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The role of systemic immune-inflammation index in predicting lymphovascular space invasion in endometrial cancer patients: A nomogram approach

Y. Li, Z. Xie, J. Liu, J. Piao*

Department 3 of Gynecological Oncology, Jilin Cancer Hospital, Changchun, Jilin, China

► ***Original article***

Corresponding author:
Jinxia Piao, M.D.,
E-mail:
13578945886@163.com

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ABSTRACT

Background: To delve into the association between preoperative immune-related markers and lymphovascular space invasion (LVSI) in patients with endometrial cancer (EC). ***Materials and Methods:*** According to the 7:3 allocation, 411 EC patients were analyzed. Clinical and pathological data were collected, and imaging histologic features were extracted from contrast-enhanced T1-weighted imaging (CE-T1WI), T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) maps, the related factors affecting LVSI were analyzed. Subsequently, a backward step-wise selection approach was adopted to select the most relevant variables for incorporation into the nomogram. ***Results:*** In the training cohort, independent predictors for LVSI were identified as systemic immune-inflammation index (SII), depth of myometrial invasion (MI), and carbohydrate antigen 125 (CA125) levels. The nomogram was used to predict the probability of LVSI, and the area under the ROC curve was 0.7813. ***Conclusion:*** LVSI positivity in EC patients is strongly associated with elevated SII, MI≥1/2, and high CA125 levels. The SII-based nomogram provides a reliable tool for predicting LVSI status in EC patients.

INTRODUCTION

In 2022, China witnessed 84,520 new Endometrial cancer (EC) cases and 17,543 associated deaths, making EC the second most prevalent gynecological malignancy in terms of incidence [1, 2]. For patients who wish to preserve fertility and meet the criteria for fertility-sparing management, progesterone-based conservative therapy may be considered. Alternatively, for early-stage EC patients deemed unsuitable for surgery, radiotherapy with or without systemic therapy is a viable option.

Lymphatic metastasis is a major route of EC spread. As a result, pelvic with or without para-aortic lymphadenectomy is a standard procedure in EC surgery [3]. However, the universal implementation of systematic lymph node dissection for all EC patients remains a subject of debate. Research indicates that lymphadenectomy in early-stage EC patients does not confer survival benefits and may instead increase the risk of vascular and nerve damage, compromise the integrity of the immune system, and negatively impact patients' quality of life [4, 5]. Lymphovascular space invasion (LVSI) is independent risk factor for lymphatic metastasis in EC patients [6, 7]. Furthermore, LVSI carries prognostic significance independent of The Cancer Genome Atlas (TCGA) molecular subtyping, age, and adjuvant therapy, as it is associated with increased risks of mortality, recurrence, and disease progression in EC patients [8]. Thus, LVSI status is a critical determinant for guiding selective lymphadenectomy and postoperative adjuvant therapy, influencing treatment strategies for fertility-preserving patients and those initially treated with radiotherapy, and ultimately impacting prognosis. However, LVSI status is typically undetectable preoperatively and is confirmed only through postoperative pathological evaluation. Additionally, its assessment is limited by diagnostic techniques and interobserver variability, highlighting challenges in accurately determining LVSI status based on postoperative histopathological findings.

Preoperative imaging, particularly multiparametric magnetic resonance imaging (mpMRI), plays a pivotal role in the non-invasive assessment of key prognostic factors in endometrial cancer. Advanced MRI techniques, including T2-weighted imaging (T2WI), contrast-enhanced T1-weighted imaging (CE-T1WI), and diffusion-weighted imaging (DWI), enable accurate evaluation of myometrial invasion (MI) depth and tumor heterogeneity. These imaging biomarkers not only guide surgical planning but also serve as critical predictors of LVSI and lymphatic metastasis. For instance, MRI-based MI assessment has been shown to correlate strongly with histopathological findings, providing a reliable preoperative indicator of disease aggressiveness [9]. Integrating imaging data with immune markers [e.g., systemic immune-inflammation index (SII)] and serum biomarkers [e.g.,

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carbohydrate antigen 125 (CA125)] could enhance the precision of preoperative risk stratification, thereby addressing the current limitations of relying solely on postoperative histopathology for LVSI determination.

This study is the first to integrate SII, mpMRI and serum tumor marker CA125 to construct and validate a novel nomogram model to achieve accurate preoperative prediction of LVSI in EC patients. These findings provide a new perspective for understanding the mechanism of EC tumor immune microenvironment and vascular invasion, and optimize the clinical decision-making process through the combination of preoperative non-invasive parameters, which has important clinical application value.

