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Original Article

Analysis of risk factors for sentinel lymph node metastasis in patients with endometrial cancer

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Abstract: Objective: To investigate the risk factors of sentinel lymph node (SLN) metastasis in patients with endometrial carcinoma (EC), and to establish a risk nomogram model. Methods: In this retrospective study, the clinical data of 79 EC patients who were treated in Zhumadian Central Hospital from January 2019 to January 2021 were analyzed. The patients were divided into SLN positive group and SLN negative group according to the occurrence of SLN metastasis. Univariate and multivariate analyses were performed to explore the factors affecting the occurrence of SLN metastasis in EC patients. The nomogram model predicting the risk of SLN metastasis in EC patients was constructed. The discrimination, accuracy and clinical benefit rate of the model were evaluated. Results: Multivariate analysis showed that body mass index (BMI) ≥ 24 kg/m^2, tumor diameter ≥ 2 cm, low differentiation, and cervical stromal involvement were risk factors for SLN metastasis in EC patients ($P < 0.05$). And the risk of SLN in EC patients increased with the increase in human epididymis protein 4 (HE4) level ($P < 0.05$). The constructed nomogram model was tested, and the area under the curve (AUC) of the model was 0.934 (95% CI: 0.878-0.979), the calibration curve obtained a Brier of 0.084. Decision curve results showed that 68 out of every 100 EC patients could benefit without compromising the interests of others, with a benefit rate of 68%. Conclusion: The occurrence of SLN in EC patients is related to their personal general characteristics, pathological characteristics, tumor markers, and other multi-dimensional indicators. The medical staff can evaluate the SLN risk of EC patients by combining multiple indicators.

Keywords: Endometrial cancer, sentinel lymph node metastasis, risk factor analysis, nomogram model

Introduction

Endometrial cancer (EC) is one of the three major malignant tumors of the female reproductive system, which originates from the endometrial glands, with an increasing trend in recent years [1, 2]. In some developed countries, the incidence of EC is higher than that of cervical cancer, accounting for about 20% to 30% of genital tract malignancies [3, 4]. About 90% of EC cases occur in people over 50 years old, of which 58 to 61 years old are the most commonly affected age. The occurrence of EC is related to long-term continuous estrogen stimulation, obesity, hypertension, diabetes, infertility, menopause and genetic factors. Most EC patients can be diagnosed early because of typical symptoms such as abnormal vaginal bleeding, vaginal discharge, or pain in the lesions, and about 75% of patients have lesions confined to the uterus at the time of initial diagnosis [5]. In the treatment of EC, surgery is the main choice [6]. For patients with advanced disease who are not suitable for surgery, like those who need to preserve fertility, or whose systemic conditions cannot tolerate surgery, other treatment options such as radiotherapy and chemotherapy, high-dose therapy, and immunosuppressive drugs are given after comprehensive evaluation [7]. At present, there are still some controversies in the choice of surgical plan, among which, whether to routinely perform systematic lymphadenectomy is one of the major issues of controversy.

Lymph node metastasis (LNM) is one of the main metastasis pathways of EC. When the disease progresses, the tumor invades the deep myometrium or involves the cervical stroma, it is prone to LNM, and the 5-year survival rate of patients with LNM is less than 50% [8, 9]. Sentinel lymph node (SLN), as an effective bar-

rier to prevent tumor cell metastasis, is the first group of lymph nodes that EC cells must pass through for lymph node metastasis [10]. Therefore, if the risk of SLN metastasis in patients with endometrial cancer can be predicted before perioperative surgery, it can provide a reference for taking targeted measures. This will significantly reduce surgical and postoperative complications, reduce hospitalization time, reduce economic burden, improve survival rate, reduce recurrence rate, and improve quality of life. At present, there is no specific diagnostic method for SLN metastasis in EC patients. The auxiliary assessment methods include the general condition of the patient, preoperative magnetic resonance imaging, preoperative computed tomography, multiple preoperative tumor markers, intraoperative SLN mapping, and surgery pathology, etc. [11, 12]. These methods all have certain evaluation value for SLN metastasis in EC patients, but there are often errors when they are evaluated individually. Relevant studies have shown that the use of certain factors alone to assess the postoperative recurrence risk of EC patients has an error rate of about 40%, which will directly and adversely affect the initial surgical treatment of EC patients [13].

