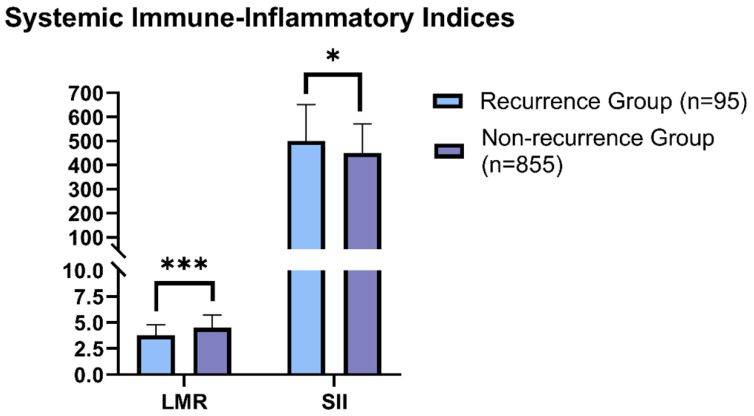

Figure 2. Comparison of systemic immune-inflammatory indices between two groups. LMR: Lymphocyte-to-Monocyte Ratio; SII: Systemic Immune-Inflammation Index. ***: P<0.001; *: P<0.05.

cient =-0.513, P<0.001). Additionally, SII had a small but significant positive association with recurrence (coefficient =0.003, P<0.001). BMI (kg/m^2) was associated with an increased risk of recurrence (coefficient =0.067, P=0.004), while disease stage (I/II) exhibited a protective effect against recurrence (coefficient =-0.585, P=0.008). Better differentiation grade was linked to decreased recurrence risk (coefficient =0.507, P<0.001). Finally, laparoscopic surgery was associated with a lower recurrence risk compared to open surgery (coefficient =0.513, P=0.019). These findings suggest that systemic immune-inflammatory indices such as LMR and SII, along with clinical factors including BMI, disease stage, differentiation grade, and surgical approach, are significant predictors of recurrence following radical surgery.

Multivariate logistic regression analysis of independent risk factors for disease recurrence

The variables displaying statistical significance in univariate analysis, including systemic immune-inflammatory indices (LMR, SII), BMI (kg/m^2), disease stage (I/II), differentiation grade (well/moderately/poorly), and surgical type (open vs. laparoscopic surgery) were included in the multivariate logistic regression analysis (**Table 6**). The analysis revealed that LMR showed a negative association with recurrence (coefficient =-0.572, P<0.001). Additionally, SII contributed a small but statistically significant prediction (coefficient =0.004, P<0.001). Other factors also showed significant associations. BMI was associated with an increased risk of recurrence (coefficient =0.056, P=0.021), while higher disease stage (coefficient =-0.597, P=0.011 and poorer differentiation grade (coefficient =0.489, P= 0.002) were linked to increased recurrence risk. Notably, surgical type did not show a significant association with recurrence (P=0.075). These findings underscore the critical roles of systemic immune-inflammatory indices such as LMR and SII, alongside key clinical factors including BMI, disease stage, and differentiation grade, as significant independent predictors of recurrence following radical surgery for early-stage endometrial cancer. These markers

