RESEARCH ARTICLE

Editorial Process: Submission:12/08/2025 Acceptance:05/08/2026 Published:20/08/2026

Preoperative Immuno-inflammatory Markers as Predictors of Deep Myometrial Invasion in Endometrial Cancer: A Retrospective Study from Southern Thailand

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Abstract

Objectives: To evaluate the predictive value of preoperative systemic inflammatory markers neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) for deep myometrial invasion (MI) in patients with endometrial cancer (EC), emphasizing their utility in resource-limited settings. **Methods:** This retrospective cohort study included 377 patients with histologically confirmed EC who underwent primary surgery at Hatyai Hospital, Southern Thailand, from October 2016 to September 2024. Preoperative hematologic markers were obtained within two weeks before surgery. Patients with active infection, other inflammatory conditions, or prior neoadjuvant treatment were excluded. Deep MI was defined as ≥50% myometrial invasion on final pathology. Logistic regression was used to identify independent predictors, and diagnostic accuracy was assessed using receiver operating characteristic (ROC) curves. **Results:** Deep MI was present in 162 patients (42.97%) and was associated with older age, postmenopausal status, advanced FIGO stage, high-grade tumors, larger size, nodal and cervical involvement, and LVSI (all $p<0.001$). NLR, PLR, MLR, and SII were significantly elevated in this group. Multivariate analysis identified FIGO stage III (OR 7.25; 95% CI, 3.55–14.82), tumor size ≥2 cm (OR 3.85; 95% CI, 1.26–11.77), LVSI (OR 5.01; 95% CI, 2.77–9.08), NLR (OR 1.20; 95% CI, 1.04–1.39), and MLR (OR 57.68; 95% CI, 3.46–960.81) as independent predictors. MLR demonstrated the highest predictive value among biomarkers (AUC 0.612; 95% CI, 0.554–0.670). **Conclusion:** Preoperative immunoinflammatory markers, particularly MLR and NLR, are independently associated with deep MI in EC. MLR, despite variability, may serve as a cost-effective adjunct for risk stratification, especially in resource-limited settings.

Keywords: Endometrial Neoplasms, Neutrophil-to-Lymphocyte Ratio, Monocyte, Myometrial Invasion, Biomarkers

Asian Pac J Cancer Prev, **27 (8)**, 2839-2845

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries, with a global age-standardized incidence rate (ASR) of 8.4 per 100,000 women-years [1]. Although its incidence remains lower in South-Central Asia, recent epidemiological trends indicate a rising burden of EC in specific regions, including Songkhla province in southern Thailand. Between 1989 and 2016, the incidence rate in this area increased from 1.5 to 5.3 per 100,000 women-years, with projections estimating a further rise to 8 per 100,000 by 2030 [2]. This underscores the growing public health relevance of EC in Southeast Asia and the need for context-specific research to inform clinical management strategies.

Among the key prognostic factors in EC, the depth of myometrial invasion (MI) holds particular importance, as it correlates strongly with lymphovascular space invasion (LVSI), lymph node metastasis, and recurrence risk [3, 4]. Accurate preoperative assessment of deep MI (≥50%) is thus essential to guide surgical decision-making, including the extent of lymphadenectomy and adjuvant therapy [5]. However, its cost, limited accessibility, and interobserver variability restrict its routine use in some clinical settings, particularly in resource-limited regions. As a result, attention has shifted toward identifying simple, cost-effective, and widely available biomarkers that can support preoperative decision-making.

This has prompted increasing interest in the use of systemic inflammatory markers derived from routine blood tests as low-cost, widely accessible adjuncts for preoperative risk stratification. Accumulating evidence supports the role of inflammation in cancer initiation and progression [6-9], with chronic inflammation now recognized as a hallmark of cancer biology [10]. In this context, hematologic indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic

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immune-inflammation index (SII) have emerged as promising prognostic and predictive biomarkers. Elevated NLR and PLR may reflect a tumor-promoting microenvironment driven by neutrophil-mediated angiogenesis and lymphopenia-associated immune suppression [11, 12]. Likewise, increased MLR suggests a predominance of monocyte-driven immune modulation, and a high SII indicates compounded systemic inflammation and immune dysregulation both of which may facilitate tumor aggressiveness [13, 14].

These biomarkers have shown prognostic value in multiple malignancies including colorectal [15], breast [16], lung [17], and ovarian cancers [18] as well as in endometrial cancer [19]. However, studies specifically investigating their role in predicting deep MI in EC remain scarce, especially across diverse ethnic and geographic populations. To date, no study in Southern Thailand has systematically assessed these hematological markers for this purpose. Addressing this gap may improve preoperative risk stratification and guide surgical planning, especially in settings with limited access to advanced imaging.

