A nomogram based on immunohistochemistry and lymphocyte-to-monocyte ratio for predicting risk stratification in endometrial carcinoma

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Abstract. Currently, the determination of the risk level for endometrial cancer (EC) needs to be made after radical surgery, based on factors such as tumour type and differentiation, extent of invasion and clinical stage. If the early diagnosis of high-risk EC can be improved, it will greatly contribute to enhancing patient survival rates. The present study aimed to construct a nomogram to predict high-risk EC by combining immunohistochemical (IHC) and serological indicators, and then evaluating and verifying the value of it. A total of 130 patients with EC admitted to Lianyungang Maternal and Child Health Hospital from December 2018 to May 2026 were included. The training set consisted of 107 cases, while the validation set contained 23 cases. All cases were divided into a high-risk group and a low-risk group on the basis of the postoperative pathological results. The clinical data, IHC staining results and preoperative serological indicators of the two groups were compared. Logistic regression analysis was used to screen the risk factors for high-risk EC. A nomogram model was created using R software and then evaluated through receiver operating characteristic (ROC) curves, calibration curves and external validation. In the training set, univariate analysis revealed that the indicators with statistically significant differences between the two groups were age, nuclear-associated antigen (Ki-67) expression, oestrogen receptor (ER) expression and the lymphocyte-to-monocyte ratio (LMR). Multivariate regression analysis revealed that age, the Ki-67 index and the LMR were independent risk factors for high-risk EC (all $P<0.05$). The results of the nomogram model and ROC curve analysis indicated that, compared with age, the Ki-67 index and the LMR individually, the combined prediction model constructed from these three factors demonstrated greater diagnostic performance [area under the curve (AUC)=0.904; 95% CI=0.840-0.968; sensitivity: 75.6%; specificity: 93.9%; $P<0.05$]. The goodness-of-fit test results suggested that the predictive model had a good fit ($X^2=9.185$; $P>0.05$). Finally, external validation was performed using the validation set, and the results revealed that the model had good predictive performance (AUC=0.846), with a prediction accuracy of 73.9%. Therefore, this study designed and validated a nomogram based on age, Ki-67 index and LMR, which has good diagnostic value for screening high-risk patients with EC.

Introduction

Endometrial cancer (EC) is a common malignant tumour of the female reproductive system, with 417,000 new cases and 97,000 associated deaths worldwide in 2020. The incidence and prevalence rank sixth among types of cancer in women (1). In 2022, a total of 423,680 cases and 97,723 deaths were reported globally (2), and there were 77,700 new cases and 13,500 deaths in China in 2022 (3). In some developed cities in China, its incidence has become the highest among malignant gynaecological tumours (4). The prognosis of early stage EC is generally favourable after surgical treatment, but patients with high-risk factors still have a risk of distant recurrence and metastasis after surgery (5). In the 2016 European Society for Medical Oncology (ESMO), European Society of Gynaecological Oncology (ESGO) and European Society for Radiotherapy and Oncology (ESTRO) guidelines, high-risk EC was defined as stage I and grade 3 endometrioid endometrial carcinoma (EEC) with deep invasion, stage II or III EEC or non-endometrioid EC, including serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, carcinosarcoma, mucinous adenocarcinoma and mixed-type carcinoma (6). Owing to its long latency period and inconspicuous early symptoms (7), early diagnosis and treatment of

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Abbreviations: EC, endometrial cancer; ROC, receiver operating characteristic; LMR, lymphocyte-to-monocyte ratio; BMI, body mass index; ER, oestrogen receptor; PR, progesterone receptor

Key words: high-risk EC, age, Ki-67, LMR, prediction model, risk stratification

EC, especially high-risk EC, remain a key factor for improving patient survival rates. Therefore, finding more convenient and effective predictive indicators is highly important. Ki-67 is a widely used clinical marker of tumour cell proliferation and is closely associated with the differentiation, invasion, metastasis and prognosis of many tumours. In EC, Ki-67 can serve as an effective predictor of deep myometrial invasion and lymph node metastasis (8,9). Previous research indicates that pre-treatment inflammatory status has a positive predictive value for high-risk EC. The lymphocyte-to-monocyte ratio (LMR), as a key marker of the inflammatory response (10), also serves as a valuable haematological biomarker for diagnosing EC (11). However, studies on the predictive value of the LMR for high-risk EC remain limited.