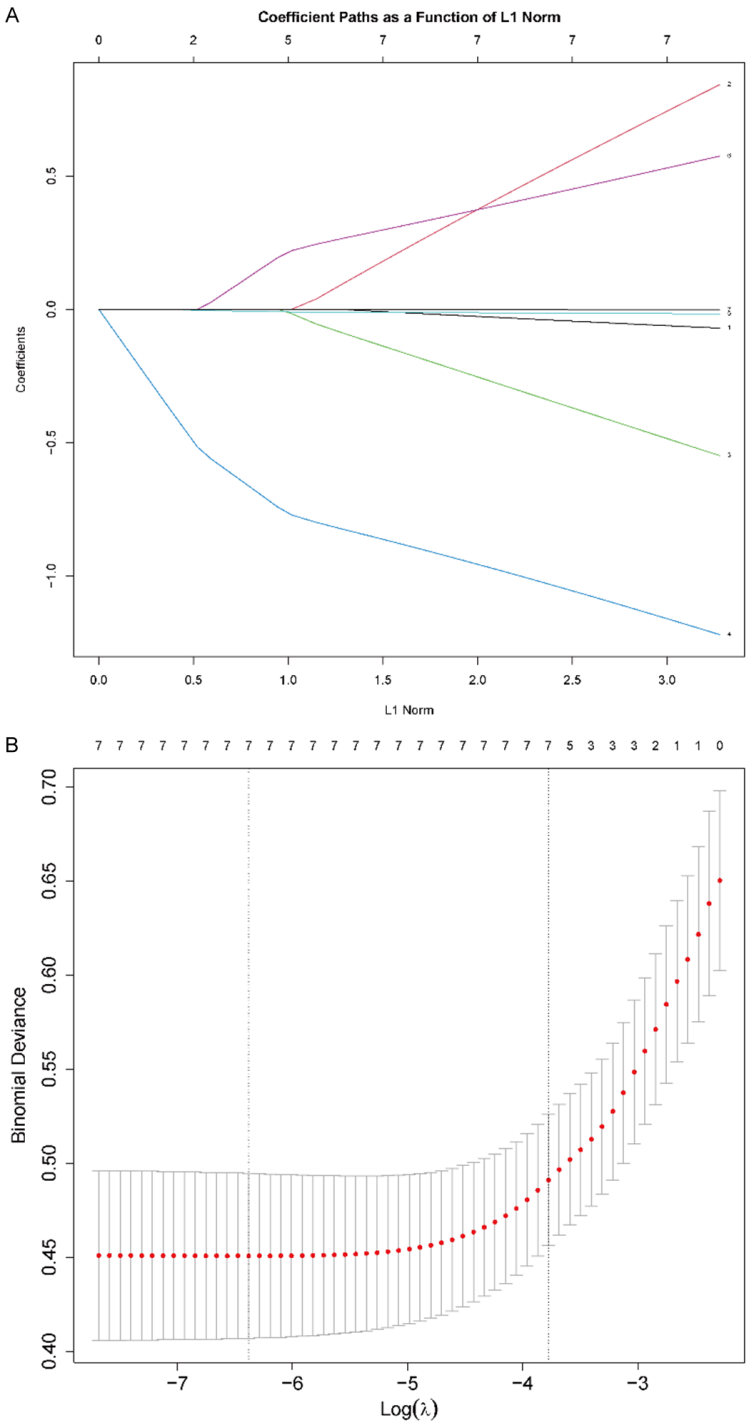

Figure 3. Variable selection using Lasso regression. A: Coefficient profiles of candidate variables; B: Cross-validation for optimal λ parameter determination.

collectively provide valuable insights into the risk assessment and management strategies for these patients.

Predictive value of systemic immune-inflammatory indices for disease recurrence

To further assess the predictive value of systemic inflammatory indices, we calculated the AUC for both LMR and SII in predicting recurrence. The LMR showed an AUC of 0.773, indicating a moderate to high predictive value. In contrast, the SII exhibited a lower predictive value, with an AUC of 0.681 (**Table 7**). This analysis demonstrated varying predictive efficacy of these indices for recurrence in stage I/II endometrial cancer.

In addition, a combined predictive model incorporating both LMR and SII was developed to predict recurrence following radical surgery for stage I/II endometrial cancer. The model achieved a high AUC of 0.876, indicating its exceptional predictive capability for identifying recurrence risk in this patient population (**Figure 4**).

The formula for the combined predictive model is as follows: Recurrence Score = (-0.572× LMR) + (0.004×SII) + C, where C is a constant term used to adjust the intercept for broader applicability across different patient populations.