Therefore, this study aims to evaluate the predictive value of preoperative NLR, PLR, MLR, and SII in identifying deep MI among patients with EC, using retrospective data from a tertiary center in Southern Thailand. By exploring these affordable and accessible markers, we hope to contribute to more equitable and effective preoperative risk stratification strategies in resource-limited settings.

Materials and Methods

Study Design and Population

We obtained approval from the Ethics Committee of Hatyai Hospital (Study code: HYH EC 063-68-01) before the study. This retrospective cohort study included patients diagnosed with endometrial cancer who underwent primary surgical treatment at Hatyai hospital between October 2016 and September 2024. Inclusion criteria were: (1) histologically confirmed endometrial cancer, (2) availability of complete preoperative laboratory data, and (3) patients who underwent total hysterectomy with or without lymphadenectomy. Patients with concurrent malignancies, prior neoadjuvant treatment, active infections (defined as documented clinical signs or symptoms of infection and/or physician-diagnosed infectious conditions at the time of preoperative assessment), chronic inflammatory diseases (identified based on documented physician diagnoses in the medical records, including autoimmune or chronic inflammatory conditions), hematologic disorders or those receiving immunosuppressive or steroid therapy were excluded. Preoperative complete blood counts were obtained as part of routine clinical practice and were not required to be collected under fasting conditions.

Data Collection

Clinicopathological data were collected from medical records, including age, menopausal status, body mass index (BMI), tumor grade, histological type, International Federation of Gynecology and Obstetrics (FIGO) stage 2009, lymph node (LN) involvement, cervical involvement, lymphovascular space invasion (LVSI), and tumor size. The depth of myometrial invasion was determined from final surgical pathology and classified as <50% or ≥50% (defined as deep). All the parameters collected were kept in unique Medical Registration Forms and digitized in an electronic database on R software anonymously, under the responsibility of the Principal Investigator. They will be destroyed after the results are published.

Inflammatory Marker Calculation

Peripheral blood samples were collected within two weeks before surgery. The following systemic inflammatory markers were calculated: Neutrophil-to-lymphocyte ratio (NLR) = absolute neutrophil count / absolute lymphocyte count, Platelet-to-lymphocyte ratio (PLR) = platelet count / absolute lymphocyte count, Monocyte-to-lymphocyte ratio (MLR) = monocyte count / absolute lymphocyte count and Systemic immune-inflammation index (SII) = platelet count × neutrophil count / lymphocyte count.

Statistical Analysis

Continuous variables were presented as medians with interquartile ranges (IQR), and categorical variables as frequencies and percentages. Comparisons between groups (<50% vs. ≥50% MI) were performed using the Mann–Whitney U test for continuous variables and chi-square test for categorical variables. Univariate and multivariate logistic regression analyses were conducted to evaluate factors associated with deep MI. Variables with $p < 0.05$ in univariate analysis were included in the multivariate model. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of NLR, PLR, MLR, and SII, and to determine optimal cut-off values based on the Youden index. All statistical analyses were performed using [program R version 4.4.1], and a p-value of <0.05 was considered statistically significant.

Results

A total of 377 patients with EC were analyzed. Of these, 162 (42.97%) had ≥50% myometrial invasion, while 215 (57.03%) had <50%. Patients with deeper invasion were significantly older (median age: 60 vs. 55 years, $p < 0.001$) and more often postmenopausal (80.25% vs. 68.84%, $p = 0.012$). No significant difference in BMI was observed ($p = 0.207$). Advanced FIGO stage (48.77% vs. 10.70%, $p < 0.001$), high-grade tumors (36.42% vs. 26.05%, $p = 0.002$), larger tumor size (5.5 vs. 4.0 cm, $p < 0.001$), lymph node metastasis (26.54% vs. 3.26%, $p < 0.001$), cervical stromal involvement (27.16% vs. 8.37%, $p < 0.001$), and LVSI (57.41% vs. 13.49%, $p < 0.001$) were all significantly more common in the ≥50% myometrial invasion group (Table 1).