Therefore, in the present study, a retrospective analysis of clinically accessible data, including clinicopathological characteristics and immunohistochemical (IHC) markers of EC combined with serological test results of the LMR, was conducted to develop a preoperative risk prediction model that can inform preoperative evaluation and clinical triage for high-risk patients with EC.

Materials and methods

General information. A retrospective analysis of the clinical data of patients with EC who were treated at the Lianyungang Maternal and Child Health Hospital (Lianyungang, China) from December 2018 to May 2026 was conducted. Patients were divided into a training set and a validation set according to the duration of surgical treatment at the Lianyungang Maternal and Child Health Hospital. The data collection and analysis for the training set (from December 2018 to July 2025) was completed in December 2025, while the data collection and analysis for the validation set (from August 2025 to May 2026) was completed in May 2026. The data included age, body mass index (BMI), preoperative serological tests for lymphocytes and monocytes, postoperative International Federation of Gynaecology and Obstetrics (FIGO) stage, pathological type, histological grade, lymph node metastasis and depth of myometrial invasion. The number of pregnancies reflected the number of births plus the number of abortions. According to the exclusion criteria of the present study, cases with missing/incomplete data were excluded.

A total of 130 patients were included in the training set (107 cases) and validation set (23 cases). In the training set, the patients were aged 37-73 years, with a mean age of 53.17±7.66 years. There were 96 cases of endometrioid carcinoma, 2 cases of serous carcinoma, 2 cases of clear cell carcinoma, 1 case of mucinous adenocarcinoma, 3 cases of undifferentiated carcinoma and 3 cases of carcinosarcoma. The histological differentiation grades were as follows: 26 cases were well differentiated (G1), 36 cases were moderately differentiated (G2), and 45 cases were poorly differentiated (G3); deep myometrial invasion (>1/2) was observed in 33 cases. The FIGO stage distribution was as follows: 78 patients were in stage I, 16 patients were in stage II, 12 patients were in stage III and 1 patient was in stage IV. In the validation set, the patients were aged 45-74 years, with a mean age of 57.78±6.78 years. There were 21 cases of endometrioid carcinoma and 2 cases of undifferentiated carcinoma. The histological differentiation grades were as follows: 5 cases were well differentiated (G1), 11 cases were moderately differentiated (G2) and 7 cases were poorly differentiated (G3); deep myometrial invasion (>1/2) was observed in 8 cases. The FIGO stage distribution was as follows: 13 patients were in stage I, 7 patients were in stage II and 3 patients were in stage III. The study protocol was reviewed and approved by the Ethical Review Committee of the Lianyungang Maternal and Child Health Hospital (approval no. XM2023027) prior to implementation.

High-risk EC grouping. Patients were categorized according to the 2016 ESMO-ESGO-ESTRO consensus guidelines (6). Among the 107 patients with EC, 41 were classified as having low-risk EC, and 66 were classified as having high-risk EC. High-risk EC was defined as follows: Stage I and grade 3 EEC with deep invasion; stage II or III EEC; or non-endometrioid endometrial carcinoma (including serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, carcinosarcoma, mucinous adenocarcinoma and mixed-type carcinoma). The inclusion criteria included the following: i) A pathological diagnosis of primary EC with complete postoperative pathological results, including tumour histological type and grade, FIGO stage, depth of myometrial invasion, lymph node metastasis status and other relevant parameters; ii) the surgical scope included extra fascial hysterectomy, bilateral salpingo-oophorectomy and pelvic and para-aortic lymphadenectomy; and iii) patients with complete medical records, including age, BMI and details of any comorbidities (such as hypertension or diabetes). The exclusion criteria were as following: i) The patient did not undergo standard surgical treatment; ii) the patient had other concurrent malignant tumours; iii) patients who had received radiotherapy, chemotherapy or endocrine therapy prior to surgery; iv) patients with missing clinical data or undefined pathological type/staging; and v) patients with severe hepatic or renal dysfunction or those with autoimmune or haematological diseases.

