Am J Transl Res 2026;18(7):5753-5764
www.ajtr.org /ISSN:1943-8141/AJTR0172387

Original Article

Predictive value of deep myometrial invasion for lymph node metastasis in low-grade endometrioid carcinoma and its implications for surgical decision-making

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Received March 3, 2026; Accepted May 20, 2026; Epub July 15, 2026; Published July 30, 2026

Abstract: Objective: To evaluate the predictive value of deep myometrial invasion (DMI) for lymph node metastasis (LNM) in low-grade endometrioid carcinoma (LGEC) and its implications for surgical decision-making. Methods: A retrospective cohort study was conducted on 212 patients with pathologically confirmed LGEC (G1/G2) who underwent surgical treatment at Women's Hospital, School of Medicine, Zhejiang University between January 2018 and December 2023. Clinicopathological variables were analyzed using univariate and multivariate logistic regression to identify independent risk factors for LNM. The predictive performance of DMI and other significant variables was assessed by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) curves. A combined predictive model incorporating all independent factors was developed and internally validated using calibration curves and the Hosmer-Lemeshow test. External validation was performed in an independent cohort of 54 patients. Results: LNM occurred in 9.4% (20/212) of patients. Multivariate analysis identified DMI ≥50% (OR=3.58, 95% CI: 1.23-10.41, P=0.019), cervical stromal invasion (CSI; OR=5.24, 95% CI: 1.47-18.73, P=0.011), and elevated preoperative CA125 >35 U/ml (OR=4.14, 95% CI: 1.42-12.07, P=0.009) as independent predictors. The combined model achieved a sensitivity of 90% and an NPV of 99% for LNM prediction; external validation yielded an NPV of 97.44%, confirming its robustness for identifying low-risk patients. Patients with DMI were more likely to undergo laparotomy than those with superficial invasion (50.0% vs. 18.3%, P<0.001) and more frequently received postoperative adjuvant therapy (52.1% vs. 12.8%, P<0.001). Conclusion: DMI, CSI, and elevated CA125 are independent risk factors for LNM in LGEC. The high sensitivity and NPV of the combined predictive model support a selective lymphadenectomy strategy to avoid overtreatment in low-risk patients, while DMI also informs surgical approach selection and adjuvant therapy decisions.

Keywords: Low-grade endometrioid carcinoma, deep myometrial invasion, lymph node metastasis, predictive value, surgical decision-making

Introduction

Endometrial carcinoma (EC) is the most common malignancy of the female reproductive tract [1]. According to global epidemiological forecast, while EC mortality may have decreased, its incidence and disease burden continue to rise significantly [2, 3]. Low-grade endometrioid carcinoma (LGEC) is the predominant subtype of EC, accounting for more than 70% of cases. Compared with other subtypes, LGEC exhibits slower growth and a more favorable prognosis [4]. Nevertheless, in LGEC patients, lymph node metastasis (LNM) represents a major adverse prognostic factor, directly influencing treatment planning, recurrence risk, and long-term survival [5]. Accurate identification of high-risk factors for LNM in LGEC is therefore essential to optimize surgical strategies and improve patient prognosis.

Surgery remains the mainstay for LGEC management. Comprehensive staging surgery, which minimally includes total hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node sampling, has been

https://doi.org/10.62347/DBCZ3095

the gold standard for early-stage disease [6, 7]. However, the role of routine lymphadenectomy in early LGEC remains controversial. Previous studies suggest that around 10% of LGEC patients harbor positive LNM [8]. Performing systematic lymph node dissection in all patients may result in overtreatment, leading to complications such as lymphocele, lower extremity lymphedema, and decreased quality of life [9]. Conversely, omission of occult LNM may lead to under-staging and insufficient adjuvant treatment, potentially compromising survival outcomes. Therefore, precise identification of patient subgroups at high risk for LNM is crucial for individualized surgical decision-making.

The International Federation of Gynaecology and Obstetrics (FIGO) staging system takes the depth of myometrial invasion (confined to the endometrium or invasion depth <50% myometrium vs. invasion depth ≥50% myometrium) as a significant pathological prognostic indicator [10]. Research has demonstrated that deep myometrial invasion (DMI) constitutes an independent risk factor for recurrence and poor survival in EC [11, 12]. This may be attributed to the increased likelihood of tumor infiltration into the rich vascular system (lymphatic vessels and blood vessels) of the myometrium [13]. However, most existing studies have focused on the overall EC population, and high-quality, large-scale retrospective studies specifically evaluating the correlation between DMI and LNM in LGEC remain scarce. In clinical practice, definitive assessment of myometrial invasion depth relies on postoperative pathology [14]. For patients with preoperative indications of potential DMI, the precise quantitative association between invasion depth and LNM risk, as well as the predictive performance of DMI in the relatively "low-risk" LGEC patients, remains to be further clarified through large-scale clinical data.