Comparison of baseline demographic and clinical parameters between the recurrence and non-recurrence groups

In the external validation set, BMI showed a significant difference between the recurrence and non-recurrence groups, with the recurrence group having a higher BMI compared to the non-recurrence group (P=0.021) (**Table 8**). No significant differences were observed in age, ethnicity,

Table 5. Univariate logistic regression analysis of postoperative recurrence

	Coefficient	Std Error	Wald	P	OR	95% CI
BMI (kg/m^2)	0.067	0.024	2.855	0.004	1.071	1.022-1.122
Disease Stage (I/II) [n (%)]	-0.585	0.222	2.635	0.008	0.557	0.362-0.866
Differentiation (Well/Moderately/Poorly) [n (%)]	0.507	0.153	3.321	<0.001	1.660	1.235-2.249
LMR	-0.513	0.093	5.494	<0.001	0.582	0.478-0.704
SII	0.003	0.001	3.676	<0.001	1.003	1.002-1.005
Surgical Type (Open Surgery/Laparoscopic Surgery) [n (%)]	0.513	0.218	2.354	0.019	1.670	1.092-2.570

BMI: body mass index; LMR: Lymphocyte-to-Monocyte Ratio; SII: Systemic Immune-Inflammation Index.

Table 6. Multivariate logistic regression analysis of factors for postoperative recurrence

	Coefficient	Std Error	Wald	P	OR	95% CI
BMI (kg/m^2)	0.056	0.024	2.315	0.021	1.058	1.009-1.110
Disease Stage (I/II) [n (%)]	-0.597	0.234	-2.551	0.011	0.550	0.348-0.871
Differentiation (Well/Moderately/Poorly) [n (%)]	0.489	0.161	3.036	0.002	1.630	1.189-2.234
LMR	-0.572	0.104	-5.516	<0.001	0.565	0.461-0.692
SII	0.004	0.001	4.052	<0.001	1.004	1.002-1.006
Surgical Type (Open Surgery/Laparoscopic Surgery) [n (%)]	0.450	0.250	1.800	0.075	1.568	0.963-2.556

BMI: body mass index; LMR: Lymphocyte-to-Monocyte Ratio; SII: Systemic Immune-Inflammation Index.

Table 7. Predictive value of systemic inflammatory indices for recurrence in stage I/II endometrial cancer

Parameters	AUC	Sensitivity (%)	Specificity (%)
LMR	0.773	0.757	0.663
SII	0.681	0.697	0.589

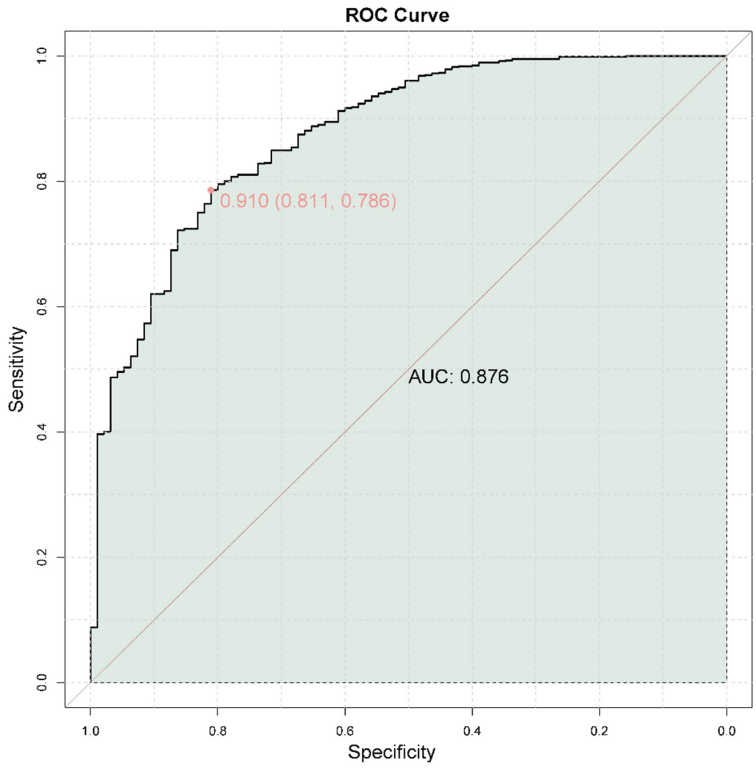

Figure 4. ROC curve for the predictive model in predicting endometrial cancer recurrence.