Histopathological and IHC inspection. First, diagnostic curettage was performed on all patients. The obtained endometrial curettage specimens were routinely fixed in formalin solution and then subjected to histopathological examination. After being diagnosed with EC, all the patients underwent IHC examination and radical surgical treatment. On the basis of parameters such as histological type and grade, FIGO stage and lymph node metastasis, these patients were subsequently classified into different risk levels. All endometrial curettage specimens were subjected to IHC using the same standardized criteria, and all pathological slides were independently reviewed by two histopathologists to reach a final diagnostic consensus. IHC detection was performed using the VENTANA method with DAB chromogenic staining on a fully automated immunostainer (Roche BenchMark GX; Roche Diagnostics GmbH), and the final staining results would be observed under a light microscope. This staining system had widespread clinical applicability, and the test results were highly consistent with those of Dako/Agilent (12). The following rabbit monoclonal antibodies were used: CONFIRM anti-oestrogen receptor (ER) (clone, SP1; cat. no. 05278392001; Roche Diagnostics); CONFIRM anti-Progesterone Receptor (PR) (clone,1E2; cat. no. 05278414001; Roche Diagnostics); and

Table I. Univariate analysis of high-risk endometrial cancer in training set data.

Characteristic	β	SE	Wals	P-value	Exp(B)	95% CI
Age, years	0.141	0.037	14.507	<0.05	1.152	1.071-1.239
BMI, kg/m^2	0.028	0.049	0.314	0.575	1.028	0.934-1.132
No. of pregnancies	0.229	0.189	1.469	0.226	1.257	0.868-1.821
No. of abortions	0.366	0.229	2.555	0.110	1.442	0.921-2.259
No. of births	0.955	0.446	2.157	0.142	1.926	0.803-4.618
Menopause, yes vs. no	0.301	0.154	3.832	0.050	1.351	1.000-1.825
Hypertension, yes vs. no	-0.005	0.085	0.004	0.950	0.995	0.842-1.175
Blood glucose, mmol/	0.429	0.407	1.107	0.293	1.535	0.691-3.411
ER labeling index, %	-0.676	0.247	7.478	0.006	0.509	0.314-0.826
PR labeling index, %	-0.254	0.177	2.070	0.150	0.775	0.548-1.096
Ki-67 labeling index, %	0.686	0.137	25.284	<0.05	1.987	1.520-2.596
LMR	0.600	0.143	17.715	<0.05	1.822	1.378-2.409

LMR, lymphocyte-to-monocyte ratio; ER, oestrogen receptor; PR, progesterone receptor; BMI, body mass index; CI, confidence interval.

Table II. Multivariate analysis of high-risk endometrial cancer in training set data.

Characteristics	β	SE	Wals	P-value	Exp(B)	95% CI
Age, years	0.146	0.051	8.156	0.004	1.157	1.047-1.279
ER labeling index, %	-0.437	0.333	1.723	0.189	0.646	0.337-1.240
Ki-67 labeling index, %	0.588	0.165	12.731	<0.05	1.800	1.303-2.487
LMR	0.435	0.164	7.069	0.008	1.545	1.121-2.129

LMR, lymphocyte-to-monocyte ratio; ER, oestrogen receptor; CI, confidence interval.

CONFIRM™ anti-Ki-67 (clone: 30-9; cat. no. 05278384001; Roche Diagnostics). The results of the IHC parameters (ER, PR and Ki-67) were recorded as continuous variables, with the proportion of positive cells expressed as a percentage (0-100%), for example, 70% ER (+), 60% PR (+) and 80% Ki-67 (+).

Laboratory tests. Following hospital admission, fasting peripheral venous blood samples were collected from all patients. The monocyte and lymphocyte counts were measured using an automated haematology analyser (BC7500CRP; Shenzhen Mindray Bio-Medical Electronics Co., Ltd.). The LMR was subsequently calculated.

