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Original Article

Predictive value of immunohistochemical parameters combined with clinicopathological features in predicting recurrence after lymph node resection in endometrial cancer patients

Xianghui Lu, Shengyan Xie, Tianjie Yu, Daying Mou

Department of Obstetrics and Gynaecology, The First People's Hospital of Zunyi, Zunyi 563000, Guizhou, China

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Abstract: Objective: To evaluate the predictive value of immunohistochemical markers combined with clinicopathological parameters for recurrence after lymph node dissection in patients with endometrial cancer (EC) and to construct a comprehensive risk assessment model. Methods: A retrospective study was conducted on 118 EC patients who underwent radical surgery with systematic lymph node dissection between January 2023 and December 2025. Clinicopathological characteristics and expression of estrogen receptor (ER), progesterone receptor (PR), p53, and Ki-67 were collected. Kaplan-Meier (KM) analysis, Log-rank test, and Cox proportional hazards regression (Cox regression) models were used to identify prognostic factors. Receiver operating characteristic (ROC) curves and the DeLong test were applied to assess predictive performance. Results: During a median follow-up of 26 months, 28 patients (23.7%) experienced recurrence. Univariate analysis showed that advanced International Federation of Gynecology and Obstetrics stage (FIGO stage), poor differentiation, deep myometrial invasion, positive lymphovascular space invasion (LVSI), lymph node metastasis, aberrant p53 expression, and high Ki-67 expression were significantly associated with recurrence (all $P<0.05$). Multivariate analysis identified lymph node metastasis ($P = 0.005$), aberrant p53 expression ($P = 0.008$), Ki-67 ≥30% ($P = 0.022$), and LVSI positivity ($P = 0.042$) as independent risk factors. The combined model achieved an area under the curve (AUC) of 0.876 (95% confidence interval (CI): 0.807-0.945), with a sensitivity of 85.7% and specificity of 82.2%, outperforming individual predictors (all $P<0.05$). Conclusion: Key clinicopathological and immunohistochemical factors are independently associated with recurrence after lymph node dissection in EC. The model may improve risk stratification and support postoperative follow-up and risk management.

Keywords: Endometrial cancer, immunohistochemistry, lymph node dissection, recurrence, predictive model

Introduction

Endometrial cancer (EC) is among the most common malignant diseases of the female reproductive tract, and its global incidence continues to rise [1]. Epidemiological data predicted that the number of newly diagnosed EC cases in the United States would exceed 66,000 in 2024, and the number of related deaths was expected to exceed 13,000 [2, 3]. Accurate identification of high-risk recurrence populations after surgery has core clinical value for optimizing individualized intervention strategies and customizing follow-up plans. Lymph node dissection is a key technical step in EC surgical staging, and its value lies in clarifying the regional lymph node involvement status, thereby laying a pathological basis for the selection of postoperative adjuvant therapy pathways [4]. However, this invasive procedure itself is also associated with an increased incidence of postoperative complications. The 2023 FIGO staging system revision first incorporated molecular subtyping parameters into the staging framework, highlighting the strategic significance of biomarkers in prognostic stratification [5]. Predictive value of immunohistochemical markers: Estrogen receptor (ER), progesterone receptor (PR), p53 tumor suppressor protein, and cell proliferation marker Ki-67 have been

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widely used in EC prognostic assessment; however, their efficacy in predicting recurrence in patients after lymph node dissection still needs systematic validation. Mature evidence for clinicopathological parameters: The strong correlation between pathological features such as tumor cell differentiation degree, myometrial invasion depth, and lymphovascular space infiltration (LVSI) and recurrence events has been established through numerous studies [6, 7]. Evidence suggests that LVSI is more closely related to distant organ metastasis, hence FIGO staging has upgraded LVSI positivity to a staging upgrade standard [8]. The degree of myometrial invasion, especially the involvement of the outer 1/3 layer, has a significant statistical association with the risk of distant recurrence [9]. Prognostic significance of p53 abnormal expression: Abnormal p53 protein expression is considered a key biological signal of poor prognosis and is positively correlated with high recurrence rate and low long-term survival [10, 11]. Limitations of single indicators and the rise of combined models: Although single clinicopathological features or immunohistochemical markers have certain predictive value for recurrence, their discriminative efficacy has a significant ceiling effect when used independently. In recent years, several research teams have been committed to developing multi-factor integrated prediction systems to improve the accuracy of risk assessment [12, 13]. However, current evidence regarding recurrence prediction in endometrial cancer has largely focused on general surgical populations, with limited attention specifically to patients undergoing systematic lymph node dissection. Lymph node dissection represents a distinct clinical scenario, as it not only refines staging accuracy but may also alter recurrence patterns and prognostic factor weighting. Previous studies have attempted to construct predictive models integrating clinicopathological and immunohistochemical features. For instance, Song et al. [14] developed a model incorporating Ki-67 and pathological characteristics, achieving a C-index of 0.85. However, this model was primarily based on early-stage patients and did not specifically address the subgroup undergoing lymph node dissection. Therefore, whether the prognostic determinants and model performance remain consistent in this specific population remains unclear. The present study aims to fill this gap by focusing on patients who underwent lymph node dissection and by constructing a tailored recurrence prediction model integrating both clinicopathological and immunohistochemical parameters.