smoking history, alcohol consumption history, medical history, gynecological diseases, marital status, educational level, or monthly household income/person between the two groups (all P>0.05). However, disease stage (P=0.044), differentiation grade (P=0.037), and surgical type (P=0.043) showed significant differences, with more advanced stages, poorer differentiation, and a higher proportion of open surgeries in the recurrence group. Furthermore, hematological parameters including LMR (P<0.001) and SII (P=0.037) were significantly different between the recurrence and non-recurrence groups, indicating that these markers may play a role in predicting recurrence after surgery for endometrial cancer. These findings suggest that patients with higher BMI, more advanced disease stages, poorer tumor differentiation, specific preoperative hematological profiles, and open surgical approach are at a higher risk of recurrence following radical surgery, consistent with the finding in modeling dataset.

Table 8. Comparison of parameters between Recurrence and Non-recurrence Groups in the external validation set

Parameters	Recurrence Group (n=45)	Non-recurrence Group (n=450)	t/χ^2	P
Age (years)	62.41 ± 9.69	60.31 ± 10.63	1.273	0.203
BMI (kg/m^2)	26.82 ± 5.16	25.11 ± 4.68	2.317	0.021
Ethnicity (Han/Other) [n (%)]	43 (95.56%)/2 (4.44%)	421 (93.56%)/29 (6.44%)	0.042	0.837
Smoking history [n (%)]	14 (31.11%)	96 (21.33%)	2.263	0.133
Drinking history [n (%)]	18 (40.00%)	139 (30.88%)	1.568	0.210
Medical History [n (%)]			3.375	0.497
Diabetes	7 (15.56%)	48 (10.67%)		
Hypertension	14 (31.11%)	118 (26.22%)		
Heart Disease	3 (6.67%)	21 (4.67%)		
Other Chronic Diseases	5 (11.11%)	41 (9.11%)		
None	16 (35.55%)	222 (49.33%)		
Gynecological Diseases [n (%)]			7.651	0.105
Endometriosis	5 (11.11%)	20 (4.44%)		
Uterine Fibroids	4 (8.89%)	25 (5.56%)		
Polycystic Ovary Syndrome	3 (6.67%)	15 (3.33%)		
Cervical Dysplasia	2 (4.44%)	10 (2.22%)		
None	31 (68.89%)	380 (84.45%)		
Marital Status [n (%)]			0.255	0.614
Married	39 (86.67%)	377 (83.78%)		
Unmarried or Divorced	6 (13.33%)	73 (16.22%)		
Educational level [n (%)]			0.279	0.598
High school or below	30 (66.67%)	317 (70.44%)		
Junior college or above	15 (33.33%)	133 (29.56%)		
Monthly household income/person [n (%)]			1.081	0.582
<5000	7 (15.56%)	59 (13.11%)		
5000-10000	26 (57.78%)	237 (52.67%)		
>10000	12 (26.66%)	154 (34.22%)		
Disease Stage [n (%)]			4.043	0.044
Stage I	27 (60.00%)	333 (74.00%)		
Stage II	18 (40.00%)	117 (26.00%)		
Differentiation [n (%)]			6.618	0.037
Well-differentiated	6 (13.33%)	139 (30.89%)		
Moderately-differentiated	24 (53.33%)	208 (46.22%)		
Poorly-differentiated	15 (33.34%)	103 (22.89%)		
LMR	3.76 ± 1.05	4.51 ± 1.23	3.934	<0.001
SII	500.42 ± 151.11	450.55 ± 121.18	2.146	0.037
Surgical Type [n (%)]			4.080	0.043
Open Surgery	25 (55.56%)	180 (40.00%)		
Laparoscopic Surgery	20 (44.44%)	270 (60.00%)		

BMI: body mass index; LMR: Lymphocyte-to-Monocyte Ratio; SII: Systemic Immune-Inflammation Index.