Statistical analysis. Statistical analysis was performed using SPSS 25.0 (IBM Corp.). Categorical data are expressed as percentages. Normally distributed continuous data (such as age and BMI) are presented as the mean ± SD ($\bar{x} \pm s$), whereas non-normally distributed continuous data (such as Ki-67, ER and PR expression) are expressed as the median (interquartile range) [M(P25, P75)]. Univariate and multivariate logistic regression analyses were employed to identify risk factors for high-risk EC. A nomogram prediction model was constructed using R software (Posit Software, PBC) with the 'rms' package. The accuracy of the model was evaluated through ROC curve analysis and external validation. The optimal cut-off value was determined by calculating the Youden's J index. The formula was: J=Sensitivity + Specificity - 1. The optimal cut-off value was the value of the independent variable when the Youden's J index reached its maximum. The Hosmer-Lemeshow test was used to verify the consistency between the predicted probabilities and the actual observed results. When P>0.05, it indicates that the model fit well. The Harman single-factor method was used to test whether there was any severe common method bias in the data. The collinearity of the independent variables in the data was verified through the variance inflation factor (VIF). P<0.05 was considered to indicate a statistically significant difference.

Results

Univariate and multivariate analyses of the training set data. When the risk category of EC was used as the dependent variable (high risk=1, low risk=0), univariate logistic regression analysis revealed that high-risk EC was significantly associated with patient age, ER expression, Ki-67 index and the serum LMR (P<0.05), but not with BMI, menopausal status or the number of pregnancies, abortions or births, hypertension and blood glucose (P>0.05) (Table I). Variables identified in the univariate analysis were included as independent variables in the multivariate logistic regression. The results demonstrated that age, the Ki-67 index and the LMR were independent risk factors for high-risk EC (P<0.05; Table II).