Materials and methods

Study subjects

This retrospective cohort study included 118 cases of endometrial cancer who underwent surgical intervention at The First People's Hospital of Zunyi between January 2023 and December 2025. Inclusion criteria included: (1) Preoperative histopathological confirmation of endometrial cancer diagnosis; (2) Complete postoperative pathology records, including immunohistochemical data; (3) No prior anti-tumor systemic therapy (radiotherapy or chemotherapy); (4) Complete clinical follow-up records. Exclusion criteria included: (1) Concurrent primary malignancy; (2) Intraoperative discovery of extraperitoneal metastases or diffuse peritoneal dissemination; (3) Final pathological diagnosis revised to uterine sarcoma; (4) Immunohistochemical staining failure or missing key data. This study was approved by the Ethics Committee of The First People's Hospital of Zunyi.

Sample size estimation

According to the event-per-variable (EPV) principle, at least 10 outcome events are generally recommended for each predictor variable in Cox regression models [15, 16]. Based on the expected inclusion of 8-10 variables, an ideal sample size would require approximately 80-100 recurrence events. However, due to the retrospective nature of this study and limited follow-up data, only 118 patients were included, with 28 recurrence events observed (EPV ≈ 3-4). This relatively low EPV may increase the risk of model overfitting. To mitigate this issue, we restricted the number of variables included in the multivariate model and applied a stepwise selection procedure. In addition, internal validation using bootstrap resampling (1000 iterations) was performed to evaluate model stability. Therefore, the present model should be interpreted as an exploratory model.

Clinical pathology data collection

The following variables were extracted using the hospital's electronic medical record sys-

tem: (1) Baseline characteristics: patient age, body mass index (BMI); (2) Preoperative laboratory indicators: serum tumor marker CA125 concentration; (3) Surgical pathology parameters: FIGO 2023 staging, histological subtype classification, tumor differentiation grade, degree of myometrial invasion, lymphovascular space involvement (LVSI) status, cervical stromal invasion, total number of lymph nodes removed, and number of positive nodes; (4) Postoperative adjuvant therapy strategies: radiotherapy, cytotoxic chemotherapy, or a combination therapy; (5) Follow-up outcome information: time of recurrence, anatomical location, and survival status.

Immunohistochemical staining procedure

Immunohistochemical staining of four protein markers [estrogen receptor (ER), progesterone receptor (PR), p53, and Ki-67)] was performed using a two-step EnVision detection system. The specific procedure was as follows: 4-micron thick tissue sections were cut from the postoperative paraffin-embedded specimen, dewaxed with xylene, and hydrated with graded ethanol. Antigen retrieval was performed using a high-pressure steam method with citrate buffer at pH 6.0. Endogenous peroxidase activity was blocked by incubation with 3% hydrogen peroxide solution at room temperature for 10 minutes.

Primary antibody incubation: The following antibodies were added and incubated overnight at 4°C in a humidified chamber: Rabbit anti-human ER monoclonal antibody (dilution 1:100, Cell Signaling Technology); Rabbit anti-human PR monoclonal antibody (dilution 1:100, Cell Signaling Technology); Mouse anti-human p53 monoclonal antibody (dilution 1:200, Dako); Mouse anti-human Ki-67 monoclonal antibody (dilution 1:150, Dako).

After washing with PBS buffer, horseradish peroxidase (HRP)-labeled polymeric secondary antibody was added, and the cells were incubated at 37°C for 30 minutes. DAB chromogenic reagent was used for development, and the cell nuclei were counterstained with hematoxylin solution. After routine dehydration and clearing, the cells were mounted with neutral resin.

Criteria for interpreting staining results

ER/PR assessment: A positive rate of ≥1% in tumor cell nuclear staining was considered positive expression [17].

p53 classification: Based on nuclear staining patterns, it was divided into: wild type (10-70% of cell nuclei show positive reaction); mutant type (<10% of cells are completely negative or >70% of cells show strong positive overexpression) [18].

Ki-67 index: Five hundred tumor cell nuclei were randomly counted in representative hotspot areas, and the percentage of positively stained nuclei was calculated. The optimal cutoff value for Ki-67 was determined by receiver operating characteristic (ROC) curve analysis using postoperative recurrence as the endpoint. The cutoff corresponding to the maximum Youden index was selected, and 30% was identified as the optimal threshold. Accordingly, Ki-67 expression was categorized as high proliferative activity (≥30%) and low proliferative activity (<30%) [19].

All slides were independently reviewed by two senior pathologists. If there was a disagreement in the interpretation results, a consensus was reached through consultation and discussion.

Follow-up monitoring plan

The postoperative monitoring plan was as follows: quarterly follow-up for the first 24 months, semi-annual assessment for the 3rd-5th years, and annual follow-up after 5 years. Follow-up procedures included: gynecological physical examination, serum CA125 dynamic monitoring, and enhanced CT or MRI scans of the chest, abdomen, and pelvis.

Recurrence was defined as localized recurrence or distant organ metastases confirmed by imaging examination or histopathological biopsy.

Data processing framework

Software environment: Analytical workflows employed SPSS Statistics 26.0 and R computational platform (build 4.2.0).