Against this backdrop, the present study aims to investigate the correlation between DMI and LNM in LGEC through a retrospective analysis. We anticipate that our findings will provide evidence-based guidance for more accurate identification of LGEC patients who may benefit from systematic lymph node dissection, thereby balancing the need to avoid overtreatment with the goal of achieving complete tumor resection and optimizing prognosis and quality of life.

Materials and methods

Patient population

This retrospective study enrolled patients who underwent surgical treatment and were pathologically confirmed as having LGEC at Women's Hospital, School of Medicine, Zhejiang University, between January 2018 and December 2023. All diagnoses were independently confirmed by two senior gynecological pathologists in accordance with the World Health Organization (WHO) classification criteria for tumors of the female reproductive system, with pathological grades of G1 to G2 [15]. All patients were newly diagnosed and had not received any preoperative anti-tumor treatment, including radiotherapy, chemotherapy, or endocrine therapy. To validate the predictive model derived from the primary cohort, a separate clinical validation cohort (n=54) was established, comprising consecutive LGEC patients who underwent surgical treatment at the same institution from January 2024 to August 2025. The same inclusion and exclusion criteria were applied to ensure consistency.

This study strictly adhered to all the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Inclusion and exclusion criteria

Inclusion criteria: (1) Age ≥18; (2) Pathologically confirmed LGEC (pathological grade G1/G2) after surgery; (3) Complete clinical pathological data.

Exclusion criteria: (1) Non-endometrioid histology (e.g., serous carcinoma, clear cell carcinoma) or high-grade endometrioid carcinoma (G3 grade, poorly differentiated); (2) FIGO stage IV disease; (3) Presence of P53 mutation or high copy number variation; (4) History of other malignancies or synchronous multiple primary tumors; (5) Missing key clinical or pathological information (e.g., unclear myometrial invasion depth, unrecorded lymph node assessment); (6) Patients undergoing only diagnostic biopsy or palliative procedures without standard surgical resection.

Table 1. Baseline characteristics of patients

Variables	Total (n=212)
Age (year)	56.60 ± 9.84
BMI (kg/m^2)	25.74 ± 3.37
Preoperative endometrial thickness (cm)	1.33 ± 0.79
Menopausal status (yes)	143 (67.45)
Hypertension (yes)	99 (46.70)
Diabetes (yes)	49 (23.11)
Elevated triglycerides (yes)	64 (30.19)
Reduced HDL-C (yes)	38 (17.92)

Note: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

Data collection

Clinical, surgical, and pathological data were extracted from the electronic medical record system. The collected variables included: (1) Demographic and clinical characteristics: age, body mass index (BMI), menopausal status, comorbidities (hypertension, diabetes mellitus, dyslipidemia); (2) Preoperative findings: endometrial thickness on preoperative ultrasound, presence of intracavitary lesions, and serum tumor marker levels (Carbohydrate Antigen 125 [CA125], Carbohydrate Antigen 199 [CA199]). Consistent with standard clinical practice, the cutoff values for CA125 and CA199 were set at 35 U/ml and 37 U/ml, respectively, based on the reference ranges provided by our laboratory [16, 17]; (3) Surgical details: surgical approach (laparoscopic vs. open), surgical extent (comprehensive staging including lymphadenectomy vs. non-staging surgery), and performance of lymph node dissection; (4) Pathological features: histological type and grade, FIGO stage, depth of myometrial invasion (<50% vs. ≥50%), presence of cervical stromal invasion (CSI), and available molecular classification data; (5) Outcome data: pelvic lymph node status, para-aortic lymph node status, overall LNM status, and postoperative adjuvant treatment. All pathological findings, especially the depth of myometrial invasion, were independently reviewed and confirmed by two senior pathologists.

Outcome measures

The primary outcome was LNM, defined as the presence of carcinoma in pelvic and/or para-aortic lymph nodes confirmed by postoperative pathology. Secondary outcomes included: (1) the incidence of LNM stratified by myometrial invasion depth; (2) the diagnostic performance of DMI in predicting LNM, assessed by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV); (3) identification of other clinicopathological factors associated with LNM.