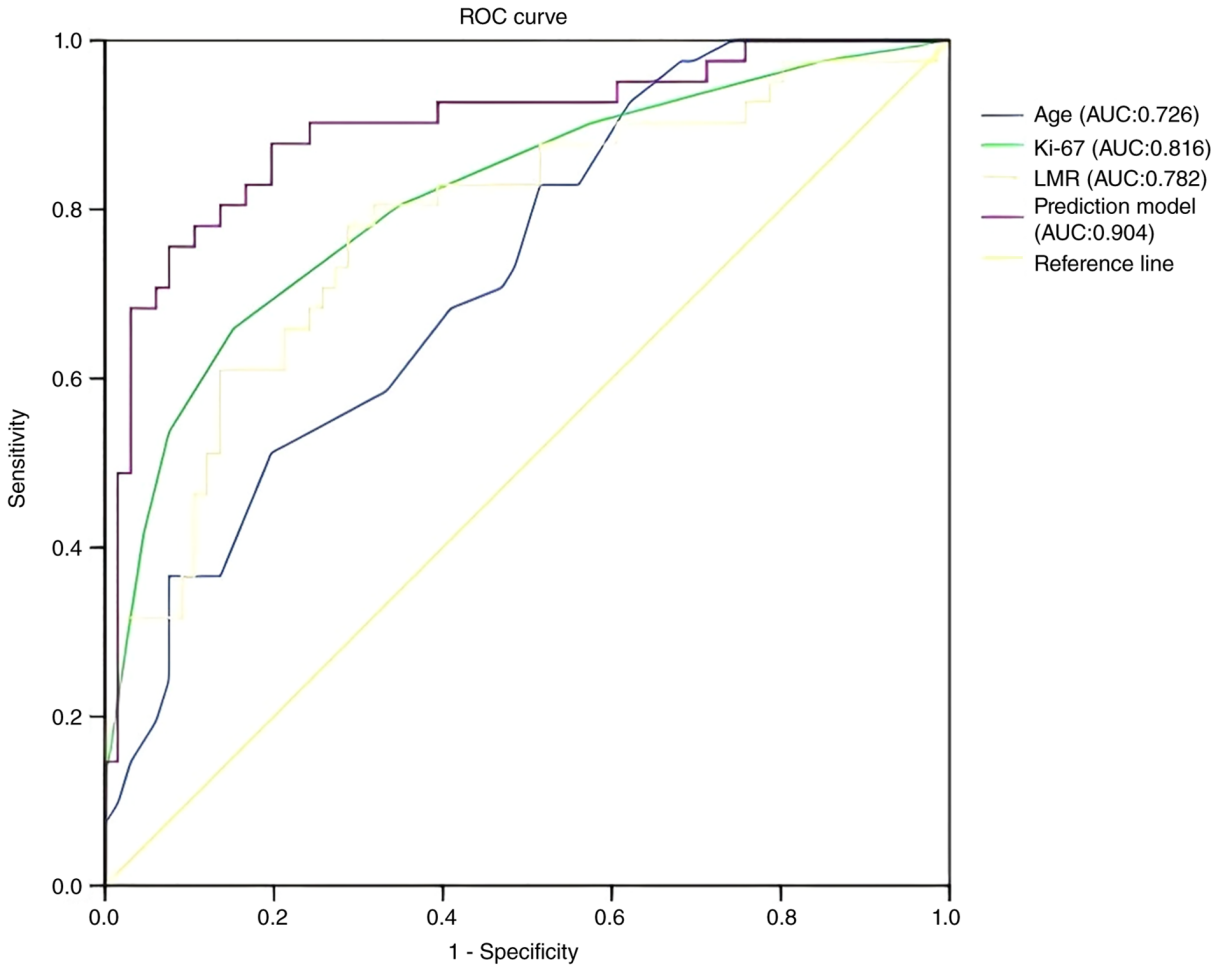

Figure 1. Receiver operating characteristic curve of Age, Ki-67, LMR and the prediction model for high-risk EC from the training set.

Internal and external validation of the predictive model for high-risk EC. Construction and internal validation of the prediction model was performed. In the training set, the ROC curve demonstrated that age [area under the curve (AUC)=0.726; 95% CI, 0.631-0.821], the Ki-67 index (AUC=0.816; 95% CI, 0.730-0.902) and the LMR (AUC=0.782; 95% CI, 0.690-0.875) each demonstrated moderate performance in individually predicting high-risk EC (Fig. 1). The combined prediction model (based on age, the Ki-67 index and the LMR) had excellent predictive value (AUC=0.904; 95% CI, 0.840-0.968; Fig. 1). The Youden's J index of the model was 0.695, with a sensitivity of 75.6%, a specificity of 93.9% and an optimal cut-off value of 0.45. The Hosmer-Lemeshow test indicated an adequate goodness-of-fit for the combined prediction model (X^2=9.185; P=0.327). As shown in Fig. 2, the calibration curve of the model primarily lies along the 45-degree line, indicating that the predicted probability is close to the actual probability and that the model is well calibrated.

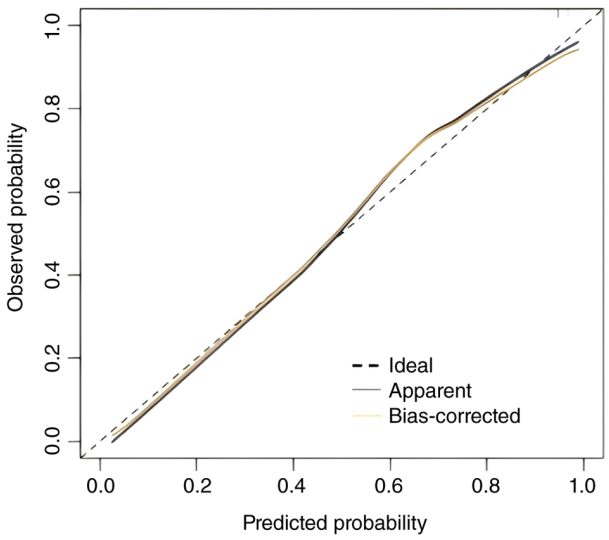

Figure 2. Calibration curve of the nomogram prediction model for high-risk EC.

External validation. The predictive model was used to evaluate the patients in the validation set. The ROC curve revealed that the model had good predictive performance (AUC=0.846; 95% CI, 0.688-1.000; P<0.05; Fig. 3). On the basis of the optimal cut-off value, patients were divided into predicted highrisk and predicted lowrisk groups, and the results were compared with the actual conditions. The results revealed that among the 8 patients predicted to be highrisk, 6 were actually high risk; among the 15 patients predicted to be lowrisk, 11 were actually lowrisk. The calculated prediction accuracy was (11+6)/23 x100%=73.9%.