A nomogram is a visual model of the results of multivariate analysis, which can be used to diagnose or predict the onset or progression of a disease by combining multiple indicators. Some scholars have constructed a nomogram model for the prognosis of patients with low-grade endometrial stromal sarcoma, and confirmed that the model has certain clinical value [14]. Xie et al. [15] reported in a study of EC patient-specific mortality that the nomogram model could accurately predict the cancer-specific mortality risk of EC patients treated with hysterectomy. From existing studies, nomogram models for predicting sentinel LNM in EC patients are still rare. Therefore, it is still of great clinical significance to analyze the risk factors of sentinel LNM in EC patients based on multi-dimensional indicators and build a nomogram model.

Method

Research objects

In this retrospective study, the clinical data of 79 EC patients who were treated in Zhumadian Central Hospital (from January 2019 to January 2021) were analyzed. There were 18 patients with SLN metastasis and 61 patients without SLN metastasis. This study complied with the ethical guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Zhumadian Central Hospital.

Inclusion criteria: (1) Confirmed EC patients by pathological examination; (2) Patients with surgical indications and received comprehensive EC staging surgery in our hospital (peritoneal flushing fluid + total hysterectomy/sub-extensive hysterectomy/extensive hysterectomy + bilateral adnexectomy Surgery + pelvic lymph node dissection + para-aortic lymph node sampling/dissection); (3) Patients with no psychiatric disease; (4) Patients with complete information required for this study.

Exclusion criteria: (1) Patients with serous papillary carcinoma and clear cell carcinoma; (2) Patients who had received radiotherapy, chemotherapy, or immunosuppressive therapy before operation; (3) Patients combined with other malignant tumors; (4) Patients with recurrent EC.

Data collection methods

The medical records of EC patients were retrospectively reviewed to collect patients' information: patients' age, preoperative body mass index (BMI), history of hypertension or diabetes, pregnancy history, menopause, tumor diameter, degree of tissue differentiation, tumor stage, cervical interstitial involvement, postoperative complications, postoperative adjuvant therapy, Carbohydrate Antigen 125 (CA125), Human Epididymis Protein 4 (HE4), neutrophils-lymphocytes ratio (NLR), Platelet-lymphocyte ratio (PLR).

Model construction and verification

The rms program package in RStudio software was used to visualize the results of multivariate analysis to obtain a nomogram model. Nomogram is a quantitative analysis chart that uses a cluster of disjoint line segments to represent the functional relationship between multiple variables in plane coordinates. Its advantage lies in that the value of a variable can be directly calculated by using the graph, such as the index score or survival probability of patients. Clinicians can add the scores corresponding to various risk factors to get the total

score, which can be used to get the probability of disease occurrence and decide the next treatment. Internal validation of the model: receiver operator characteristic curve (ROC), calibration curve, and decision curve (DC) were used to evaluate the discrimination, accuracy, and clinical benefit rate of the model. The area under the ROC curve (AUC) was between 0.5 and 1.0. AUC = 0.5, no diagnostic value; AUC: 0.5-0.7, low; AUC: 0.7-0.9, medium; AUC: 0.9, high.

Statistical analysis

SPSS 25.0 and R Studio statistical software was used for preliminary analysis of the research data. Qualitative data were expressed by frequency and percentage, and analyzed by χ^2 test. Quantitative data conforming to a normal distribution were presented in the form of (meanantitativ deviation), and a t-test was performed. $P < 0.05$ indicated that the difference was significant.

Results

Univariate analysis

The clinical data of 18 SLN-positive patients and 61 SLN-negative patients were analyzed by univariate analysis. The results showed that the BMI, tumor diameter, tissue differentiation degree, stage, cervical interstitial involvement, CA125, HE4, and other indicators of the two groups of patients were significantly difference (all $P < 0.05$), as shown in **Table 1**.