Descriptive characterization: Continuous parameters were reported as arithmetic mean ± standard deviation (for Gaussian distributions with equal variance) or median accompanied by 25th-75th percentile range; comparative tests applied Student's t or Mann-Whitney U procedures accordingly. Count data were tabulated as absolute frequencies (relative percent-

ages) with between-strata comparisons via chi-square or Fisher's exact probability assessment.

Recurrence-free survival estimation: Product-limit (Kaplan-Meier) curves depicted temporal patterns; log-rank statistic evaluated inter-group survival divergence. Candidate prognostic factors (univariate screening P<0.10) underwent multivariable Cox proportional hazards modeling via forward likelihood-ratio selection. Variables with P<0.10 in univariate analysis were considered candidate predictors and entered into the multivariate model, and the final model was established using forward stepwise likelihood-ratio selection. Adjusted effect magnitudes were expressed as HR (95% CI).

Prognostic tool formulation: Independent predictors from multivariable analysis formed a composite scoring system. Discrimination ability was gauged through ROC methodology; pairwise AUC comparisons utilized DeLong's variance estimation approach. The "rms" R package generated visual nomograms; calibration diagnostics confirmed prediction-observation concordance; clinical net benefit across decision thresholds was mapped via DCA. Inferential testing maintained two-tailed orientation with type I error rate fixed at 5%. To facilitate clinical application, a simplified risk scoring system was further derived from the final multivariate Cox model. Because the regression coefficients of the retained predictors were of similar magnitude, each independent predictor was assigned 1 point. The total score therefore ranged from 0 to 4, and patients were stratified into low-, intermediate-, and high-risk groups according to the cumulative score.

Results

General information and clinicopathological features of patients

This study enrolled 118 endometrial cancer patients, aged 28-78 years, with median age 57 years (IQR: 51-64 years); BMI ranged 18.5-38.2 kg/m^2, with mean BMI of 25.8 ± 4.3 kg/m^2. Among these, 102 cases (86.4%) were endometrioid adenocarcinoma, and 16 cases (13.6%) were non-endometrioid adenocarcinoma, including 8 serous carcinoma cases, 5 clear cell carcinoma cases, and 3 carcinosarcoma cases. FIGO staging: Stage I 78 cases (66.1%), Stage II 19 cases (16.1%), and Stage III 21 cases (17.8%). Tumor grade: G1 42 cases (35.6%), G2 45 cases (38.1%), and G3 31 cases (26.3%). Among the 65 patients (55.1%) with muscle layer infiltration <50%, 53 patients (44.9%) had ≥50%. LVSI positivity occurred in 33 patients (28.0%), and lymph node metastasis presented in 24 patients (20.3%). Postoperative adjuvant therapy comprised radiotherapy alone in 26 patients (22.0%), chemotherapy alone in 35 patients (29.7%), combined radiotherapy and chemotherapy in 21 patients (17.8%), and no adjuvant therapy in 36 patients (30.5%). Immunohistochemical results revealed ER positivity in 86 patients (72.9%), PR positivity in 82 patients (69.5%), abnormal p53 expression in 35 patients (29.7%), and high Ki-67 expression (≥30%) in 51 patients (43.2%). Median follow-up time was 26 months (range 3-36 months). During follow-up, 28 patients (23.7%) experienced recurrence, including 10 pelvic recurrence cases (35.7%), 13 distant metastasis cases (46.4%), and 5 cases with combined pelvic recurrence and distant metastasis (17.9%). Median recurrence time was 15 months (IQR: 9-21 months). The 1-year, 2-year, and 3-year RFS rates for the entire cohort were 85.6%, 78.2%, and 73.5%, respectively.

Comparison of baseline indicators

Significant differences were found between the two groups in FIGO stage, tumor grade, histological type, depth of muscle layer invasion, LVSI, lymph node metastasis, p53 expression, and Ki-67 expression (all P<0.05) (**Table 1**).

Multivariate regression results

Variables showing statistical significance or borderline significance in univariate analysis (P<0.10) were entered into the multivariate Cox regression model. After adjustment, only lymph node metastasis, aberrant p53 expression, Ki-67≥30%, and LVSI positivity remained statistically significant, whereas other factors lost significance, suggesting that their prognostic contribution may be partly explained by overlap with stronger independent predictors. Variables with P<0.10 in univariate analysis were included in the multivariate Cox regression model, and a forward stepwise selection method was applied to identify independent predictors. Including the variables that were meaningful in the single-factor model into the Cox regression