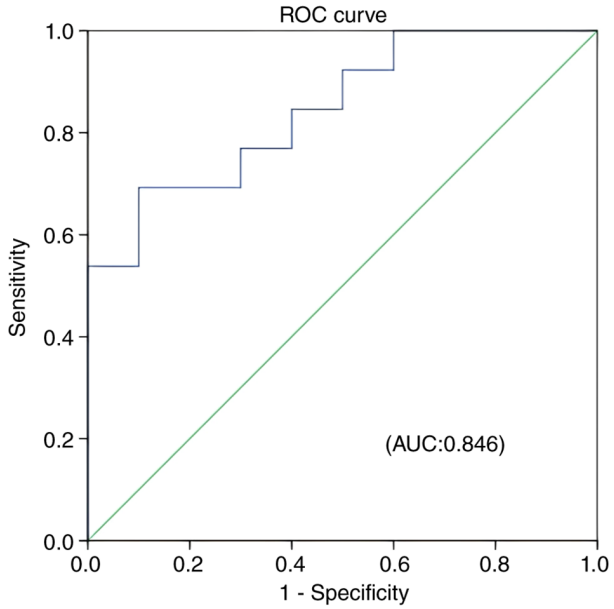

Figure 3. Receiver operating characteristic curve of the prediction model for high-risk EC from validation set (area under the curve=0.846 and P<0.05).

Development of a nomogram prediction model. Firstly, the Harman single-factor method was used to test the data bias correction, and the first common factor accounted for only 39.04% of the total variance explained, which was <40% of the evaluation criterion. Therefore, it could be considered that there was no serious bias. Secondly, the VIF was used to assess the multicollinearity of the data. The results showed that the VIF values for age, Ki-67 and LMR were 1.009, 1.073 and 1.068, respectively, all of which were <5, indicating that there was no strong collinearity among them. Then, a nomogram prediction model was developed using R software (Fig. 4), and a higher total score in the nomogram indicated a greater probability of developing high-risk EC. As shown in Fig. 4, the patient's age score was 100 points, the Ki-67 expression score was 87.5 points and the LMR score was 83.75 points.

Discussion

EC is the most common gynaecological malignancy in postmenopausal women (13). The incidence of EC is steadily increasing (14), and it ranks as the 14th leading cause of cancer-related mortality among women worldwide (15). EC treatment is primarily surgical, with radiotherapy and chemotherapy being common adjuvant treatment modalities. Generally, for patients with suspected EC or endometrial lesions, a hysteroscopic endometrial biopsy is first performed. The obtained endometrial specimen is examined pathologically to determine the pathological type and differentiation grade of the tumour. Subsequently, radical surgical treatment is carried out. The basic surgical procedures include total hysterectomy plus bilateral salpingo-oophorectomy, with or without pelvic and para-aortic lymphadenectomy. Intraoperative peritoneal washing fluid is collected for cytological examination. Sentinel lymph node biopsy combined with pathological ultra staging may be chosen as an alternative to systematic lymphadenectomy. For patients whose diagnostic curettage pathological examination reveals endometrial serous carcinoma, carcinosarcoma or undifferentiated carcinoma, omentectomy or omental biopsy is also needed (16,17). Although the majority of patients can be cured with surgery, 10-20% of patients experience distant recurrence (18). Patients with high-risk EC are more prone to lymphatic metastasis and distant invasion, which complicates treatment and leads to a worse prognosis (19). Owing to the lack of effective early screening markers and diagnostic indicators (20), early prevention and management of these high-risk patients remain major challenges and priorities in clinical practice (21).