Pre-treatment inflammatory markers were significantly higher in patients with deeper MI: NLR (2.19 vs. 1.94, $p = 0.010$), PLR (145.85 vs. 127.05, $p = 0.027$), MLR

Table 1. Clinicopathological Characteristics of Patients with Endometrial Cancer according to Depth of Myometrial Invasion

Variables	All	Myometrial invasion		p-value
	n = 377	< 50%, n = 215	≥ 50%, n = 162	
Age, years, median (IQR)	57 (50,64)	55 (48,62)	60 (54.25,66)	< 0.001*
≤ 59, n (%)	220 (58.36)	143 (66.51)	77 (47.53)	< 0.001*
> 59, n (%)	157 (41.64)	72 (33.49)	85 (52.47)	
Post-menopausal status, n (%)				0.012*
No	99 (26.26)	67 (31.16)	32 (19.75)	
Yes	278 (73.74)	148 (68.84)	130 (80.25)	
Body Mass Index (BMI), kg/m2				0.207
< 30	264 (70.03)	145 (67.44)	119 (73.46)	
≥ 30	113 (29.97)	70 (32.56)	43 (26.54)	
FIGO stage, n (%)				< 0.001*
I	244 (64.72)	178 (82.79)	66 (40.74)	
II	31 (8.22)	14 (6.51)	17 (10.49)	
III	82 (21.75)	15 (6.98)	67 (41.36)	
IV	20 (5.31)	8 (3.72)	12 (7.41)	
Tumor grade, n (%)				0.002*
1	154 (40.85)	104 (48.37)	50 (30.86)	
2	108 (28.65)	55 (25.58)	53 (32.72)	
3	115 (30.50)	56 (26.05)	59 (36.42)	
Histology, n (%)				0.527
Endometrioid	308 (81.70)	178 (82.79)	130 (80.25)	
Non-endometrioid	69 (18.30)	37 (17.21)	32 (19.75)	
Tumor size, cm				
Median (IQR)	4.5 (3,6.5)	4 (2.5,5.5)	5.5 (4,7.15)	< 0.001*
< 2, n (%)	33 (8.75)	27 (12.56)	6 (3.70)	0.002*
≥ 2, n (%)	344 (91.25)	188 (87.44)	156 (96.30)	
LN involvement, n (%)				< 0.001*
No	327 (86.74)	208 (96.74)	119 (73.46)	
Yes	50 (13.26)	7 (3.26)	43 (26.54)	
Cervical involvement, n (%)				< 0.001*
No	315 (83.55)	197 (91.63)	118 (72.84)	
Yes	62 (16.45)	18 (8.37)	44 (27.16)	
LVSI, n (%)				< 0.001*
No	255 (67.64)	186 (86.51)	69 (42.59)	
Yes	122 (32.36)	29 (13.49)	93 (57.41)	

FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lympho-vascular space invasion.

Table 2. Pre-Treatment Systemic Markers of Inflammation of Patients with Endometrial Cancer According to Depth of Myometrial Invasion

Variables¶	All	Myometrial invasion		p-value
	n = 377	< 50%, n = 215	≥ 50%, n = 162	
NLR	2.03 (1.58,2.83)	1.94 (1.54,2.64)	2.19 (1.63,3.04)	0.010*
PLR	133.33 (102.52,174.20)	127.05 (101.55,169.60)	145.85 (105.45,192.76)	0.027*
MLR	0.17 (0.13,0.22)	0.16 (0.12,0.21)	0.19 (0.14,0.25)	<0.001*
SII	630.31 (421.24,917.12)	584.97 (403.42,842.12)	705.02 (470.77,994.26)	0.005*

¶Median (IQR); NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index.

(0.19 vs. 0.16, p < 0.001), and SII (705.02 vs. 584.97, p = 0.005) (Table 2).

Univariate logistic regression identified multiple factors significantly associated with deep MI, including

Table 3. Univariate and Multivariate Logistic Regression Analyses for Depth of Myometrial Invasion

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.04 (1.02, 1.06)	< 0.001*	1.03 (0.99, 1.06)	0.152
Post-menopausal status	1.84 (1.14, 2.98)	0.012*	1.41 (0.59, 3.4)	0.441
FIGO stage		< 0.001*		< 0.001*
II	3.27 (1.53, 7.01)		2.13 (0.89, 5.11)	
III	12.05 (6.43, 22.55)		7.25 (3.55, 14.82)	
IV	4.05 (1.58, 10.34)		1.68 (0.56, 5.05)	
Tumor grade		0.002*		0.322
II	2 (1.21, 3.32)		0.87 (0.47, 1.62)	
III	2.19 (1.33, 3.6)		0.61 (0.31, 1.19)	
Non-endometrioid histology	1.18 (0.7, 2)	0.528	0.58 (0.23, 1.47)	0.251
Tumor size ≥ 2 cm	3.73 (1.5, 9.27)	0.002*	3.85 (1.26, 11.77)	0.009*
LVSI positive	8.64 (5.24, 14.25)	< 0.001*	5.01 (2.77, 9.08)	< 0.001*
NLR	1.21 (1.06, 1.37)	0.002*	1.20 (1.04, 1.39)	0.011*
PLR	1.0030 (1.0002,1.0057)	0.029*	0.0018 (0.0083,1.0053)	0.302
MLR	54.02 (5.32, 548.82)	< 0.001*	57.68 (3.46, 960.81)	0.003*
SII	1.0004 (1.0001,1.0007)	< 0.001*	1.0003 (0.9999,1.0007)	0.108