To further evaluate the representativeness and reliability of the external validation cohort, we compared its baseline characteristics with those of the modeling dataset (**Table 9**). The results indicate no significant statistical differences between the two cohorts regarding age, BMI, ethnicity, smoking history, drinking history, medical history, gynecological diseases, mari-

Table 9. Comparison of baseline characteristics between modeling dataset and external validation set

Parameters	Modeling Dataset (n=950)	External Validation Set (n=495)	t/χ^2	P
Age (years)	60.12 ± 10.28	61.03 ± 10.27	1.604	0.109
BMI (kg/m^2)	26.14 ± 4.91	25.81 ± 4.98	1.206	0.228
Ethnicity (Han/Other) [n (%)]	890 (93.68%)/60 (6.32%)	464 (93.74%)/31 (6.26%)	0.002	0.969
Smoking history [n (%)]	209 (22.00%)	110 (22.22%)	0.009	0.923
Drinking history [n (%)]	302 (31.79%)	157 (31.72%)	0.001	0.978
Medical History [n (%)]			0.002	0.986
Diabetes	106 (11.16%)	55 (11.11%)		
Hypertension	254 (26.74%)	132 (26.67%)		
Heart Disease	46 (4.84%)	24 (4.85%)		
Other Chronic Diseases	88 (9.26%)	46 (9.29%)		
None	456 (48.00%)	238 (48.08%)		
Gynecological Diseases [n (%)]			1.103	0.894
Endometriosis	61 (6.42%)	25 (5.05%)		
Uterine Fibroids	56 (5.89%)	29 (5.86%)		
Polycystic Ovary Syndrome	34 (3.58%)	18 (3.64%)		
Cervical Dysplasia	23 (2.42%)	12 (2.42%)		
None	776 (81.68%)	411 (83.03%)		
Marital Status [n (%)]			0.007	0.933
Married	800 (84.21%)	416 (84.04%)		
Unmarried or Divorced	150 (15.79%)	79 (15.96%)		
Educational level [n (%)]			0.002	0.968
High school or below	665 (70.00%)	347 (70.10%)		
Junior college or above	285 (30.00%)	148 (29.90%)		
Monthly household income/person [n (%)]			3.381	0.184
<5000	153 (16.11%)	66 (13.33%)		
5000-10000	516 (54.32%)	263 (53.13%)		
>10000	281 (29.57%)	166 (33.54%)		

BMI: body mass index.

tal status, educational level, and monthly household income (all P>0.05). These findings indicate that the baseline characteristics of the modeling dataset and the external validation set are comparable across all assessed parameters, supporting the use of the external validation set for assessing the generalizability of the predictive model.

External validation of predictive model

The ROC curve form the external validation cohort demonstrated strong predictive performance of the combined predictive model, with an AUC of 0.832 (95% CI: 0.733, 0.889). This indicates that the model has a high discriminatory ability in distinguishing between patients with recurrence and those without recurrence in the external validation set. The optimal cut-off point on the ROC curve yielded a sensitivity of 0.852 and a specificity of 0.848, suggesting that the model effectively balances true positive and true negative predictions. These findings support the robustness and generalizability of the predictive model for recurrence risk in endometrial cancer patients (**Figure 5**).

Discussion

Significance of the findings

This study underscores the potential of systemic immune-inflammation indices, specifically the SII and LMR, as robust predictors of postoperative recurrence in patients with stage I/II endometrial cancer. These indices, derived from routine blood tests, offer a non-invasive, cost-effective, and clinically feasible approach