Multivariate analysis

Multivariate logistic regression analysis was performed (as shown in **Table 2** for variable assignments), and the results of multivariate analysis showed that BMI ≥ 24 kg/m^2, tumor diameter ≥ 2 cm, low differentiation, and cervical stromal involvement were independent risk factors for SLN metastasis in EC patients ($P < 0.05$). And the risk of SLN in EC patients increased with the increase of HE4 level ($P < 0.05$), as shown in **Table 3**.

Model construction

According to the results of multifactorial analysis, SLN metastasis in EC patients is affected by multiple factors. Combining multiple factors, we got a prediction model: Logit P = -33.024 + 0.919 * BMI + 0.122 * diameter + 1.338 * differentiated + 0.064 * Stage + 1.187 * Surgical street + 1.448 * HE4. In order to improve the readability of the model, we have visualized the model and obtained the nomogram prediction model as shown in **Figure 1**. It can be seen from the nomogram that when the patient's BMI is < 24, the single score of BMI is 0, and when n 24, it is 12.5. The scoring principle of other indicators is the same as that of BMI. The sum of the individual scores of all indicators is the total score of the evaluated patient, and the corresponding risk value can be obtained according to the position of the total score on the risk axis.

Verification of the nomogram model

From the ROC curve in **Figure 2**, the AUC of the model is 0.934 (95% CI: 0.878-0.979). The calibration curve in **Figure 3** shows a Brier score of 0.084. The decision curve in **Figure 4** shows that the threshold probability of the model ranges from 2% to 88%. Taking this cutoff value of the ROC curve as the diagnostic criterion, the threshold probability of the model was calculated to be 39%. When 39% was used as the basis for judging whether to take measures to intervene, 68 out of every 100 EC patients could benefit without harming the interests of others.

Discussion

At present, EC has become the No. 1 gynecological malignancy in some regions of China, and the onset tends to be in younger age of women. Identification of the influencing factors of LNM in EC patients has always been a research hotspot in this filed [16]. In this study, we analyzed the personal characteristics, surgical and pathological characteristics, and clinical detection indicators of patients to find the risk factors for LNM in EC patients. Among the multiple personal characteristics of patients, obesity has been reported by multiple studies as a risk factor for lymph node metastasis in EC patients [17-19]. This study showed that the risk of LNM in EC patients with BMI ≥ 24 kg/m^2 was 2.508 times that of EC patients with BMI < 24 kg/m^2. Obesity can affect the generation and development of lymphatic vessels, causing structural damage and increased lymphatic permeability, thereby affecting the generation and transport of lymph fluid [20]. Therefore, clinical attention should

Table 1. Univariate analysis of SLN metastasis in EC patients

Factor	SLN positive group (n = 18)	SKN negative group (n = 61)	χ^2/t	*P*
Age (years)			0.591	0.442
≥ 50	11 (26.19)	31 (73.81)		
< 50	7 (18.92)	30 (81.08)		
BMI (kg/m^2)			4.606	0.032
≥ 24	14 (31.82)	30 (68.18)		
< 24	4 (11.43)	31 (88.57)		
Hypertension or diabetes			1.490	0.222
yes	10 (29.41)	24 (70.59)		
no	8 (17.78)	37 (82.22)		
Pregnancy history			1.171	0.279
yes	6 (18.75)	10 (66.67)		
no	12 (25.53)	51 (79.69)		
Menopause			0.736	0.391
yes	13 (20.31)	35 (74.47)		
no	5 (33.33)	26 (81.25)		
Tumor diameter (cm)			4.347	0.037
≥ 2	13 (32.50)	27 (67.50)		
< 2	5 (12.82)	34 (87.18)		
Degree of tissue differentiation			4.511	0.034
Poor	8 (40.00)	12 (60.00)		
Medium or high	10 (16.95)	49 (83.05)		
Stage			4.107	0.043
II-III	11 (34.38)	21 (65.63)		
I	7 (14.89)	40 (85.11)		
Cervical interstitial involvement			4.725	0.030
yes	12 (34.29)	23 (65.71)		
no	6 (13.64)	38 (86.36)		
Postoperative complications			1.100	0.294
yes	6 (31.58)	13 (68.42)		
no	12 (20.00)	48 (80.00)		
Postoperative adjuvant therapy			0.599	0.439
yes	13 (25.49)	38 (74.51)		
no	5 (17.86)	23 (82.14)		
CA125 (U/mL)	41.22±10.38	29.31±8.61	4.917	0.000
HE4 (pmol/L)	137.29±29.16	109.93±22.07	4.283	0.000
NLR	2.01±0.39	2.17±0.31	1.811	0.074
PLR	151.08±31.22	159.87±35.41	0.949	0.346