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lympho-vascular space invasion; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index. Multivariate analysis adjusted by age, menopause, FIGO stage, tumor grade, tumor size and LVSI.

Table 4. ROC Analysis Results for Depth of Myometrial Invasion

Variables	AUC	95% CI	Cut-off	Sensitivity	Specificity	PPV	NPV
NLR	0.577	0.518-0.636	≥ 2.23	48.76	66.51	52.31	63.27
PLR	0.566	0.507-0.625	≥ 147.80	49.38	64.18	50.95	62.72
MLR	0.612	0.554 -0.670	≥ 0.17	56.32	64.15	53.93	66.34
SII	0.583	0.524-0.642	≥ 624	59.25	59.27	50.52	64.7

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index

age, menopausal status, FIGO stage, tumor grade, tumor size ≥2 cm, LVSI, and elevated NLR, PLR, MLR, and SII. In multivariate analysis, FIGO stage III (OR: 7.25, $p < 0.001$), tumor size ≥2 cm (OR: 3.85, $p = 0.009$), LVSI (OR: 5.01, $p < 0.001$), NLR (OR: 1.20, $p = 0.011$), and MLR (OR: 57.68, $p = 0.003$) remained independent predictors (Table 3).

ROC analysis showed that MLR had the highest AUC (0.612), followed by SII (0.583), NLR (0.577), and PLR (0.566). MLR ≥0.17 yielded 56.32% sensitivity and 64.15% specificity. Overall, MLR demonstrated the best predictive performance among the evaluated markers (Table 4). ROC-derived cut-off values (Table 4) were applied in multivariate logistic regression models to evaluate the independent predictive value of inflammatory markers (Table 5). Elevated NLR and MLR remained independently associated with deep MI after adjustment for clinicopathological factors, whereas PLR and SII were not. ROC curves for NLR, PLR, MLR, and SII are presented in Figure 1.

Discussion

This study evaluated the association between preoperative systemic inflammatory markers NLR, PLR, MLR and SII and deep MI in patients with EC. Our findings demonstrate that elevated NLR and MLR were independently associated with deep MI. Conversely, while PLR and SII showed statistical significance in univariate analysis, they lost their independent predictive value in multivariate modeling. PLR demonstrated a borderline association with deep MI, suggesting a potential clinical relevance that warrants further validation in larger cohorts.

This discrepancy may be explained by the more

Table 5. Multivariate Logistic Regression Analysis of Inflammatory Markers using ROC-Derived Cut-Off Values for Predicting Deep Myometrial Invasion.

Variables (cut-off based)	Adjusted OR (95% CI)	p-value
NLR ≥ 2.23	2.03 (1.21,3.4)	0.007*
PLR ≥ 147.8	1.65 (0.99,2.74)	0.055
MLR ≥ 0.17	1.77 (1.06,2.97)	0.029*
SII ≥ 624	1.79 (1.07,3)	0.26

Cut-off values were determined using receiver operating characteristic (ROC) curve analysis (Table 4) based on the Youden index. Multivariate analysis adjusted by age, menopause, FIGO stage, tumor grade, tumor size and LVSI