MATERIALS AND METHODS

Patient selection

A total of 411 EC patients treated at the Department of Gynecologic Oncology, Jilin Cancer Hospital, between January 20 to December 2023, were included in this study.

Inclusion Criteria: (1) Postoperative histopathological confirmation of EC; (2) Completion of comprehensive staging surgery; (3) Age 18–75 years.

Exclusion Criteria: (1) Preoperative neoadjuvant radiotherapy or chemotherapy; (2) Concurrent other malignancies, hematological diseases, or autoimmune disorders; (3) Recent infections; (4) Inability to tolerate surgery or anesthesia.

The study protocol was approved by the Jilin Cancer Hospital's ethics committee (202401-02-01). Using a random seed method, patients were divided into training (n=288) and validation (n=123) cohorts at a 7:3 ratio. The training cohort was used for variable selection, nomogram development, and ROC analysis, while the validation cohort served for internal validation.

Data collection

(1) Demographic Information: Age at diagnosis and menopausal status. (2) Comorbidities: Presence of diabetes and hypertension. (3) Laboratory Tests: Lymphocyte, neutrophil, platelet counts, fibrinogen level, total T lymphocytes, T-helper, T-suppressor, natural killer (NK) cells, total B lymphocytes, and CA125 levels. (4) Imaging Findings: Depth of MI assessed via transvaginal ultrasound or pelvic MRI. (5) Pathological Features: LVSI status, peritoneal cytology, pathological type, histological grade, lymph node metastasis, and depth of MI.

Imaging examination

Using a Siemens MAGNETOM Espree 1.5 T MRI (Germany) with a 6-channel abdominal coil or a Verio-dot 3.0 T MRI with an 8-channel abdominal phased-array coil. Patients fasted for 4 hours prior to the examination and drank moderate water to fill the bladder. They were positioned supine, head-first. Intravenous injection of 0.1 mmol/kg gadopentetate dimeglumine (Gd-DTPA) (Xi 'an Qiyue Biotechnology Co., LTD., China) was administered at a rate of 2-3 mL/s. The enhanced equilibrium phase sequence was acquired 150 seconds after contrast agent injection. Apparent diffusion coefficient (ADC) maps were generated from images with b-values of 0 and 800 or 1000 s/mm^2 (figure 1).

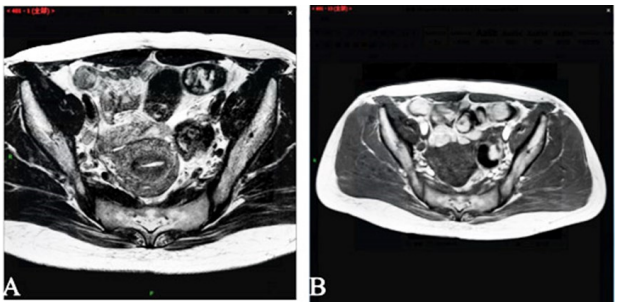

Figure 1. Female, 67 years old, grade 3 endometrioid carcinoma invading 2/3 of the myometrium, LVSI+. **(A)** CE-T1WI shows that the tumor is low signal compared to normal myometrium **(B)** T2WI shows that the tumor is inhomogeneous high signal.

Tumor segmentation and radiomics feature extraction

T2WI, DWI, ADC, and CE-T1WI were acquired. Two radiologists with 13 and 15 years of pelvic imaging experience manually delineated regions of interest (ROIs) slice by slice using ITK-SNAP (v. 3.8.0, www.itk-snap.org).

Statistical methods

Statistical analyses (IBM, USA) were conducted using SPSS 26.0. For normally distributed measurement data, we reported them as ($\bar{x}\pm s$) and used the independent-samples t-test for group comparisons. Count data were expressed as the number of cases (percentage) [n (%)], and the chi-square test was used for between-group comparisons. Statistical significance was set at $P<0.05$. Univariate logistic regression was employed to assess associations between EC patients' LVSI risk, clinicopathological parameters, and laboratory test results. Backward stepwise selection was then employed to identify candidate variables for inclusion in the nomogram. The performance of the nomogram was evaluated based on discrimination, calibration, and clinical utility. First, discrimination was quantified by calculating the area under the receiver operating characteristic (ROC) curve (AUC). Next, calibration curves were used to assess the nomogram's calibration, graphically visualizing the agreement between predicted and observed outcomes.