Some researchers have classified patients with FIGO stage I-II EC into a younger group (<70 years) and an older group (≥70 years) and reported that patients (≥70 years) belong to a higher-risk group (22). Additionally, a previous study (23) revealed that patients >50 years tended to have worse 5-year overall survival and disease-free survival rates, with a greater proportion of high-risk patients in the older age group. Additional studies have indicated that the incidence of metabolic diseases increases progressively with age, thereby increasing the risk of EC development and progression (24,25). In addition, oestrogen is commonly used to treat menopausal syndrome in elderly women to reduce the incidence of osteoporosis and postmenopausal cardio-cerebrovascular events. However, this hormone therapy can increase the risk of developing EC (26). In the present study, logistic multivariate regression and ROC curve analyses revealed that patient age was an independent influencing factor for high-risk EC. The age of patients in the high-risk group was significantly greater than that in the low-risk group, which is consistent with the findings of the aforementioned studies. Moreover, age demonstrated diagnostic value in predicting high-risk EC (AUC=0.726; 95% CI, 0.631-0.821).

Previous studies have suggested that pregnancy, miscarriage and childbirth might influence the occurrence and development of EC. Husby *et al* (27) reported that both childbirth and miscarriage could affect the risk of EC to a certain extent, and this effect was influenced by factors such as age, socioeconomic status and pregnancy duration; in addition, there was a marginally smaller risk reduction of EC in women who gave birth compared with women who induced abortions, perhaps because the pregnancy duration of the former was longer than that of the latter. Jordan *et al* (28) reported that the risk of EC decreases with increasing age during pregnancy. However, owing to the lack of other pregnancy-related data in the present study, a comprehensive understanding of the relationship between pregnancy and EC risk remains limited.

However, relying solely on traditional clinical parameters has limited effectiveness in predicting high-risk EC. These findings suggest that new predictive markers should be explored to improve prognostic accuracy. Numerous studies have shown that IHC markers play a notable role in the diagnosis and treatment of various tumours. The ER can activate tumour cell proliferation in multiple types of cancer and is closely associated with the recurrence and metastasis of EC (29,30). In the present study, although both the positive expression rate and the intensity of ER expression were greater in high-risk patients than in low-risk patients, logistic multivariate analysis revealed no correlation between ER expression and EC risk stratification. This lack

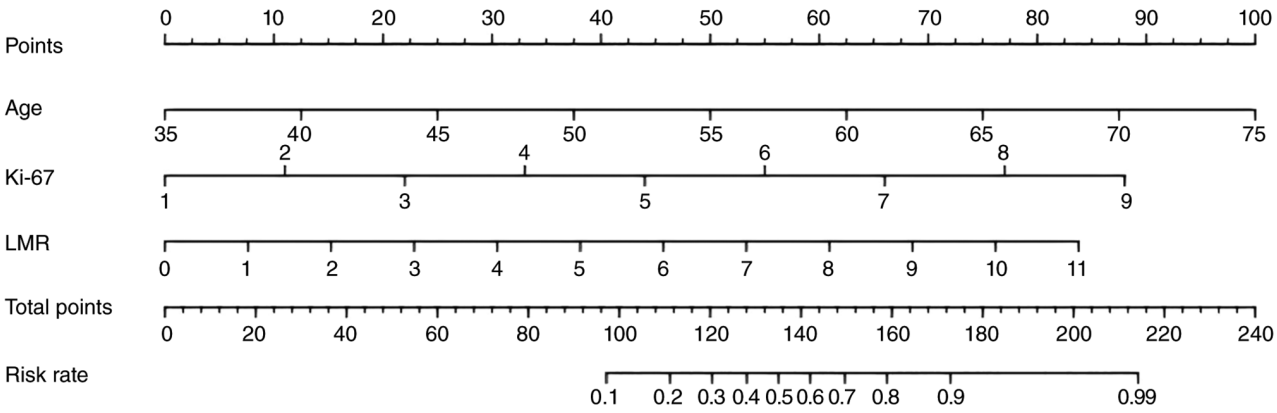

Figure 4. Nomogram prediction model for high-risk EC.