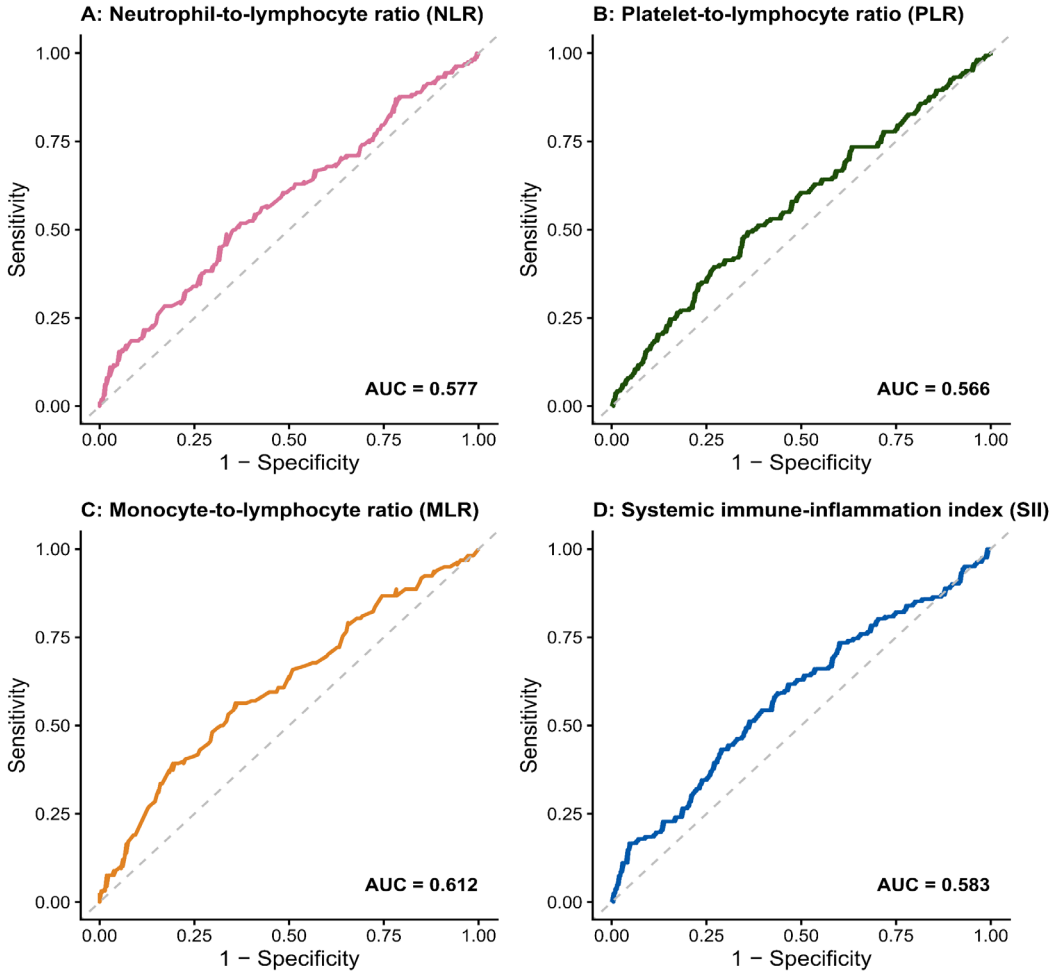

Figure 1. ROC Curve of Pre-Treatment Systemic Markers of Inflammation of Patients with Endometrial Cancer. (A) neutrophil-to-lymphocyte ratio (NLR), (B) platelet-to-lymphocyte ratio (PLR), (C) monocyte-to-lymphocyte ratio (MLR) and (D) systemic immune-inflammation index (SII)

direct roles that monocytes and neutrophils play in promoting tumor progression and modulating the tumor microenvironment, compared to platelets or composite indices. Monocytes can differentiate into tumor-associated macrophages (TAMs), which facilitate invasion, while neutrophils contribute to inflammation and angiogenesis, both of which are critical for myometrial invasion [20, 21]. Notably, MLR demonstrated a wide confidence interval in the multivariate analysis, which should be interpreted with caution. This finding likely reflects a relatively low number of events among patients with markedly elevated MLR values, as well as potential collinearity with other inflammatory markers derived from overlapping hematologic components. Among the evaluated markers, MLR demonstrated the highest discriminative performance. However, its diagnostic accuracy was modest (AUC = 0.612; sensitivity = 54.6%; specificity = 63.6%). Despite this, its utility should be considered in light of its accessibility, low cost, and ease of measurement. These attributes position MLR as a viable adjunct in preoperative risk stratification, particularly in settings where advanced diagnostics are limited, thus supporting its potential integration into existing evaluation frameworks.