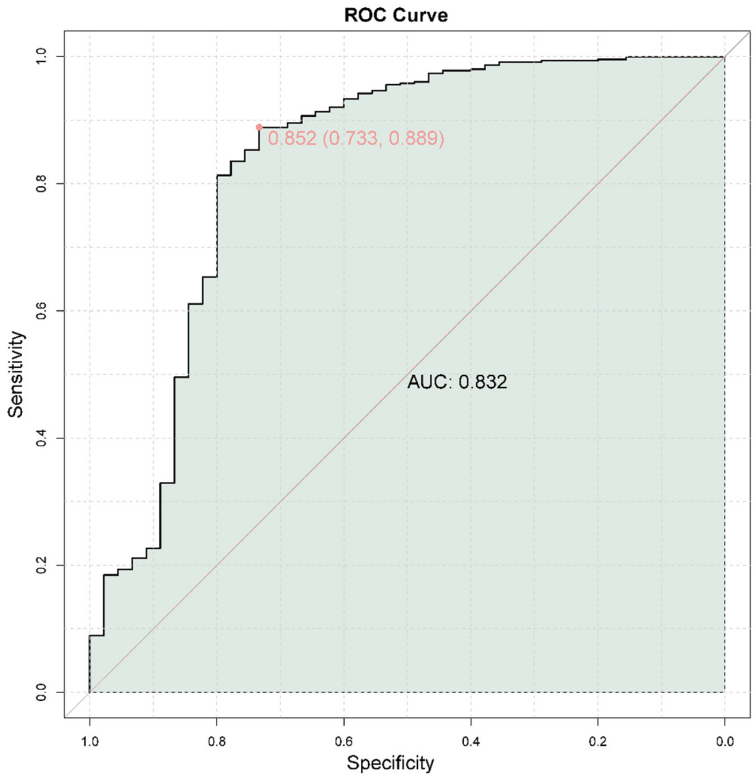

Figure 5. ROC curve for predictive model in External validation dataset.

to stratify patients at higher risk of recurrence following radical surgery.

Relation to existing evidence

Our findings align with accumulating evidence suggesting that systemic inflammation and immune dysfunction play critical roles in cancer progression and recurrence, particularly in gynecological malignancies. For instance, Li YX et al. demonstrated that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) correlate with recurrence in endometrial cancer, but their predictive specificity is inferior to LMR and SII [19]. Similarly, Song YJ et al. reported that preoperative SII is associated with poor prognosis in endometrial cancer, reinforcing its utility as a prognostic tool [20]. However, this study extends existing knowledge by demonstrating the superior predictive performance of LMR and SII in combination, particularly in early-stage disease [21].

Mechanistic insights

The SII integrates platelet, neutrophil, and lymphocyte counts, reflecting a dynamic interplay between coagulation, innate immunity, and adaptive immunity. Elevated SII levels, as observed in the recurrence group, likely indicate a pro-tumor inflammatory microenvironment [22]. Platelets contribute to tumor progression by shielding circulating tumor cells from immune surveillance and facilitating metastasis through adhesion to endothelial cells [23]. Neutrophils contribute to tumor growth by releasing reactive oxygen species and proteases that degrade the extracellular matrix, enabling cancer cell invasion [24]. Conversely, lymphocytes, particularly cytotoxic T cells and natural killer (NK) cells, are essential for anti-tumor immunity. Similarly, the LMR showed a significant inverse relationship with cancer recurrence. Monocytes can differentiate into macrophages that promote tumor progression through several mechanisms, including tissue remodeling, immune suppression, and tumor cell survival [25]. A low LMR implies a higher monocyte and a lower LC, suggesting an immunosuppressive tumor microenvironment favorable to cancer recurrence [26]. The combined analysis of SII and LMR thus captures both systemic inflammation and immune suppression, providing a comprehensive assessment of the host's anti-tumor capacity.

The biological framework underlying these observations can be attributed to the tumor microenvironment, where immune cells and inflammatory processes play pivotal roles in tumor growth, invasion, and dissemination. In response to a tumor, the body elicits an inflammatory reaction that can paradoxically support cancer progression. Systemic inflammation, as indicated by these indices, often promotes a milieu conducive to tumor cell survival, immune evasion, and metastasis. Besides, the chronic inflammatory state may induce genetic mutations and epigenetic alterations that sustain tumor recurrence [27, 28].