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RESULTS

Patient characteristics

In the training set, the majority of patients were aged 60 years or younger (64.6%), with a mean age of 63.23±8.27 years, and most of them were postmenopausal women (94.7%). Among these patients, 87.5% were diagnosed with endometrioid carcinoma, 88.2% (254/288) had low-grade tumors, 78.9% (230/288) exhibited negative peritoneal cytology, 75% (216/288) had no lymph node metastasis, and 66.3% (191/288) demonstrated a MI depth < 1/2. In the validation cohort, 68.3% of patients were over 60 years old, with a mean age of 63.20±8.28 years, and the majority were postmenopausal women (94.3%). Among these patients, 86.2% had endometrioid carcinoma, 87.0% (107/123) had low-grade tumors, 79.7% (98/123) showed negative peritoneal cytology, 79.7% (98/123) had no lymph node metastasis, and 65.0% (80/123) had MI depth of less than half. Additionally, the overall incidence of LVSI in the training set was 43.1% (124/288), with a mean CA125 level of 53.97 ± 174.81 U/mL. In the validation cohort, the overall incidence of LVSI was 45.5% (56/123), and the average CA125 level was 95.27 ± 443.35 U/mL (table 1).

Univariate and multivariate risk factor analysis of LVSI

The findings of this analysis clearly indicated that five candidate factors, namely neutrophils, CA125, total T lymphocytes, systemic immune-inflammation index (SII), and MI depth, exhibited a positive correlation with the development of LVSI (P<0.05). The analysis revealed that SII, MI depth, and CA125 level were significant independent predictors of LVSI (table 2). In the validation cohort, similar trends were observed (table 3).

Development and validation of the nomogram

For each independent risk factor, a weighted score was assigned by drawing vertical lines on the point scale axis. The points corresponding to each variable value were summed to derive the total score, which reflected the cumulative contribution of the specific risk factor. The total score ranged up to a maximum of 140 points, with the LVSI probability scale spanning from 0.2 to 0.99 (figure 2A).

In the training set, the AUC for the nomogram based on SII was 0.7813, while in the validation set, the AUC was 0.7591 (figure 2B). The same is true for Calibration plots (figure 2C), confirming the nomogram's reliability in predicting LVSI. The decision curve analysis (DCA) showed that the map provided significant clinical benefit (figure 2D).

Table 1. Baseline demographic, clinical, and pathological characteristics of patients in the training and validation cohorts.

	Training Cohort (288)	Validation Cohort (123)
Age	63.23±8.27	63.20±8.28
Lymphocyt	1.90±0.60	1.91±0.58
Neutrophils	3.81±1.43	4.19±2.03
Platelet	236.53±66.38	244.57±83.78
Fibrinogen	3.19±0.68	3.22±0.72
$CD3^+$T cells	66.23±9.54	67.37±9.79
NK cells	13.44±7.52	13.50±7.14
$CD19^+$B cells	10.51±4.76	10.70±4.17
$CD4^+$ T cells	40.16±9.13	40.04±8.74
$CD8^+$ T cells	24.62±7.78	24.74±7.55
CA125	53.97±174.81	95.27±443.35
Menopause status		
Yes	273(94.7%)	116(94.3%)
No	15(5.2%)	7(5.6%)
Diabetes		
Yes	44(15.3)	18(14.6%)
No	244(84.7%)	107(85.4%)
Hypertension		
Yes	90(31.3%)	36(29.3%)
No	198(68.7%)	87(70.7%)
Ascites cytology		
Negative	230(78.9%)	98(79.7)
Positive	28(9.7%)	7(5.7%)
Missing	30(10.4%)	18(14.6%)
LNM, n (%)		
Negative	216(75%)	98(79.7%)
Positive	45(15.6%)	14(11.4%)
Missing	27(9.4%)	11(8.9%)
Histology , n (%)		
Adenocarcinoma	252(87.5%)	106(86.2%)
Others	36(12.5%)	17(13.8%)
MI, n (%)		
<1/2	191(66.3%)	80(65.0%)
≥1/2	97(33.7%)	43(35.0%)
Grade, n (%)		
Low	254(88.2%)	107(87.0%)
High	34(11.8%)	16(13.0%)
LVSI		
Negative	164(56.9%)	67(54.5%)
Positive	124(43.1%)	56(45.5%)

Note: Abbreviations: CA125, cancer antigen 125; LNM, lymph node metastasis; MI, myometrial invasion; LVSI, lymphovascular space invasion.