Statistical analysis

Statistical analyses were performed using SPSS software (IBM Corp., Armonk, NY, USA). Continuous variables following a normal distribution were presented as mean ± standard deviation (SD) and compared using the independent samples t-test; non-normally distributed data were expressed as median (interquartile range) and compared using the Mann-Whitney U test. Categorical variables were presented as frequency (percentage) and compared using the Chi-square test or Fisher's exact test, as appropriate. Univariate analysis was used to screen clinicopathological factors associated with LNM, and variables with $P<0.1$ in univariate analysis were subsequently included in multivariate Logistic regression analysis to determine whether DMI is an independent predictor of LNM. The predictive value of DMI for LNM was assessed using receiver operating characteristic (ROC) curve, and the area under the curve (AUC), sensitivity, specificity, PPV, and NPV were calculated. An AUC >0.7 indicated good predictive performance. Model calibration was evaluated using calibration curves and the Hosmer-Lemeshow goodness-of-fit test. All statistical tests were two-tailed, with a test level $\alpha=0.05$, and $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of the study population

A total of 212 patients with LGEC, who met the inclusion criteria, were enrolled in this retrospective analysis. Baseline clinical characteristics of the cohort are summarized in **Table 1**. The mean age at diagnosis was 56.6 ± 9.8 years, with a mean BMI of 25.7 ± 3.4 kg/m^2. Most patients were postmenopausal (67.5%).

Table 2. Pathological and surgical information of patients

Category	Characteristics	Total (n=212)
Pathological information		
Myometrial invasion depth	<50%	164 (77.36)
	≥50%	48 (22.64)
Pelvic lymph node status	Negative	198 (93.40)
	Positive	14 (6.60)
Para-aortic lymph node status	Negative	204 (96.23)
	Positive	8 (3.77)
Overall lymph node status	Negative	192 (90.57)
	Positive	20 (9.43)
Intrauterine space-occupying lesion	Present	61 (28.77)
	Absent	151 (71.23)
Complicated with adenomyosis	Present	51 (24.06)
	Absent	161 (75.94)
Cervical stromal invasion	Present	16 (7.55)
	Absent	196 (92.45)
CA125	>35 U/ml	44 (20.75)
	≤35 U/ml	168 (79.25)
CA199	>37 U/ml	46 (21.70)
	≤37 U/ml	166 (78.30)
Surgical information		
Surgical approach	Laparoscopy	158 (74.53)
	Laparotomy	54 (25.47)
Surgical scope	Comprehensive staging surgery	158 (74.53)
	Unstaged surgery	54 (25.47)
Lymphadenectomy	No	57 (26.89)
	Yes	155 (73.11)

Note: CA125, carbohydrate antigen 125; CA199, carbohydrate antigen 199.

Common comorbidities included hypertension (46.7%), diabetes mellitus (23.1%), elevated triglycerides (30.2%), and reduced high density lipoprotein cholesterol (HDL-C) (17.9%).

Pathological and surgical features

The distribution of key pathological and surgical features is presented in **Table 2**. DMI was observed in 22.6% of patients (n=48), and CSI was present in 7.5% of cases. Elevated preoperative serum levels of CA125 and CA199 were observed in 20.8% and 21.7% of patients, respectively. LNM was confirmed in 20 patients (9.4%), with pelvic LNM in 6.6% and para-aortic LNM in 3.8%. Regarding surgical management, 74.5% of patients underwent comprehensive staging surgery, and 73.1% received lymphadenectomy. Laparoscopic surgery was performed in 74.5% of cases.

Univariate analysis of factors associated with LNM

Univariate analyses comparing patients with (n=20) and without (n=192) LNM are detailed in **Table 3**. Statistically significant differences were observed for DMI (χ^2=15.32, P<0.001), CSI (χ^2=19.71, P<0.001), and preoperative serum CA125 level (χ^2=18.13, P<0.001). The proportion of patients with LNM was higher in those with DMI (60.0% vs. 18.8%), CSI (35.0% vs. 4.7%), and elevated CA125 (60.0% vs. 16.7%) compared with the non-LNM group. Other variables, including age, BMI, menopausal status, hypertension, diabetes, elevated triglycerides, reduced HDL-C, intrauterine space-occupying lesion, adenomyosis, and CA199 level, were not significantly associated with LNM.