Table 1. Comparison of baseline indicators between the two groups

Feature	Recurrent Group (n = 28)	Non-recurrent Group (n = 90)	Test Statistic	*P*-value
Age (years)	58.5 ± 8.2	56.8 ± 9.1	t = 0.913	0.364
BMI (kg/m^2)	26.2 ± 4.6	25.6 ± 4.2	t = 0.645	0.521
FIGO Stage			χ^2 = 17.353	<0.001
Stages I-II	15 (53.6%)	82 (91.1%)		
Stage III	13 (46.4%)	8 (8.9%)		
Histological Type			χ^2 = 4.102	0.043
Endometrioid adenocarcinoma	21 (75.0%)	81 (90.0%)		
Non-endometrioid adenocarcinoma	7 (25.0%)	9 (10.0%)		
Tumor Grade			χ^2 = 10.678	<0.001
G1-G2	14 (50.0%)	73 (81.1%)		
G3	14 (50.0%)	17 (18.9%)		
Myometrial Invasion Depth			χ^2 = 7.818	<0.001
<50%	9 (32.1%)	56 (62.2%)		
≥50%	19 (67.9%)	34 (37.8%)		
Lymphovascular Space Invasion			χ^2 = 11.956	<0.001
Negative	13 (46.4%)	72 (80.0%)		
Positive	15 (53.6%)	18 (20.0%)		
Lymph Node Metastasis			χ^2 = 19.937	<0.001
Negative	14 (50.0%)	80 (88.9%)		
Positive	14 (50.0%)	10 (11.1%)		
ER Expression			χ^2 = 1.374	0.254
Positive	18 (64.3%)	68 (75.6%)		
Negative	10 (35.7%)	22 (24.4%)		
PR Expression			χ^2 = 1.338	0.252
Positive	17 (60.7%)	65 (72.2%)		
Negative	11 (39.3%)	25 (27.8%)		
p53 Expression			χ^2 = 13.674	<0.001
Wild-type	11 (39.3%)	69 (76.7%)		
Abnormal expression	17 (60.7%)	21 (23.3%)		
Ki-67 Expression			χ^2 = 15.117	<0.001
<30%	7 (25.0%)	60 (66.7%)		
≥30%	21 (75.0%)	30 (33.3%)		

Note: Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; ER, estrogen receptor; PR, progesterone receptor.

model, results indicated that lymph node metastasis, abnormal p53 expression, Ki-67≥30%, and LVSI positivity constituted independent risk factors for postoperative recurrence in endometrial cancer patients (**Table 2**; **Figure 1**).

Construction and evaluation of combined predictive model

ROC curve analysis: ROC curve analysis evaluated the discriminatory capacity of individual predictive factors and the combined model. Individual AUC values were: lymph node metastasis 0.708 (95% CI: 0.612-0.804), abnormal p53 expression 0.675 (95% CI: 0.572-0.778), Ki-67≥30% 0.647 (95% CI: 0.543-0.751), and LVSI positivity 0.654 (95% CI: 0.550-0.758). The integrated four-factor model demonstrated substantially enhanced discriminatory performance with AUC 0.876 (95% CI: 0.807-0.945, P<0.001), significantly exceeding individual parameter performance (all P<0.01, DeLong test) (**Table 3**; **Figure 2**). For Ki-67, ROC analysis

Table 2. Multivariate regression results

Variable	Univariate Analysis			Multivariate Analysis		
	HR (95% CI)	Test Statistic (Wald χ^2)	P	HR (95% CI)	Test Statistic (Wald χ^2)	P
Age ≥60 years	1.42 (0.68-2.97)	0.875	0.348			
BMI ≥30 kg/m^2	1.28 (0.52-3.15)	0.291	0.589			
FIGO Stage III	4.85 (2.31-10.18)	18.457	<0.001	1.89 (0.76-4.71)	1.864	0.172
Non-endometrioid carcinoma	2.67 (1.14-6.25)	5.142	0.023	1.42 (0.54-3.76)	0.504	0.478
Grade G3	5.42 (2.58-11.39)	21.368	<0.001	1.76 (0.71-4.38)	1.485	0.224
Myometrial invasion ≥50%	4.68 (2.08-10.52)	16.892	<0.001	1.58 (0.64-3.91)	0.993	0.319
LVSI positive	4.52 (2.15-9.50)	16.547	<0.001	2.18 (1.03-4.62)	4.125	0.042
Lymph node metastasis	6.85 (3.28-14.31)	28.743	<0.001	3.24 (1.42-7.38)	7.896	0.005
ER negative	2.89 (1.36-6.14)	1.374	0.254	1.62 (0.68-3.87)	1.198	0.274
PR negative	1.68 (0.81-3.48)	1.924	0.164	-	-	-
p53 abnormal	5.68 (2.67-12.08)	22.145	<0.001	2.87 (1.31-6.29)	7.021	0.008
Ki-67 ≥30%	5.24 (2.28-12.03)	18.936	<0.001	2.45 (1.14-5.27)	5.247	0.022

Note: Abbreviations: HR, hazard ratio; CI, confidence interval; LVSI, lymphovascular space invasion.