Comparison with other prognostic factors

In addition to inflammatory markers, our analysis identified BMI, disease stage (I/II), and differentiation grade (high/medium/low) as important prognostic factors. Higher BMI was associated with a greater risk of recurrence, suggesting that obesity may increase the risk of tumor recurrence by promoting chronic inflammation and hormonal imbalances. Early disease stages (Stage I and II) were associated with a lower risk of recurrence, underscoring the importance of early diagnosis and treatment. Poorly differentiated tumors showed higher recurrence rates, indicating that well-differentiated tumors generally grow more slowly and are more predictable, whereas poorly differentiated tumors are more aggressive and unpredictable. Combining these traditional factors with inflammatory markers can provide a more comprehensive risk assessment, helping to identify high-risk patients and guide personalized postoperative management strategies.

Multivariate analysis results

Multivariate logistic regression analysis confirmed that LMR and SII as independent predictor of recurrence. LMR emerged as the strongest independent predictor of recurrence, with SII also contributing significantly to the model. This hierarchy of predictive strength is consistent with biological plausibility, where immune suppression (reflected by LMR) being more directly linked to tumor recurrence than systemic inflammation (reflected by SII). Furthermore, the combined model of LMR and SII achieved an AUC of 0.876, significantly outperforming individual indices. This highlights the value of integrating multiple immune-inflammatory markers to enhance predictive accuracy, as no single parameter fully encapsulates the complexity of the tumor microenvironment.

Comparison with existing models

To demonstrate the superiority of these biomarkers, we compared them with existing predictive models. Traditional predictive models are typically based on clinical staging, pathological features, and routine laboratory parameters but often lack precision in predicting recurrence in early-stage endometrial cancer patients. For example, while FIGO staging and tumor grading are useful, they fail to fully capture inter-individual heterogeneity [29]. In contrast, LMR and SII not only consider local tumor characteristics but also incorporate systemic inflammation and immune status, thus providing enhanced predictive accuracy [30].

Clinical application suggestions

The integration of SII and LMR into clinical practice could improve postoperative management strategies for endometrial cancer. Patients identified as high-risk based on these indices could benefit from closer surveillance, adjuvant therapies (e.g., chemotherapy or immunotherapy), or enrollment in clinical trials targeting immune modulation. For example, interventions aimed at enhancing lymphocyte function (e.g., checkpoint inhibitors) or reducing systemic inflammation (e.g., anti-cytokine therapies) may mitigate recurrence risk in high-risk patients. Additionally, these markers could complement traditional prognostic factors such as BMI, disease stage, and differentiation grade, enabling a more nuanced risk stratification [15, 31].

Limitations and future directions

While our study provides novel insights, several limitations warrant attention. The retrospective nature of the study invites potential biases, although rigorous adherence to STROBE guidelines was maintained. Additionally, while the sample size was substantial, further external validation in diverse populations and prospective trials would strengthen the findings. The potential influence of other, unmeasured inflammatory diseases or conditions that may alter these indices cannot be entirely excluded. Furthermore, as our cohort was confined to stage I/II cases, the applicability of these indices to more advanced stages remains to be determined. Future research should explore the role of SII and LMR in combination with emerging biomarkers, such as tumor mutational burden (TMB) or PD-L1 expression, to refine risk prediction models. Additionally, interventional studies evaluating immune-modulating therapies in high-risk patients identified by these indices could provide actionable insights for clinical practice.

Conclusion

In conclusion, our findings emphasize the significant prognostic value of systemic immune-inflammation indices, specifically SII and LMR, as non-invasive, cost-effective biomarkers for predicting recurrence in early-stage endometrial cancer patients following radical surgery. Our study also advocates further research to explore the mechanistic pathways linking systemic inflammation and cancer recurrence, which could unveil new therapeutic targets and improve patient prognostication and management. As our understanding expands, these indices may not only serve as markers of recurrence risk but also guide tailored interventions, potentially enhancing outcomes and quality of life for patients with endometrial cancer.

Acknowledgements

This study was supported by the Quanzhou City Science and Technology Plan Project 2022NS085.

Disclosure of conflict of interest

None.

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