Table 3. Univariate analysis of factors associated with lymph node metastasis

Variables	Non-LNM group (n=192)	LNM group (n=20)	Statistic	*P* value
Age (year)	56.99 ± 9.45	52.85 ± 12.68	t=1.80	0.073
BMI (kg/m^2)	25.78 ± 3.39	25.27 ± 3.15	t=0.64	0.521
Preoperative endometrial thickness (cm)	1.34 ± 0.79	1.26 ± 0.83	t=0.43	0.667
Menopausal status, n (%)			χ^2=0.07	0.798
No	63 (32.81)	6 (30.00)		
Yes	129 (67.19)	14 (70.00)		
Hypertension, n (%)			χ^2=0.03	0.873
No	102 (53.12)	11 (55.00)		
Yes	90 (46.88)	9 (45.00)		
Diabetes, n (%)			χ^2=3.03	0.082
No	144 (75.00)	19 (95.00)		
Yes	48 (25.00)	1 (5.00)		
Elevated triglycerides, n (%)			χ^2=0.28	0.595
No	133 (69.27)	15 (75.00)		
Yes	59 (30.73)	5 (25.00)		
Reduced HDL-C, n (%)			χ^2=1.38	0.241
No	160 (83.33)	14 (70.00)		
Yes	32 (16.67)	6 (30.00)		
Myometrial invasion depth, n (%)			χ^2=15.32	<0.001
<50%	156 (81.25)	8 (40.00)		
≥50%	36 (18.75)	12 (60.00)		
Intrauterine space-occupying lesion, n (%)			χ^2=0.02	0.899
Absent	137 (71.35)	14 (70.00)		
Present	55 (28.65)	6 (30.00)		
Complicated with adenomyosis, n (%)			χ^2=0.52	0.471
Absent	144 (75.00)	17 (85.00)		
Present	48 (25.00)	3 (15.00)		
Cervical stromal invasion, n (%)			χ^2=19.71	<0.001
Absent	183 (95.31)	13 (65.00)		
Present	9 (4.69)	7 (35.00)		
CA125, n (%)			χ^2=18.13	<0.001
≤35 U/ml	160 (83.33)	8 (40.00)		
>35 U/ml	32 (16.67)	12 (60.00)		
CA199, n (%)			χ^2=3.25	0.072
≤37 U/ml	154 (80.21)	12 (60.00)		
>37 U/ml	38 (19.79)	8 (40.00)		

Note: LNM, lymph node metastasis; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; CA125, carbohydrate antigen 125; CA199, carbohydrate antigen 199.

Multivariate analysis of independent risk factors for LNM

Variables with P<0.1 from the univariate analysis were included in a multivariate logistic regression model (**Table 4**). Three factors were identified as independent risk factors for LNM: DMI (OR=3.58, 95% CI: 1.23-10.41, P=0.019), CSI (OR=5.24, 95% CI: 1.47-18.73, P=0.011), and elevated preoperative serum CA125 (OR=4.14, 95% CI: 1.42-12.07, P=0.009).

Predictive performance of independent risk factors and combined model

The diagnostic performance of the three independent risk factors, both individually and in

Table 4. Multivariate analysis of independent risk factors for lymph node metastasis

Variables	β	S.E	Z	*P*	OR (95% CI)
Intercept	-3.51	0.44	-7.98	<0.001	0.03 (0.01-0.07)
Myometrial invasion depth					
<50%					Reference
≥50%	1.27	0.54	2.34	0.019	3.58 (1.23-10.41)
Cervical stromal invasion					
Absent					Reference
Present	1.66	0.65	2.55	0.011	5.24 (1.47-18.73)
CA125					
≤35 U/ml					Reference
>35 U/ml	1.42	0.55	2.60	0.009	4.14 (1.42-12.07)

Note: SE, standard error; OR, odds ratio; CI, confidence interval; DMI, deep myometrial invasion; CSI, cervical stromal invasion; CA125, carbohydrate antigen 125.

Table 5. Predictive efficacy of each independent risk factors and their combination for lymph node metastasis

Indicators	Accuracy	Sensitivity	Specificity	PPV	NPV
Myometrial invasion depth	0.79 (0.73-0.84)	0.60 (0.39-0.81)	0.81 (0.76-0.87)	0.25 (0.13-0.37)	0.95 (0.92-0.98)
CA125	0.81 (0.75-0.86)	0.60 (0.39-0.81)	0.83 (0.78-0.89)	0.27 (0.14-0.40)	0.95 (0.92-0.98)
Cervical stromal invasion	0.90 (0.85-0.93)	0.35 (0.14-0.56)	0.95 (0.92-0.98)	0.44 (0.19-0.68)	0.93 (0.90-0.97)
Combination	0.72 (0.65-0.78)	0.90 (0.77-1.00)	0.70 (0.63-0.76)	0.24 (0.14-0.33)	0.99 (0.97-1.00)

Note: LNM, lymph node metastasis; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; DMI, deep myometrial invasion; CSI, cervical stromal invasion; CA125, carbohydrate antigen 125.