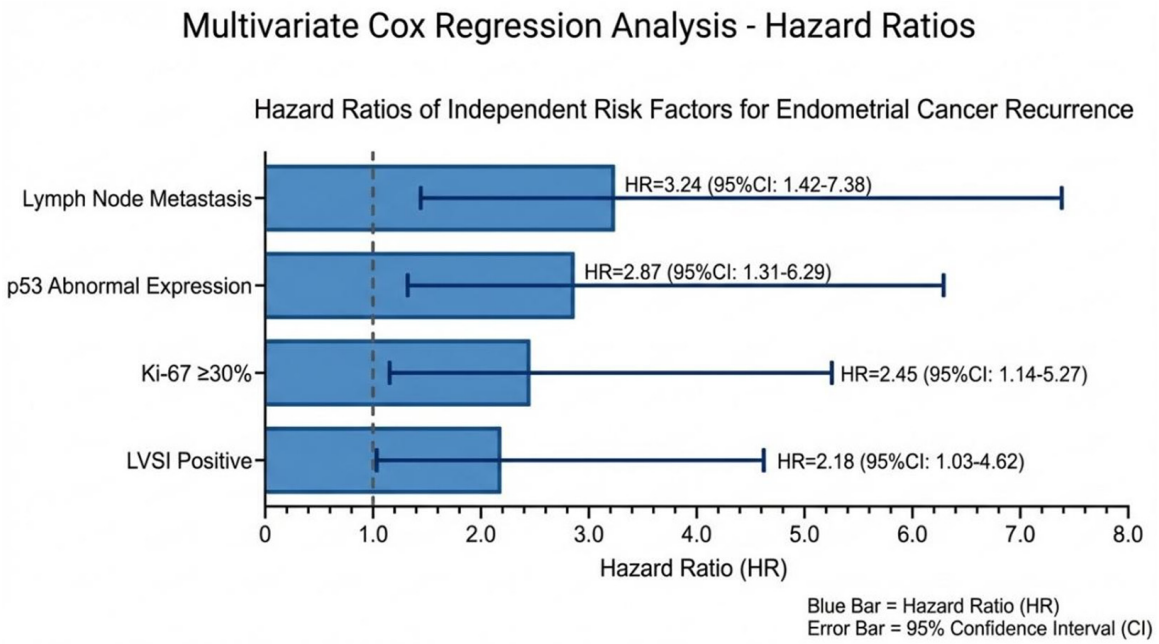

Figure 1. Forest plot of multifactor regression model. Abbreviations: HR, hazard ratio; CI, confidence interval.

identified 30% as the optimal cutoff value according to the maximum Youden index, which was therefore used for subsequent dichotomization in survival analyses.

Internal validation and calibration: Bootstrap internal validation (1000 resamplings) showed that the model had good stability, with a corrected AUC of 0.868 (95% CI: 0.795-0.941). The calibration curves show a good agreement between the predicted and actual probabilities (Hosmer-Lemeshow test, P = 0.742, **Figure 3**).

Decision curve analysis: Decision curve analysis showed that when the threshold probability ranged from 10% to 70%, the combined prediction model provided a greater net benefit than any single predictor as well as the "treat-all" and "treat-none" strategies (**Figure 4**). Clinically, this threshold range may correspond to decision-making scenarios in which physicians consider closer surveillance intensity, more frequent imaging or CA125 monitoring, or further evaluation for postoperative management in

Table 3. ROC curve analysis of predictive factors

Predictive Factor	AUC	95% CI	Optimal Cutoff	Sensitivity (%)	Specificity (%)	Youden Index
Lymph node metastasis	0.708	0.612-0.804	Positive	50.0	88.9	0.389
p53 abnormal	0.675	0.572-0.778	Abnormal	60.7	76.7	0.374
Ki-67 ≥30%	0.647	0.543-0.751	≥30%	75.0	66.7	0.417
LVSI positive	0.654	0.550-0.758	Positive	53.6	80.0	0.336
Combined model	0.876	0.807-0.945	Score ≥2	85.7	82.2	0.679

Note: Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

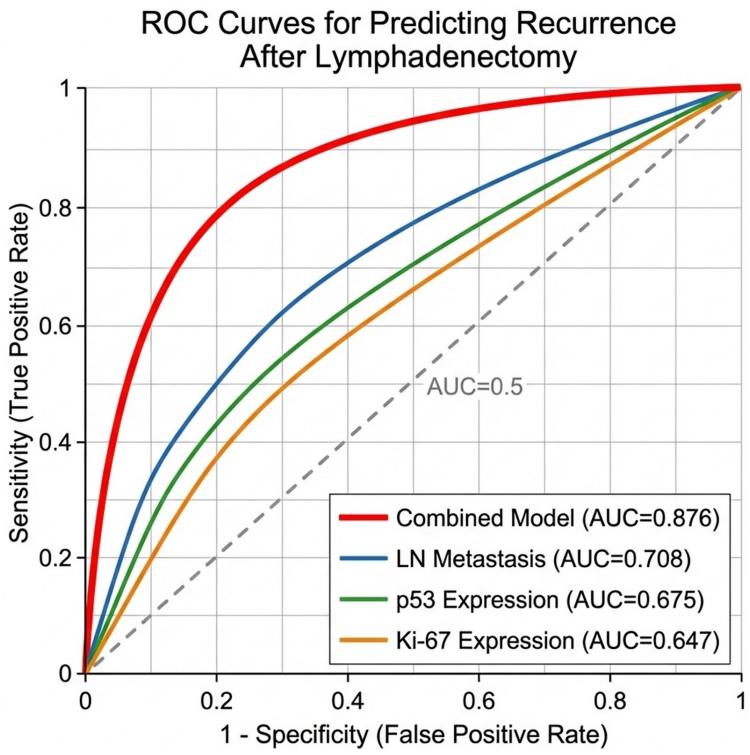

Figure 2. ROC curves comparing individual predictors and combined model. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve.

patients judged to be at elevated recurrence risk.

