

Development and validation of a nomogram for preoperative prediction of lymph node metastasis in pathological T1 esophageal squamous cell carcinoma

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Abstract

Endoscopic resection is increasingly used to treat patients with pathological T1 (pT1) esophageal squamous cell carcinoma (ESCC) because of its small surgical trauma. However, reports of the risk factors for lymph node metastasis (LNM) have been controversial. Therefore, we aim to build a nomogram to individually predict the risk of LNM in pT1 ESCC patients, to make an optimal balance between surgical trauma and surgical income.

One hundred seventy patients with pT1 esophageal cancer in our hospital were analyzed retrospectively. Logistic proportional hazards models were conducted to find out the risk factor associated with LNM independently, and those were imported into R library "RMS" for analysis. A nomogram is generated based on the contribution weights of variables. Finally, decision analysis and clinical impact curve were used to determine the optimal decision point.

Twenty-five (14.7%) of the 170 patients with pT1 ESCC exhibited LNM. Multivariable logistic regression analysis showed that smoking, carcinoembryonic antigen, vascular tumor thromboembolus, and tumor differentiation degree were independent risk factors for LNM. The nomogram had relatively high accuracy (C index of 0.869, 95% confidence interval: 0.794–0.914, $P < .0001$). The decision curve analysis provided the most significant clinical benefit for the entire included population, with scores falling just above the total score of 85 in the nomogram.

Smoking, carcinoembryonic antigen, vascular tumor thromboembolus, and tumor differentiation degree may predict the risk of LNM in tumor 1 ESCC. The risk of LNM can be predicted by the nomogram.

Abbreviations: CEA = carcinoembryonic antigen, DCA = decision curve analysis, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, G = grade, LNM = lymph node metastasis, LVSI = vascular tumor thromboembolus, M = metastasis, pT1 = pathological T1, SCC = squamous cell carcinoma antigen, T = tumor.

Keywords: decision curve, lymph node metastasis, nomogram, pathological T1 esophageal squamous cell carcinoma

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LC and KP contributed equally to this work.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. The study protocol was approved by the ethics committee of Fujian Union hospital and informed consent was taken from all the patients. The study did not constitute harm and potential risks to donors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

All data generated or analysed during this study are included in this published article.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

The incidence rate of China's esophageal squamous cell carcinoma (ESCC) is the highest in the world. The incidence rate of ESCC is 20.9/10 million, and it is also the fifth leading cause of cancer and the fourth leading cause of cancer-related death in China.^[1] Radical esophagectomy and lymph node dissection are the gold standards of treatment. While there has been no strict prospective, randomized, controlled clinical studies to provide supporting evidence, with the use of a lymph node cleaning scope, the greater the surgical effect is, and the better the radical cure effect; however, the operation risk and postoperative complications will also increase, affecting the patients' rapid recovery and quality of life.^[2-4]

In recent years, to achieve a less invasive and better quality of life, endoscopic therapies for tumor (T) 1 esophageal carcinoma have been increasingly used.^[5,6] And the advanced therapeutic endoscopic techniques can, resection of superficial lesions and ablation of residual mucosa, preserving esophagus without radical resection that is performed with lower mortality and morbidity.^[2,3] However, the application of these procedures has been limited by without lymph nodes removed, the possibility of regional lymph node metastasis (LNM) in T1 esophageal carcinoma. LNM is not only an important factor affecting the prognosis but also an important factor in the treatment strategy of pathological T1 (pT1) ESCC.^[5,7] Therefore, how to accurately predict the risk of LNM in ESCC at stage T1 and then use this as a basis to choose a reasonable surgical method to ensure the curative effect while reducing the adverse effects of the operation is a problem that needs to be solved urgently.

The nomogram model has been widely and successfully used for prediction and survival analyses of a variety of cancers, quantifying risks by considering all known clinical variables, thus allowing individualized risk assessment and prognosis prediction of a variety of cancers. Therefore, we intend to establish a nomogram model to quantitatively evaluate the risk of LNM in patients with pT1 ESCC to select the optimal treatment and lymphadenectomy strategy.

2. Study definitions

2.1. Surgical procedure

All patients underwent gastroscopy, upper gastrointestinal radiography, and computed tomography (CT) examination of the neck, chest, and upper abdomen before surgery. Patients with unclear lesions were stained with esophageal mucosa and underwent esophageal biopsy to confirm a preoperative diagnosis. No preoperative neoadjuvant therapy was performed and no contraindications were found.

Experienced pathologists complete postoperative pathologic reporting. The differentiation degree, and lymphatic metastasis were analyzed in all specimens. For patients with multifocal tumors, the lesions with the greatest depth of infiltration were selected for tumor depth classification and lymph node status assessment.

3. Methods

3.1. Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study did not constitute harm

and potential risks to donors. All samples were obtained with the written informed consent of all participants.