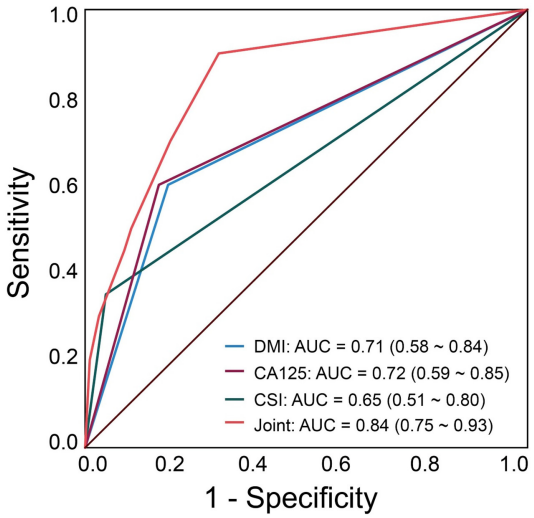

Figure 1. ROC curve analysis of each independent risk factors and the combine model in predicting LNM risk. Note: ROC, receiver operating characteristic curve; LNM, lymph node metastasis; DMI, deep myometrial invasion; CA125, carbohydrate antigen 125; CSI, cervical stromal invasion; AUC, area under the curve.

combination, for predicting LNM was evaluated (**Table 5**; **Figure 1**). CSI demonstrated the highest specificity (0.95, 95% CI: 0.92-0.98) and PPV (0.44, 95% CI: 0.19-0.68), albeit with low sensitivity (0.35, 95% CI: 0.14-0.56). DMI and elevated CA125 showed moderate sensitivity (both 0.60) and specificity (0.81 and 0.83, respectively). The combined predictive model, incorporating all three factors, achieved the highest sensitivity (0.90, 95% CI: 0.77-1.00) and NPV (0.99, 95% CI: 0.97-1.00), though with a lower specificity (0.70) and PPV (0.24).

Comparison of predictive efficacy using the DeLong test

The DeLong test was employed to compare the AUCs for the combined model versus each individual predictor (**Table 6**). The combined model demonstrated a significantly higher predictive performance compared with each factor alone (P<0.05). Specifically, the AUC differences were -0.13 (P=0.020) compared with DMI, -0.12 (P=0.007) compared with CA125, and -0.19 (P<0.001) compared with CSI.

Calibration of the multivariate predictive model

The calibration curve for the multivariate logistic regression model is shown in **Figure 2**. The Hosmer-Lemeshow goodness-of-fit test yielded

Table 6. Delong test

Indicators	AUC Diff.	SE of Diff.	Z	95% CI	*P* value
Myometrial invasion depth vs. Combination	-0.13	0.32	-2.33	-0.24–-0.02	0.020
CA125 vs. Combination	-0.12	0.32	-2.69	-0.21–-0.03	0.007
Cervical stromal invasion vs. Combination	-0.19	0.31	-3.84	-0.28–-0.09	<0.001

Note: AUC, area under the curve; SE, standard error; CI, confidence interval; DMI, deep myometrial invasion; CSI, cervical stromal invasion; CA125, carbohydrate antigen 125.

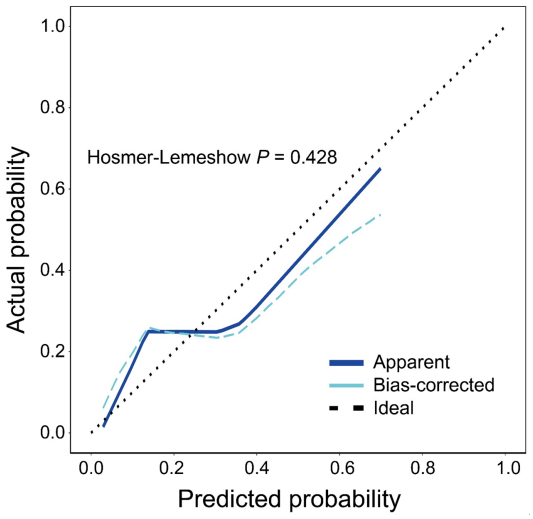

Figure 2. Calibration curve analysis of the joint model.

a non-significant *P*-value of 0.428, indicating that the predicted probabilities were consistent with the observed frequencies, supporting acceptable model calibration.