Note: SLN: Sentinel Lymph Node; EC: Endometrial Carcinoma; BMI: Body Mass Index; CA125: Carbohydrate Antigen 125; HE4: Human Epididymis Protein 4; NLR: Neutrophils-Lymphocytes Ratio; PLR: Platelet-Lymphocyte Ratio.

be paid to obese EC patients, and patients should be helped to lose weight if necessary. Yang et al. [21] indicated in their study that hypertension and diabetes are risk factors for LNM in EC patients after treatment. However, in this study, hypertension or diabetes were not risk factors for LNM in EC patients. It may be due to the fact that EC patients with hypertension or diabetes in this study had blood pressure and glycemic level within the normal range, which reduced their effect on cancer cell metastasis, but the specific mechanism remains to be explored.

Surgical pathology is a decisive factor for EC staging. Tumor diameter, pathological type, tis-

Table 2. Assignment of each factor

Variable	Assignment
Dependent variable	
SLN transfer	1 = "positive", 0 = "negative"
Independent variable	
BMI	1 = "≥ 24 kg/m^2", 0 = "< 24 kg/m^2"
Tumor diameter	1 = "≥ 2 cm", 0 = "< 2 cm"
Tissue differentiation	1 = "poor", 0 = "medium or high"
Stage	1 = "II-III", 0 = "I"
Cervical interstitial involvement	1 = "yes", 0 = "no"
CA125	Enter the actual value
HE4	Enter the actual value

Note: SLN: Sentinel Lymph Node; BMI: Body Mass Index; CA125: Carbohydrate Antigen 125; HE4: Human Epididymis Protein 4.

sue grade, depth of myometrial invasion, cervical stromal involvement, and vascular invasion are all considered to be factors that may affect the prognosis of EC patients [22-24]. This study analyzed the pathological characteristics of EC patients such as tumor diameter, tissue differentiation, stage, cervical stromal involvement, and found that patients with ≥ 2 cm had a significantly higher risk of SLN metastasis than those with < 2 cm. Larger tumor diameter suggests that tumor cells proliferate faster and have a higher risk of LNM [22]. These also suggests that in actual clinical work, medical staff need to pay more attention to breast cancer patients with larger tumor diameters, such as early completion of tissue biopsy with active postoperative review, in the expectation that patients will benefit more from treatment. In addition, the degree of differentiation and clinical stage also have a significant impact on the risk of SLN metastasis in EC patients. For most types of cancers, a low degree of differentiation indicates a high degree of tumor malignancy and therefore a high risk of invasion and metastasis [25-27]. The higher the clinical stage, the more likely the cancer cells are to spread. Therefore, aggressive lymph node biopsy should be performed for patients with poorly differentiated tumor tissue and in the middle and late stages. Cervical interstitial involvement is one of the independent risk factors for SLN metastasis in EC patients, which is consistent with the conclusions of scholars such as Li [28].