of association may be attributed to the greater proportion of non-endometrioid carcinomas in the high-risk group (11/66). Clarke *et al* (31) suggested that non-endometrioid tumours are oestrogen independent and exhibit a weaker association with ER expression, which is consistent with the findings of the present study. Ki-67, a nuclear antigen associated with proliferating cells, is currently the most widely used and highly sensitive marker of cell proliferation and plays a notable role in the development and progression of various malignant tumours (21,32). Wei *et al* (30) demonstrated that Ki-67 is closely associated with distant metastasis and clinical staging of malignant tumours, suggesting its potential as a reliable molecular marker for assessing disease stage and prognosis. Furthermore, high expression of the Ki-67 protein promotes rapid tumour cell proliferation, metastasis and deep myometrial invasion in EC (33). In the present study, high expression of Ki-67 was identified as an independent influencing factor for high-risk EC, which is consistent with the aforementioned findings mentioned. ROC curve analysis demonstrated that Ki-67 expression is valuable for predicting high-risk EC (AUC=0.816; 95% CI: 0.730-0.902). These results suggest that Ki-67 could serve as a valuable biomarker for predicting high-risk EC.

As a biomarker, serum LMR has many advantages such as simple calculation, low cost and easy availability, and can be used for high-risk stratification assessment and prognosis prediction of various tumors. Researchers have found that the LMR values for low-, intermediate- and high-risk patients with thyroid cancer were 4.7 (range, 1-10), 5 (range, 2.3-15) and 3.7 (range, 1.6-7.7), respectively, indicating that LMR is associated with tumour risk stratification (34). In a retrospective analysis of EC, the LMR was found to be associated with worse prognosis in patients (35), and markedly elevated LMR levels were observed in patients with advanced EC (36). The present study revealed that compared with low-risk patients, those in the high-risk group had markedly higher LMRs. The LMR was identified as an independent risk factor for high-risk EC and demonstrated a certain predictive value (AUC=0.782; 95% CI, 0.690-0.875), which aligns with the findings mentioned above. Inflammatory cells in peripheral blood and related haematological indicators reflect the level of systemic immune and inflammatory responses and can promote tumour cell proliferation, invasion and migration (37). Lymphocytes play a key role in chronic inflammatory responses (38), and changes in lymphocyte status may directly affect tumour progression (39). Qiu *et al* (40) reported that individuals in the high lymphocyte count group had a notably increased risk of thyroid cancer, suggesting that the lymphocyte count may be closely associated with the occurrence of thyroid malignancy. Monocytes can exert their immune evasion effects by limiting the biological function of $CD8^+$ T cells in lymphocytes (41). In the present study, the high LMR in patients with high-risk EC indicated an immune status characterized by increased lymphocytes and decreased monocytes, reflecting an association among the inflammatory status, immune level and disease progression in these patients with tumours.

Serum tumour marker testing offers advantages such as simple operation, minimal invasiveness and high reproducibility (42), whereas IHC staining is characterized by high sensitivity, rapid processing and low cost. Both methodologies are widely adopted in clinical practice and demonstrate favourable cost-effectiveness. Therefore, the integration of appropriate serum tumour markers, IHC markers, and clinicopathological parameters for predicting high-risk EC has significant practical value (43). In the present study, individual analyses of patient age, the Ki-67 index and LMR each demonstrated certain predictive value for high-risk EC. However, compared with any single indicator alone, a nomogram model incorporating these three indicators showed significantly superior predictive performance, with good sensitivity, specificity and fit. The results of the external validation also demonstrated that the model has good predictive value.

In summary, the nomogram model incorporating age, Ki-67 expression and the LMR demonstrated predictive efficacy for high-risk EC, indicating that this approach can effectively enhance early diagnostic capability and holds notable value for formulating treatment strategies. However, the overall sample size of the present study was limited. Although external validation was performed using cases from another time period, this remains a singlecentre retrospective analysis, and some selection bias is inevitable. To further improve the accuracy of the present study and validate the predictive value of the model, future studies with larger sample sizes and a multicentre design are necessary.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YYC and JWL analysed the data and wrote the manuscript. LY, PLL and FFM were involved in the collection and processing of data. YJZ was involved in the present study design and participated in the evaluation of the results. All authors read and approved the final version of the manuscript. YJZ and YYC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Ethical Review Committee of the Lianyungang Maternal and Child Health Hospital (approval no. XM2023027). Informed consent was waived for the present study by the Medical Ethics Committee of Lianyungang Maternal and Child Health Hospital (approval no. XM2023027).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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