Clinical validation of the predictive model

To further validate the predictive model, an independent cohort of 54 consecutive LGEC patients, meeting the same inclusion and exclusion criteria, was enrolled from January 2024 to August 2025. Among them, 6 patients (11.1%) were diagnosed with LNM postoperatively (**Table 7**). When the previously established multivariate predictive model (incorporating DMI, CSI, and elevated CA125) was applied to this validation cohort, it demonstrated a sensitivity of 83.33%, specificity of 79.17%, PPV of 33.33%, and NPV of 97.44%. The high NPV (97.44%) is consistent with the findings from the primary cohort, reinforcing the model's utility in identifying patients at very low risk of LNM.

Impact of myometrial invasion depth on surgical and adjuvant treatment decisions

Differences in surgical management and postoperative adjuvant therapy based on the depth of myometrial invasion are presented in **Tables 8** and **9**. Patients with DMI (n=48) were significantly more likely to undergo laparotomy compared to those with superficial myometrial invasion (SMI group, n=164) (50.0% vs. 18.3%, χ^2= 19.66, P<0.001). However, the rates of comprehensive staging surgery (81.3% vs. 72.6%, P=0.224) and lymphadenectomy (79.2% vs. 71.3%, P=0.282) did not differ significantly between the two groups. Postoperatively, patients with DMI received adjuvant therapy (radiotherapy, chemotherapy, or chemoradiotherapy) significantly more frequently than the SMI group (52.1% vs. 12.8%, P<0.001).

Discussion

This retrospective cohort study of 212 cases of LGEC confirms that DMI is an independent risk factor for LNM. The combined model incorporating DMI, CSI, and CA125 demonstrated high sensitivity (90%) and a robust NPV (99% in the derivation cohort, 97% in the validation cohort), supporting its potential utility in identifying patients who can safely forego lymphadenectomy. Conversely, the model's low PPV (24%) limits its ability to independently predict which patients will benefit from lymphadenectomy. Additionally, DMI was associated with more frequent laparotomy and postoperative adjuvant therapy, reflecting its impact on real-world surgical decision-making.

Although LGEC has traditionally been regarded as a 'low-risk' type, it still carries a 9%-10% incidence of LNM, suggesting that conventional pathological grading alone cannot fully eliminate the risk of metastasis [18]. In a study by

Table 7. Clinical verification process

		Postoperative diagnosis		Total
		LNM	Non-LNM	
Model judgment	LNM	5	10	15
	Non-LNM	1	38	39
Total		6	48	54

Note: Sensitivity =83.33%; Specificity =79.17%; PPV=33.33%; NPV=97.44%. LNM, lymph node metastasis; PPV, positive predictive value; NPV, negative predictive value.

Ronsini et al. [19], the incidence of DMI in patients with LGEC was 22.22% (32/144), which is similar to the results of this study. Cao et al. [20] reported in a retrospective study that the incidence of LNM in patients with LGEC was 7.8%, and confirmed the independent associations of DMI, CSI, and CA125 with LNM. The predictive value of DMI for LNM in LGEC is supported both by the pathophysiological mechanisms of tumor invasion and clinical evidence. Mechanistically, the uterine myometrium is richly supplied with a network of lymphatic and blood vessels [21], which provides conduits for tumor cell dissemination once the myometrial barrier is sufficiently breached [13]. When tumor infiltration reaches ≥50% of the myometrial thickness, it becomes more likely to penetrate the basement membrane and invade the vascular system, thereby accessing lymphatic channels that drain to regional lymph nodes [22]. In our multivariate analysis, the OR for DMI was 3.58, indicating that even in LGEC with relatively indolent biological behavior, DMI still increases the risk of LNM by more than threefold [22, 23]. This finding provides crucial evidence for risk stratification in low-risk EC populations, aligning with the conclusions of Wang et al.'s meta-analysis involving 68,870 EC patients [11]. It further validates the universal prognostic value of DMI across different EC subtypes. The 60% sensitivity of DMI indicates that over half of LNM events can be identified using DMI. Its specificity of 81% and high NPV (95%) provide a reliable safety margin for clinical decision-making: those without DMI can be regarded as low-risk, providing a strong rationale for omitting systematic lymph node dissection. However, the 24% PPV underscores the limitation of relying on DMI alone; exclusive use of DMI as a decision criterion may lead to potentially unnecessary surgeries in many "false positive" patients. This highlights that DMI must be used in combination with other metrics to optimize the accuracy of decision-making.