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Table 2. Univariate and multivariate logistic regression analysis of lymphovascular space invasion (LVSI) in the training cohort.

		Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	P Value	OR (95% CI)	P Value
Lymphocyt		0.57(0.37-0.87)	0.009	0.83(0.49-1.41)	0.490
Neutrophils		1.21(1.02-1.44)	0.270	0.79(0.61-1.03)	0.078
CA125		1.01(1.00-1.02)	0.005	1.01(1.00-1.01)	0.021
$CD3^+$T cells		1.03(1.01-1.06)	0.018	1.02(0.99-1.05)	0.150
$CD19^+$B cells		1.00 (0.96-1.06)	0.853		
NK cells		1.01 (0.98-1.04)	0.495		
$CD4^+$ T cells		1.02 (0.99-1.04)	0.205		
$CD8^+$ T cells		1.02 (0.99-1.05)	0.200		
SII	<341.05				
	≥341.05	4.91 (2.78-8.69)	<0.001	4.79(2.22-10.35)	<0.001
MI	<1/2				
	≥1/2	5.79 (3.37-9.94)	<0.001	4.47(2.46-8.15)	<0.001

Note: Abbreviations: LVSI, lymphovascular space invasion; CA125, cancer antigen 125; SII, systemic immune-inflammation index; MI, myometrial invasion.

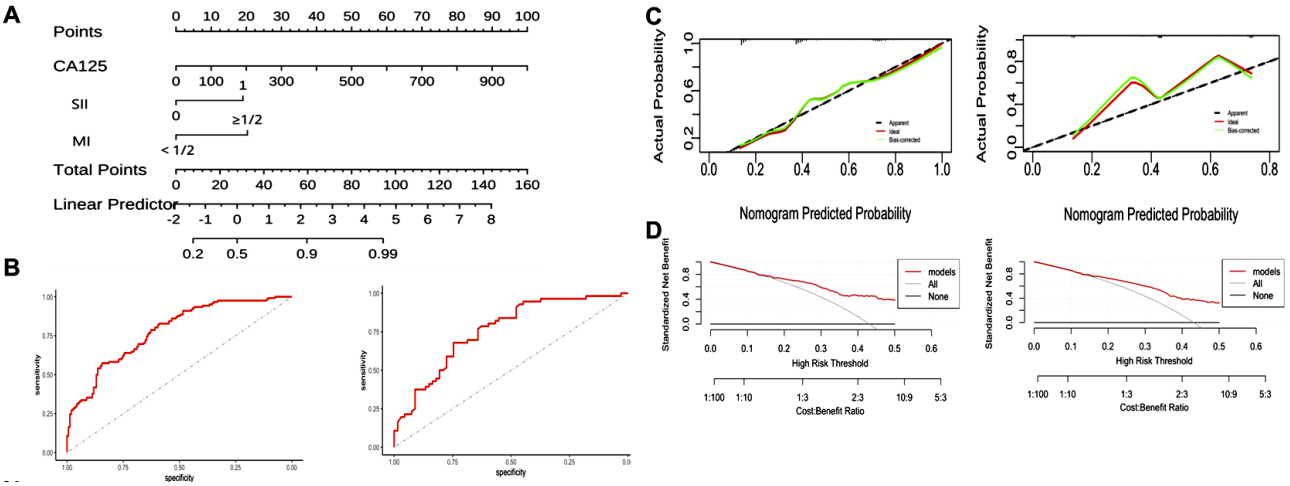

Figure 2. Development and validation of the nomogram. **(A)** Nomogram to predict LVSI for EC patients. **(B)** AUC of SII-based nomogram for prediction of LVSI in EC in (left) training cohort and (right) validation cohort. **(C)** Calibration plots of the nomogram to predict LVSI in (left) training cohort and (right) validation cohort. **(D)** DCA of the SII-based nomogram for predicting LVSI in the training cohort and validation cohort.

Table 3. Univariate and multivariate logistic regression analysis of lymphovascular space invasion (LVSI) in the validation cohort.

		Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	P Value	OR (95% CI)	P Value
Lymphocyt		0.50 (0.26-0.97)	0.040	0.49 (0.24-1.01)	0.053
Neutrophils		1.13 (0.92-1.39)	0.233		
CA125		1.00 (1.00-1.00)	0.762		
$CD3^+$T cells		1.03 (0.99-1.07)	0.157		
$CD19^+$B cells		1.05 (0.96-1.14)	0.272		
NK cells		1.01 (0.96-1.06)	0.789		
$CD4^+$ T cells		1.04 (0.99-1.08)	0.105		
$CD8^+$ T cells		0.99 (0.94-1.04)	0.617		
SII	<341.05				
	≥341.05	5.46 (1.91-15.57)	0.002	4.19(1.40-12.5)	0.010
MI	<1/2				
	≥1/2	3.99 (1.81-8.78)	<0.001	3.71 (1.60-8.60)	0.002

Note: LVSI, lymphovascular space invasion; CA125, cancer antigen 125; SII,systemic immune-inflammation index; MI, myometrial invasion.

DISCUSSION

In this study, we found that five candidate factors—neutrophil count, CA125 level, total T lymphocyte count, SII, and MI depth. Logistic analysis further confirmed SII, MI, and CA125 as independent predictors of LVSI. SII, a novel inflammatory marker that integrates peripheral platelet, lymphocyte, and neutrophil counts, offers a more comprehensive assessment of immune status and inflammatory balance compared to individual inflammatory indicators. The prognostic significance of SII has been demonstrated across various cancers, including cervical [10], endometrial [11], pancreatic [12], and colorectal cancers [13]. However, the mechanisms underlying increased SII in EC and its association with disease aggressiveness remain poorly understood. Elevated SII reflects a state of reduced lymphocytes and increased neutrophil and platelet counts.

The relationship between elevated SII and LVSI may be driven by several interconnected mechanisms: (1) Neutrophils and platelets promote tumor angiogenesis by secreting vascular endothelial growth factors [14-16]. (2) Induction of epithelial-mesenchymal transition (EMT): Neutrophils promote EMT of tumor cells, thereby enhancing the invasiveness of tumor cells [17]. Platelets contribute to this process by directly interacting with tumor cells and activating key signaling pathways, which drive EMT [14]. Moreover, platelet-derived PDGF recruits'

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cancer-associated fibroblasts, leading to excessive extracellular matrix deposition that impedes immune cell infiltration into tumors [18]. The incorporation of preoperative imaging parameters, particularly MI depth assessed via MRI or transvaginal ultrasound, significantly enhances the predictive capacity of our nomogram. MI≥1/2, as a robust imaging-derived marker, reflects both tumor invasiveness and microenvironmental interactions, such as angiogenesis and stromal remodeling, which are closely linked to LVSI development. Moreover, the high spatial resolution of MRI allows for precise delineation of tumor margins and heterogeneity, which may correlate with immune cell infiltration patterns and inflammatory responses quantified by SII [19]. This synergy between imaging and immune markers underscores the importance of a multimodal approach in preoperative risk assessment.

In this study, multivariate analysis identified three independent risk factors for LVSI, and the constructed joint prediction model demonstrated robust discriminative ability, with an AUC of 0.7813 in the training set and 0.7591 in the validation set. Preoperative assessment of LVSI status was facilitated by incorporating SII and CA125 levels, obtainable from routine laboratory tests, along with MI evaluated via preoperative pelvic MRI or transvaginal ultrasound. Notably, this study is the first to integrate immune-related indicators and develop a novel SII-based nomogram for predicting LVSI status in EC patients.

Future studies should explore the integration of radiomic features with SII and CA125 to further refine LVSI prediction. Radiomics captures tumor heterogeneity and microenvironmental dynamics that may complement systemic immune-inflammatory indices, potentially improving model sensitivity and specificity. For example, low ADC values have been associated with high cellularity and disrupted microvasculature, which may synergize with elevated SII to indicate aggressive tumor phenotypes.

CONCLUSION

The SII and MI-based predictive nomogram demonstrates robust performance in assessing LVSI status, offering a valuable tool for evaluating lymph node metastasis and informing clinical decision-making.

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***Conflicts of Interest*:** The authors report no conflict of interest.

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***Ethical Approval*:** The study involving human subjects complied with the Declaration of Helsinki and was approved by the ethical committee of the Jilin Cancer Hospital (No. 202401-02-01), and all participants provided written informed consent.

***Authors" Contributions*:** JX.P. conceived and designed the study, YY.L. wrote and revised the manuscript, ZL.X. collected and analyzed the data, JY.L. visualization the data, All authors read and approved the final submitted manuscript.

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