Risk stratification system: Based on the final multivariate Cox regression model, a simplified additive scoring system was constructed using the four independent predictors (lymph node metastasis, aberrant p53 expression, Ki-67≥30%, and LVSI positivity). Each predictor was assigned 1 point, resulting in a total score ranging from 0 to 4. According to the score distribution and recurrence risk gradient, patients were categorized into three groups: low risk (<2), intermediate risk (2-3), and high risk (≥4). As the total risk score increased, the incidence of recurrence rose markedly, whereas the 3-year recurrence-free survival rate declined substantially (**Table 4**; **Figure 5**).

Nomogram development: The constructed nomogram (**Figure 6**) can calculate the individual recurrence risk based on the scores of each predictor factor. Each predictor factor obtains a point value proportional to the Cox regression coefficient, thereby enabling the calculation of the total score corresponding to the predicted recurrence probability at 1, 2, and 3 years.

Comparative performance analysis: Comparative ROC analysis via DeLong testing confirmed the combined four-parameter model's statistically significant superiority over all individual predictors (**Table 5**). The integrated model achieved AUC 0.876, substantially exceeding single-parameter AUC values ranging 0.647-0.708 (all pairwise P<0.01).

Discussion

This study retrospectively included 118 cases of endometrial cancer that underwent lymph node dissection, and screened lymph node involvement, p53 protein abnormality, Ki-67 overexpression, and LVSI invasion as independent high-risk factors for postoperative recurrence. The risk assessment system established by integrating the above four indicators showed excellent discriminative ability (area under the curve 0.876), and supported risk stratification and follow-up management. Lymph node involvement is the strongest predictor of recurrence risk. Data showed that patients with lymph node metastasis had a recurrence prob-

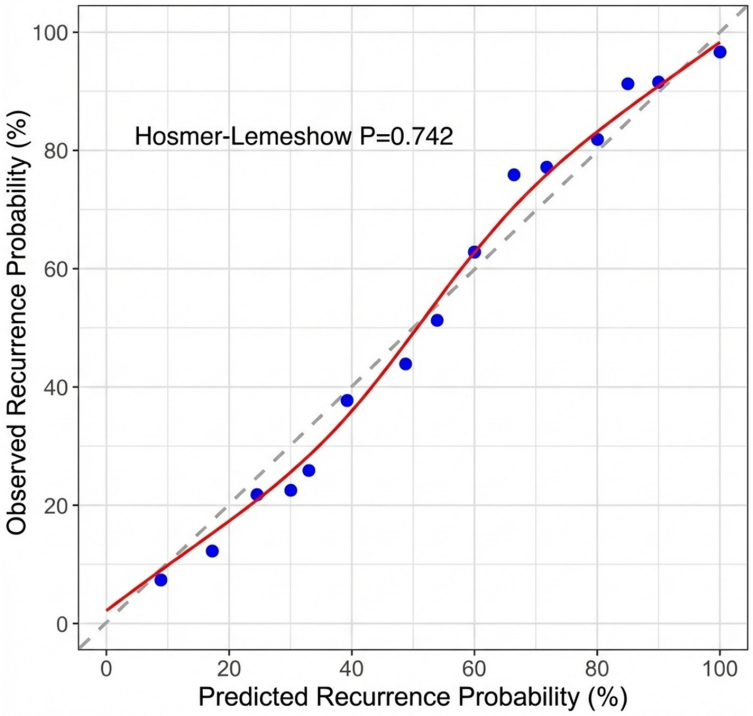

Figure 3. Calibration curve for recurrence prediction model.

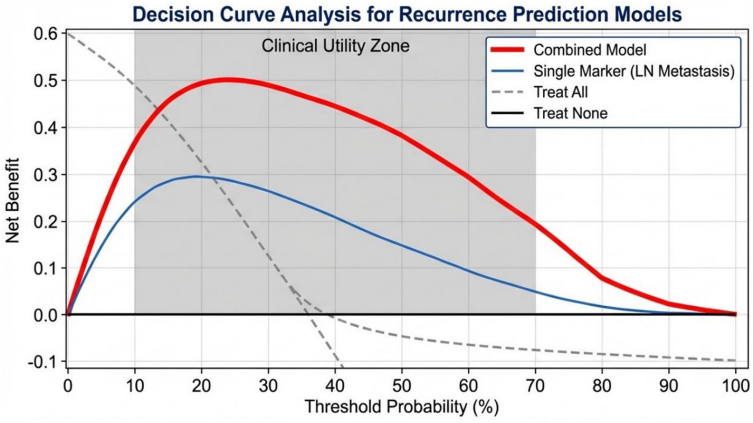

Figure 4. Decision curve analysis for recurrence prediction models.