Previous studies have established a close association between CSI, LNM and prognosis in patients with EC [24, 25]. Mechanistically, CSI likely reflects direct tumor extension through the lower uterine segment, providing a contiguous anatomical pathway for malignant cells to reach parametrial and pelvic lymph nodes without requiring extensive myometrial penetration [24]. In this study, CSI exhibited the highest odds ratio (OR=5.24) and extremely high specificity (95%). This finding has important clinical implications: pathologically confirmed CSI can be considered a high-risk marker for LNM regardless of the depth of myositis infiltration. Although other scales, such as the Cuntz Scale Index, may offer better prediction ability, they are not routinely used in clinical practice. The incidence of CSI in this study was 7.5%, lower than that of DMI (22.6%) [26]. Moreover, accurate diagnosis of CSI is dependent on the integrity of specimen sampling, which may introduce subjective bias [27].

Preoperative serum CA125 was also an independent predictor of LNM (OR=4.14). Elevated CA125 likely reflects the release of antigens into the blood following cellular destruction owing to tumor invasion [28, 29]. However, CA125 has relatively low specificity, as it can be elevated in benign conditions such as pelvic inflammatory disease, endometriosis, or impaired liver and kidney function [30, 31]. When compared to the other two indicators, DMI is a composite measure with a higher incidence, objective assessment, as well as balanced sensitivity and specificity, making it a more reliable core indicator for LNM risk stratification in LGEC patients. Combining DMI with CSI and CA125 enhances predictive accuracy, as reflected in the superior performance of the multivariate model compared to any individual indicator.

The combined prediction model integrating three independent risk factors demonstrated a sensitivity of 90% for identifying LNM and a NPV of 99%. Furthermore, this model was validated in an independent clinical cohort of 54 patients, maintaining a high NPV of 97%, corroborating its robust performance in identifying

Table 8. Comparison of surgical choices between patients with different myometrial invasion depths

Variables	SMI group (n=164)	DMI group (n=48)	Statistic	*P* value
Surgical scope			χ^2=1.48	0.224
Comprehensive staging surgery	119 (72.56)	39 (81.25)		
Unstaged surgery	45 (27.44)	9 (18.75)		
Lymphadenectomy			χ^2=1.16	0.282
No	47 (28.66)	10 (20.83)		
Yes	117 (71.34)	38 (79.17)		
Surgical approach			χ^2=19.66	<0.001
Laparoscopy	134 (81.71)	24 (50.00)		
Laparotomy	30 (18.29)	24 (50.00)		

Note: SMI, superficial myometrial invasion (<50%); DMI, deep myometrial invasion (≥50%).

Table 9. Comparison of postoperative adjuvant treatment choices between patients with different myometrial invasion depths

Variables	SMI group (n=164)	DMI group (n=48)	Statistic	*P* value
Postoperative adjuvant treatment			-	<0.001
None	143 (87.20)	23 (47.92)		
Radiotherapy	4 (2.44)	12 (25.00)		
Chemotherapy	11 (6.71)	5 (10.42)		
Chemoradiotherapy	6 (3.66)	8 (16.67)		

Note: SMI, superficial myometrial invasion (<50%); DMI, deep myometrial invasion (≥50%).

low-risk individuals. In clinical practice, preoperative imaging and intraoperative frozen section analysis can provide approximate invasion information, enabling the model to guide real-time surgical decision-making.

Patients categorized as 'low-risk' by the model (i.e. those lacking all three factors) have an exceptionally low probability of developing LNM (approximately 1%). From a clinical perspective, this supports the safe omission of systematic lymphadenectomy in this specific subgroup, potentially reducing unnecessary complications such as lymphocysts and lymphedema [32]. Conversely, the model demonstrated a PPV of only 24%, meaning that among patients classified as 'high-risk' (those with at least one positive factor), only one-quarter were confirmed to have LNM on final pathology. Consequently, performing systematic lymphadenectomy solely based on the high-risk prediction would result in approximately 76% of patients undergoing the procedure without oncologic benefit. This low PPV is not a flaw unique to our model but rather an inherent limitation of predictive models for rare events, as the overall LNM prevalence in LGEC was only 9.4% in this cohort. In any model designed to achieve high sensitivity for rare outcomes, a high false-positive rate is an inevitable trade-off. Therefore, the primary clinical application of this model lies in its high NPV, which reliably identifies patients who can safely forego lymphadenectomy. It should not, however, be used in isolation to mandate systematic lymphadenectomy for high-risk-predicted patients. For such patients, additional factors - such as intraoperative findings, patient comorbidities, and surgical risk assessment - should be integrated into shared decision making. In this context, sentinel lymph node biopsy may represent a balanced alternative, offering diagnostic information with lower morbidity than complete lymphadenectomy, especially for intermediate risk patients.