During the process of malignant tumor progression or disease invasion, there may be "shedding" of cancer cell antigens. These shed proteins are deposited in the lymphatic system, participate in the circulation in the body, and increase the serum antigens of cancer cells. Therefore, we can label these antigens, namely tumor markers, and detect the levels of these antigens to determine the progression of the disease and explore tumor markers that have predictive value for lymph node metastasis of endometrial cancer. Although no specific tumor markers for EC have been found so far, a variety of tumor markers have been used in the field of gynecological tumors for auxiliary diagnosis. The elevation of CA125 is associated with the stimulation of the peritoneum in states such as menstruation, pregnancy, and postpartum stress, and it is usually significantly elevated in benign conditions such as inflammatory response, adenomyoma, and ovarian endometriomas, but it is not highly specific for the diagnosis of EC [29-31]. In the univariate analysis results of this study, the CA125 levels of the positive group and the negative group were significantly different, but the multivariate analysis showed that the elevated CA125 level was not a risk factor for sentinel lymph node metastasis in EC patients. HE4 is a novel tumor marker that has emerged in recent years, and was first discovered in epithelial cells distal to the male epididymal duct. HE4 is encoded by the whey acidic protein gene and is a member of the protease inhibitor family with protective immune functions. Relevant studies have shown that HE4 is expressed in the re-productive tract epithelium, but the content is not high, while the sensitivity to EC is 46-67%, and the specificity is over 90% [32]. This suggests that HE4 has a certain diagnostic value for EC. The analysis of this study found that with the increase of HE4 level, the risk of sentinel LNM in EC patients was significantly increased. Therefore, in the process of nursing EC patients, we should pay close attention to the changes of HE4 in patients. If HE4 abnormally increases, corresponding measures should be taken to intervene.

Disease prediction is the estimation of disease progression based on surveillance data, which aims to improve the predictability of disease prevention and control and to establish proac-

Table 3. Multivariate analysis of risk factors for SLN

Variable	*B*	*SE*	*Wald* χ^2	*P*	*OR*	*95% CI*
BMI ≥ 24 kg/m^2	0.919	0.534	2.959	0.045	2.508	0.880-7.149
Diameter of tumor ≥ 2 cm	0.122	0.022	31.898	0.000	1.129	1.083-1.178
Poorly differentiated	1.338	0.475	7.940	0.005	3.812	1.503-9.669
Stage II-III	0.064	0.028	5.061	0.024	1.066	1.008-1.127
Cervical interstitial involvement	1.187	0.485	5.993	0.014	3.276	1.267-8.473
CA125	0.337	0.505	0.446	0.504	1.401	0.520-3.772
HE4	1.448	0.550	6.932	0.008	4.253	1.448-12.495
Constant	-33.024	5.159	40.983	0.000	-	-

Note: BMI: Body Mass Index; CA125: Carbohydrate Antigen 125; HE4: Human Epididymis Protein 4.

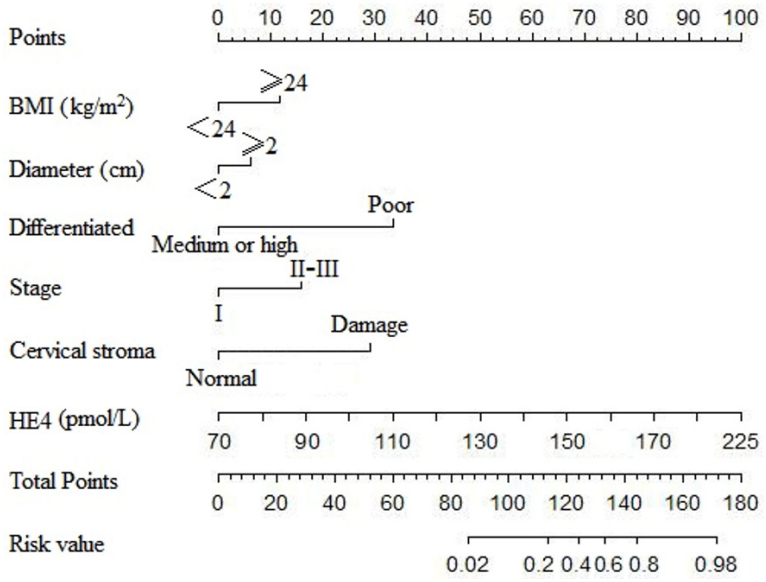

Figure 1. Nomogram model for predicting SLN metastasis in EC patients. Note: BMI: Body Mass Index; HE4: Human Epididymis Protein 4; SLN: Sentinel Lymph Node; EC: Endometrial Carcinoma.