ability 3.24 times higher than those without metastasis, which finding is consistent with the observation result of Ting's team [20]. The team's analysis of cases with clinical staging in the uterine body found that positive para-aortic lymph nodes were the only significant predictor of recurrence (hazard ratio 7.60). Leon-Castillo's research group [21] also verified in cases with poor differentiation that even after lymph node dissection, the status still dominated the prognosis. However, the risk ratio of lymph node metastasis in this group (3.24) was significantly lower than that reported by Ting et al., which may be attributed to differences in the composition of the enrolled population, the different distribution of disease stages, and changes in adjuvant therapy strategies. This study included more cases that received postoperative systemic treatment, which may have improved the outcome of the lymph node-positive population to some extent. Abnormal p53 protein expression is closely associated with poor prognosis. In this study, p53 abnormal expression increased the risk of recurrence by 2.87 times, which is highly consistent with the current consensus of molecular subtyping research. Mechanistically, p53 stability and function are tightly regulated by post-translational modifications, particularly ubiquitination. The E3 ubiquitin ligase MDM2 promotes p53 ubiquitination and proteasomal degradation, thereby reducing its tumor-suppressive functions and potentially contributing to recurrence risk [22]. The Uijterwaal research group [23] found that the p53 abnormal subtype accounted for 61.6% of the patients in stage IV. Although the prognostic differentiation ability of molecular subtyping in the late stage population is limited, p53abn is still a key adverse marker. The FIGO staging system revised in 2023 listed p53abn as a basis for upgrading [5], highlighting its judgment value. Data from Yamazaki's team [24] showed that even in early (stage I-II) cases, the 5-year recurrence rate of p53abn patients was 36.7%, far exceeding that of other molecular types. This study further confirmed that p53 abnormality is still an independent recurrence risk signal in people who have completed lymph node dissection, suggesting that such patients should receive more aggressive

Table 4. Risk stratification system and corresponding recurrence rates

Risk Category	Score Range	Patient Count	Recurrence Events (%)	3-Year RFS (%)	95% CI
Low risk	<2	58	3 (5.2%)	91.4	82.7-100
Intermediate risk	2-3	42	11 (26.2%)	73.8	60.5-87.1
High risk	≥4	18	14 (77.8%)	33.3	14.6-52.0

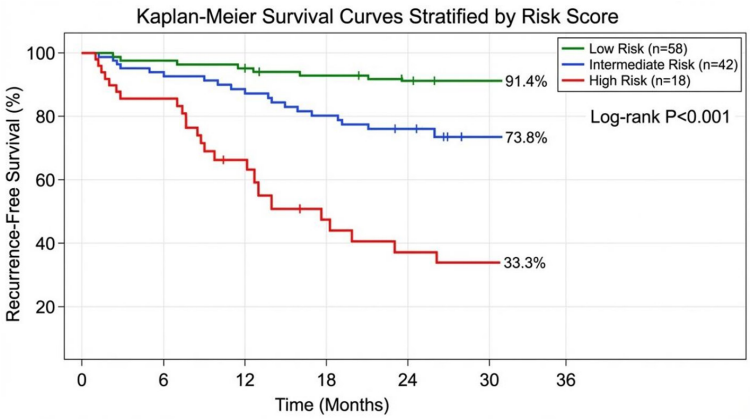

Figure 5. Kaplan-Meier recurrence-free survival curves by risk category.

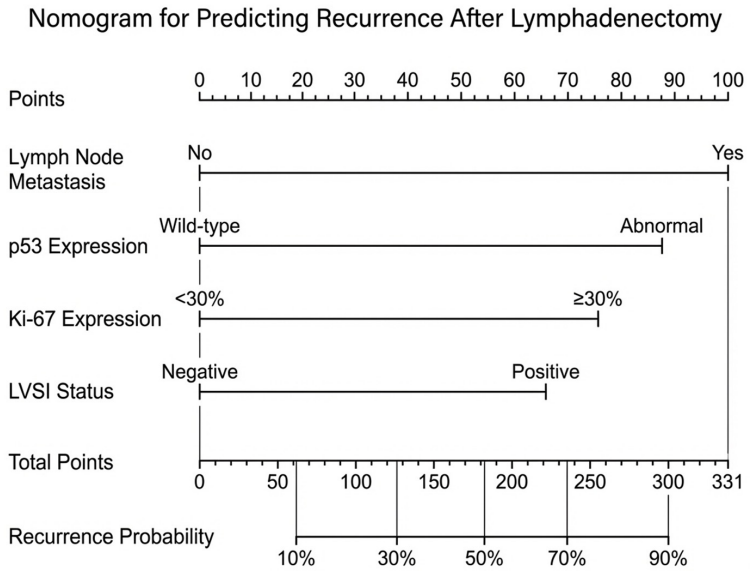

Figure 6. Prognostic nomogram for recurrence risk prediction.