The utility of DMI in guiding surgical decisions for LGEC lies in optimizing both the surgical approach and resection scope. In this study, laparotomy was significantly more common in DMI patients (50.0% vs. 18.3% in SMI group), reflecting the need to manage DMI-related tumor invasiveness. Laparotomy provides adequate exposure for metastasis assessment and thorough lymphadenectomy, especially in complex cases such as obesity or pelvic adhe-

sion [33]. In contrast, SMI patients, who have a lower LNM risk, may benefit more from minimally invasive laparoscopic surgery (e.g., reduced postoperative pain, faster recovery, fewer complications) [34, 35]. Despite similar lymphadenectomy rates (79.2% vs. 71.3%), patients with DMI generally require comprehensive staging surgery, potentially including paraaortic lymph node assessment, while SMI patients without CSI or elevated CA125 may forgo lymphadenectomy to avoid complications, aligning with FIGO 2023 staging recommendations and principles of precision oncology [10]. The ESGO guidelines classify DMI (≥50%) as an intermediate-risk feature in low-grade endometrioid carcinoma, warranting consideration of lymph node assessment. Our findings support this threshold, as DMI was independently associated with LNM (OR=3.58). However, the ESGO system does not explicitly incorporate CSI or CA125. Our model, showing a 99% NPV for patients lacking DMI, CSI, and elevated CA125, provides quantitative support for a selective lymphadenectomy approach. Nonetheless, the model's low PPV (24%) suggests that indiscriminately applying current guideline criteria may still result in substantial overtreatment.

There are several limitations to this study. First, as a single-center retrospective study, it is subject to potential selection bias. Second, the statistical stability of the multivariate model is constrained by the relatively limited number of LNM events (n=20) compared with the number of predictors included. With only 20 events and 3 predictors, the events-per-variable (EPV) ratio is approximately 6.7, below the commonly recommended threshold of 10-20 events per variable. This raises concerns regarding potential overfitting, model instability, and the reliability of odds ratio estimates. The relatively wide 95% confidence interval for the odds ratio of DMI (3.58, 95% CI: 1.23-10.41) suggests that the estimate of effect size is somewhat imprecise, likely related to the limited number of outcome events in this study. Third, the external validation cohort was small (n=54) with only 6 LNM events, limiting the robustness and generalizability of the validation findings. Fourth, the predictive model was developed based on definitive postoperative pathological features, which may restrict its immediate application for preoperative or intraoperative surgical decision-making. Nevertheless, previous evidence has demonstrated that preoperative MRI and intraoperative frozen section evaluation yield high diagnostic accuracy for assessing DMI and CSI, suggesting that these key indicators can be reliably obtained pre- or intraoperatively [36, 37]. Future studies should consider incorporating the accuracy of preoperative/intraoperative evaluations or directly using imaging-based features as surrogates to further optimize the model's real-time clinical utility. Finally, molecular classification, an important prognostic and predictive factor in endometrial carcinoma, was not incorporated into the model. Future studies incorporating molecular features and assessing long-term survival outcomes will be important to develop enhanced and more comprehensive risk stratification tools to guide surgical management in LGEC.

Conclusion

DMI, CSI and elevated CA125 are independent risk factors for LNM in LGEC. A predictive model combining these three factors demonstrated high sensitivity and NPV in identifying a subgroup of patients with a very low risk of LNM; this finding was validated in an independent clinical cohort. For these low-risk patients, systematic lymphadenectomy may be safely omitted. However, due to the model's low PPV (24%), it should not be used in isolation to mandate lymphadenectomy in high-risk-predicted patients. Future prospective studies are needed to integrate this model with intraoperative findings and patient preferences to optimize surgical decision-making. Quantified performance metrics (sensitivity, NPV) can provide valuable evidence-based guidance for patient-specific surgical decision-making. In summary, incorporation of these clinicopathological parameters can help balance the avoidance of overtreatment with adequate staging in LGEC patients.

Acknowledgements

This work was supported by Zhejiang Provincial Traditional Chinese Medicine Science and Technology Plan - Traditional Chinese Medicine Clinical Research Project (2025ZL393), Ministry of Education Industry-University Collaborative Education Project Teacher Training Project (2509251535), Zhejiang Medical health science and technology plan (WKJ-ZJ-2321) and

National Natural Science Foundation of China (82201843).

Disclosure of conflict of interest

None.

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