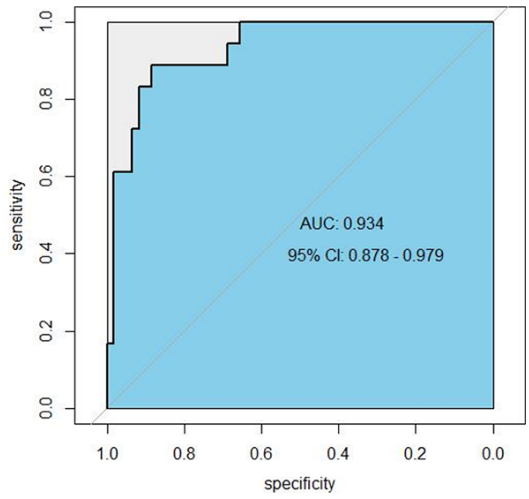

Figure 2. Receiver operating characteristic curve.

tive safeguard mechanisms. With the continuous development of mathematical models, computer simulation technology, and even machine learning, many prediction models are gradually applied to the prediction of disease development trends and epidemic laws. Nomogram is a commonly used clinical disease prediction tool. It integrates multiple predictors based on multivariate regression analysis, assigns values according to the impact of each index on the outcome event, and predicts the probability of individual outcome events through a certain functional transformation relationship. At present, the Nomogram model has become a mainstream method for predicting the occurrence and development of diseases, and has been applied in different fields, such as predicting the survival probability of different cancers, predicting infectious diseases, predicting cardiovascular diseases, and predicting diabetes. In this study, based on the results of multivariate analysis, a nomogram model of the risk of SLN in EC patients was constructed. The model was verified by the ROC curve, and the AUC was 0.934, indicating that the model has a high degree of discrimination. A Brier of 0.084 was obtained from the calibration curve, indicating that the model-predicted value was in good agreement with the actual probability. Decision curves also showed that the model had a good rate of clinical benefit. However, this study did

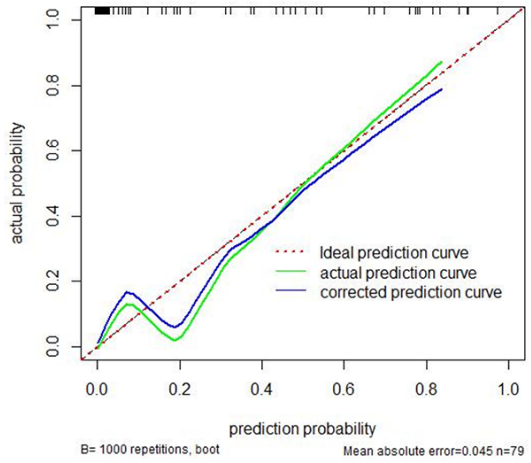

Figure 3. Calibration curve.

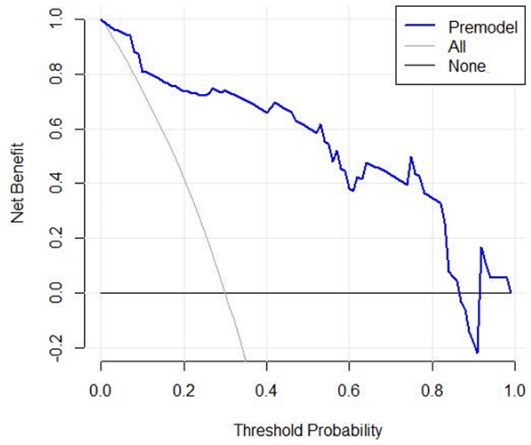

Figure 4. Decision curve.

not carry out external verification, and large-scale external verification is still required to apply the model to the clinic.

Conclusion

In conclusion, the occurrence of SLN in EC patients is related to their personal characteristics, pathological characteristics, tumor markers and other multi-dimensional indicators, and the combination of multiple indicators is more conducive to assessing the risk of SLN. In this study, the nomogram model predicting the risk of SLN in EC patients was constructed, and the model was verified to have good discrimination and prediction accuracy.

Disclosure of conflict of interest

None.

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