adjuvant intervention and intensive monitoring. High Ki-67 expression reflects vigorous tumor cell proliferation. The study set 30% as the cutoff point, and the results showed that Ki-67≥30% increased the risk of recurrence by 2.45 times. The risk model developed by Song et al. [14] also integrated the Ki-67 parameter and showed excellent predictive performance in early cases (C-index 0.85). The debate about the ideal cutoff value of Ki-67 continues, with the range reported in the literature ranging from 15% to 30% [25]. This study locked 30% as the best cutoff value through ROC curve analysis, achieving the best balance between sensitivity and specificity. The Liu team [26] also used Ki-67≥30% as a high-risk threshold in the machine learning framework, proving that its combined application can enhance the accuracy of prediction. It is worth emphasizing that Ki-67 detection results are easily affected by experimental methods, and establishing standardized operating procedures is a prerequisite for ensuring clinical application. LVSI status is the core indicator for predicting metastasis and recurrence. Data from this study showed that LVSI positivity increases the risk of recurrence by 2.18 times. The Buechi research group [27] verified in a real-world cohort that LVSI is an independent warning signal of recurrence in lymph node-negative patients. The FIGO staging update in 2023 has set LVSI positivity as a condition for stage II advancement [5], and the RAINBO clinical trial project [28] also uses it as a key stratification standard for molecular subtyping-driven treatment. However, the interpretation and grading of LVSI (focal vs. substantial) depends on subjective assessment, and the consistency of judgment among observers needs to be improved. This study did not subdivide the degree of LVSI, which may limit its predictive power. Future work should adopt a more standardized LVSI evaluation system, such as using immunohisto-

Table 5. Pairwise AUC comparison: combined model versus individual parameters

Comparison	AUC Difference	95% CI	DeLong Z	*P*-value
Combined vs. LN metastasis	0.168	0.089-0.247	4.23	<0.001
Combined vs. p53 abnormal	0.201	0.118-0.284	4.76	<0.001
Combined vs. Ki-67 ≥30%	0.229	0.145-0.313	5.28	<0.001
Combined vs. LVSI positive	0.222	0.139-0.305	5.14	<0.001

Note: Abbreviations: AUC, area under the curve; CI, confidence interval.

chemical staining to assist in identification, in order to improve the accuracy and repeatability of interpretation.

The conclusions of this study partially overlap with the findings of the Dinoi team [29], but there are some differences. Dinoi et al. confirmed in a lymph node-negative stage I endometrioid adenocarcinoma population that the degree of myometrial invasion (≥71% of the outer 1/3 layer) and tumor grade are independent predictive factors for distant metastasis, while in the multivariate model of this group of data, these two factors did not reach statistical significance. Possible reasons for the differences include: first, this study covers different clinical stages (stages I-III) and histological subtypes, and the population composition is more diverse; second, 45% of the cases in this group received postoperative systemic treatment, which may have changed the prognostic weight of traditional risk factors; third, the difference in sample size (118 cases in this study compared to 386 cases in the Dinoi study) may affect the power of the test. Notably, this study introduced immunohistochemical markers (p53, Ki-67) to overcome the limitations of relying solely on clinicopathological features, providing a more comprehensive prognostic framework. It is noteworthy that several variables significant in univariate analysis, such as FIGO stage, tumor grade, histological type, and myometrial invasion depth, did not remain significant in the multivariate model. This finding suggests that part of their prognostic effect may be captured by more proximal or biologically dominant predictors, particularly lymph node status, LVSI, and immunohistochemical markers.

This study has several limitations. First, the relatively small sample size and limited number of recurrence events may increase the risk of model overfitting, despite the use of bootstrap internal validation. Second, this was a single-center retrospective study, which may introduce selection bias and limit generalizability. Third, external validation was not performed. Therefore, the predictive performance of the model requires further validation in larger, multicenter cohorts. The comprehensive prediction system developed in this study achieved an area under the curve (AUC) of 0.876, significantly outperforming the discriminative power of single indicators and consistent with multiple literature reports [30, 31]. The four elements included in the model (lymph node status, p53, Ki-67, and LVSI) are all routine clinical tests, making data acquisition convenient and cost-effective, and possessing good practical operability. Using nomograms, clinicians can intuitively quantify the recurrence probability of individual patients, providing an objective basis for treatment selection. For example, the 3-year recurrence-free survival rate for high-risk groups (score ≥4) is only 33.3%, and intensive adjuvant interventions such as combined radiotherapy and chemotherapy or molecular targeted therapy should be considered; while the 3-year recurrence-free survival rate for low-risk patients (score <2) is as high as 91.4%, allowing for appropriate reduction in treatment intensity and avoiding overtreatment. Compared with the nomogram, the simplified point-based scoring system may be more convenient for bedside risk stratification and routine postoperative follow-up planning. The decision curve analysis also confirmed the model's clinical net benefit, particularly within the threshold probability range of 10%-70%. In practical terms, this range may reflect scenarios in which clinicians would consider intensifying follow-up schedules, increasing surveillance frequency, or performing additional postoperative risk evaluation for patients estimated to have a higher recurrence probability. Therefore, the DCA findings support the model's utility in recurrence risk management rather than direct treatment assignment. The relatively low EPV in this study may affect model stability; however, similar exploratory models with limited sample sizes have been reported in previous oncological prognostic studies.

In summary, recurrence after lymph node dissection in endometrial cancer patients is influenced by key factors such as lymph node metastasis, abnormal p53 expression, high Ki-67 expression, and LVSI positivity. The combined predictive model has good predictive value and provides new insights for screening and preventing recurrence rates in these patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Daying Mou, Department of Obstetrics and Gynecology, The First People's Hospital of Zunyi, No. 98 Fenghuang North Road, Huichuan District, Zunyi 563000, Guizhou, China. Tel: +86-0851-23238722; E-mail: mudaying1976@163.com

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