Several prior studies have reported the prognostic significance of MLR in EC. Ahn et al. [22] reported that an MLR ≥0.220 (AUC = 0.835, $p < 0.001$) was significantly associated with poor disease-free survival (DFS) and recurrence in early-stage endometrioid EC. Similarly, Song et al. [23] identified MLR ≥0.191 (AUC = 0.718, $p < 0.001$) as an independent predictor of recurrence and cancer-specific mortality in patients with non-endometrioid histology. While existing literature has primarily focused on MLR's role in long-term oncologic outcomes, such as DFS and recurrence, our study uniquely contributes by establishing MLR's independent association with deep MI. This is crucial as deep MI is a well-established surrogate for tumor aggressiveness and adverse oncologic outcomes, thereby broadening the clinical applicability of MLR beyond survival prognostication.

In contrast, Leng et al. [24] reported no significant association between MLR and survival, highlighting inconsistencies that may arise from variations in population characteristics, methodologies, and ethnicity. Our findings, derived from a Southeast Asian cohort, underscore the importance of population-specific validation and provide novel regional insights. The biological plausibility of our results is supported by the role of monocyte-derived

TAMs, which are often elevated in high MLR states. These cells promote invasion, angiogenesis, and immune escape [13], processes integral to deep MI.

Regarding NLR, our results partially align with prior data. Muangto et al. [25], using a smaller Thai cohort (n = 49), identified NLR ≥1.93 with high sensitivity (83.3%) but low specificity (52.8%). Our study found a higher cut-off (NLR ≥2.23), yielding improved specificity (66.5%) but lower sensitivity (48.8%). This divergence in optimal thresholds highlights the need for contextual calibration of biomarker cut-offs, reflecting differences in patient demographics, tumor biology, and clinical practices. Demir Çendek et al. [26] found NLR ≥2.88 to predict deep MI (AUC = 0.693), whereas our AUC was lower (0.577), again suggesting ethnic and systemic variability. Ronsini et al. [27] reported both NLR and MLR as univariate predictors, but only NLR remained significant in multivariate analysis. In contrast, our findings underscore MLR as the sole independently significant marker, reinforcing its emerging role in risk stratification.

Notably, this is the first study from Southeast Asia to explore SII in relation to deep MI. Our cut-off (SII ≥624; AUC = 0.583) was lower than those used in survival studies—Matsubara (≥931) [28], Njoku (≥910) [29], Zhang (≥763.1) [30] likely due to differences in endpoints and underlying inflammation profiles. Although SII had limited accuracy, its theoretical basis and affordability justify future exploration in larger, prospective studies across regional populations. Systemic inflammatory markers have been investigated in other cancers such as colorectal [15], breast [16], and ovarian [18], but their relevance to histopathologic features in EC especially in Asian populations is underexplored. Our region-specific data address this gap, enhancing the global applicability of these markers and contributing to more inclusive risk assessment strategies beyond Western-centric evidence.

Strengths of this study include its relatively large sample size, use of final pathology for deep MI assessment, and simultaneous marker evaluation, allowing internal comparison of predictive efficacy. However, limitations exist. Its retrospective design may introduce selection bias and unmeasured confounding. Inflammatory markers are influenced by factors such as infections, comorbidities, and timing of blood sampling. Nevertheless, alignment with established biological mechanisms and consistency with select prior studies lend credibility to our findings.

Future research should prioritize prospective, multicenter validation studies across diverse ethnic populations to confirm these findings and establish definitive cut-off values. Integrating these readily available markers with advanced imaging modalities and emerging molecular classifiers (e.g., POLE mutations, p53 status, microsatellite instability) holds significant promise. Furthermore, exploring machine learning approaches to develop comprehensive predictive models incorporating clinical, pathological, and inflammatory parameters could ultimately lead to more personalized, accurate, and timely preoperative risk stratification and treatment planning for EC patients.

In conclusion, pre-treatment systemic inflammatory markers, particularly MLR and NLR, are significantly associated with deep MI in patients with EC. Among these, MLR demonstrated the highest predictive value, maintaining statistical significance in both multivariate and ROC analyses. Despite its wide confidence interval, MLR may serve as a practical, low-cost adjunct for preoperative risk stratification, especially in resource-limited settings. Additionally, tumor size ≥2 cm and LVSI were independently predictive of deep MI, reinforcing their importance in preoperative evaluation. Although the overall predictive accuracy of inflammatory markers was modest, their accessibility and cost-effectiveness support their use as complementary tools in clinical decision-making. Further prospective studies are needed to validate these findings and define their role in optimizing individualized treatment strategies for EC.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

The authors acknowledge the staff members of Gynecologic Oncology Unit at Hatyai hospital for their assistance and providing data. We thank Dr. Sorawat Sangkaew and Khodeeyoh Kasoh, Department of Social Medicine for assistance with statistical analysis and valuable comment.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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