3.2. Patients

A retrospective analysis of all patients with pT1 ESCC who underwent esophagectomy in Union Hospital from January 1, 2010 and December 31, 2016 was performed, and the enrollment of the required cases was completed within 1 year. A total of 170 eligible patients were enrolled in this study according to the following criteria:

- (1) Inclusion criteria: Patients with primary ESCC; patients who underwent radical esophagectomy (Ivor-Lewis esophagectomy, McKeown esophagectomy) and standard radical dissection of the 2-field thoracic and abdominal lymph nodes; reevaluation of the postoperative pathology showed that the tumor only infiltrated the mucosal layer or the submucosa; preoperative Eastern Cooperative Oncology Group physical condition score was 0 to 1; preoperative American Society of Anesthesiologists score was I to III; and informed consent was obtained from the patients.
- (2) Exclusion criteria: Severe mental illness; 5-year history of other malignancies, including lymphatic and hematologic malignancies; patients with esophageal cancer who had received preoperative neoadjuvant chemoradiotherapy; a history of unstable angina or myocardial infarction within 6 or 6 months; a history of cerebral infarction or cerebral hemorrhage within 6 or 6 months; a history of continuous systemic corticosteroid therapy within 1 month; simultaneous surgical treatment for other diseases was required; and pulmonary function forced expiratory volume in the first second < estimated value 50%.
- (3) Rejection criteria: Cases confirmed as metastasis (M) 1 intraoperative/postoperative: no evidence of distant metastasis was found in the preoperative examination, while distant metastasis was confirmed from intraoperative exploration/postoperative pathology; intraoperatively/postoperatively it was confirmed to be non-T1; it was proven intraoperatively that regional lymph node fusion into clusters could not ensure R0 resection or the resectability of wrapping the important vessels; simultaneous surgical treatment of other diseases was required; and after inclusion, due to preoperative sudden severe complications (unable to tolerate surgery or anesthesia) the treatment plan of this study was not suitable or could not be implemented as planned.

The following variables were extracted from the database: gender, age, smoking history, drinking history, carcinoembryonic antigen (CEA) level (the normal value of CEA is 0–5 ng/mL), SCC (squamous cell carcinoma antigen), level preoperative electrocardiogram, CT chest and abdomen plain scan, preoperative lung function, surgical method, anastomotic route, tumor location, tumor differentiation degree, T1 substage, tumor size, LNM, vascular tumor plug, tumor infiltration degree, tumor TNM stage, node stage, M stage, cutoff follow-up time, whether death, survival time, time of death, etc.

Among the clinical data, the surgical methods were divided into Ivor-Lewis esophagectomy and McKeown-esophagectomy, and the anastomosis methods were divided into intrathoracic anastomosis and left neck anastomosis. The tumor locations were divided into 3 types according to the 3-way method,

namely, upper, middle, and lower thoracic segments. The tumor length was measured by pathology after the intraoperative resected specimen. LNM is a dichotomous variable, that is, whether there is LNM. The degree of tumor differentiation was defined as high differentiation, medium differentiation, low differentiation, and undifferentiation. This study was based on the American Joint Commission on Cancer and the International Union for Cancer Control 8th edition esophageal cancer (EC) TNM classification criteria for tumor anatomy, pathological stage, and lymph node status. The cutoff time for follow-up was December 2020. In particular, the time of death of postoperative patients was the cutoff time for follow-up.

3.3. Statistical analysis

All statistical analyses were performed using SPSS21 for mac (Chicago, IL) and RStudio-1.2.1335 (Ross Ihaka, Robert Jetman) (<http://www.r-project>) with packages of Hmisc, grid, lattice, formula, ggplot2, survminer, RMS, survival, peperm, rmda, and mass, etc. The continuous variables were presented as mean \pm standard deviation or median with quartiles and the categorical variables were presented as number and percentage. All the significant variables identified in the multivariable logistic regression analysis were utilized to generate another logistic model and converted to a nomogram by library “RMS” in R to predict the risk of LNM. The variable with the largest coefficient absolute value was set as a reference whose scale range was from 0 to 100. The performance of the nomogram was examined by the concordance index (c-index) and assessed by the calibration plot. The calibration plot was generated by 1000 bootstrapped replications internally to illustrate the association between actual probability and the predicted probability. Clinical utility was estimated by decision curve analysis (DCA) and clinical impact curve, using the library “rmda (risk model decision analysis)” in R. DCA compared the net benefits of each prediction model at any threshold probability. Net benefit = (true positives/N) – (false positives/N) \times (weighting factor). Weighting factor = threshold probability/(1 – threshold probability). The external validation was carried out in the validation cohort by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A 2-tailed *P* value $< .05$ was considered statistically significant. Finally, the Kaplan–Meier curve was used to describe the survival rate of patients, and the Cox proportional hazard model was used to test the relationship between risk factors and death.

4. Results

4.1. Characteristics and baseline of the participants

A total of 170 patients were included, including 116 males (68.24%) and 54 females (31.76%). The mean age was 58.59 ± 7.01 years. The tumor locations of all patients were: 20 (11.76%), 102 (60%), and 48 (28.24%), located in the upper, middle, and lower esophagus, respectively. Distribution of tumor differentiation degree: Grade (G) 1, G2, and G3 were 18 (10.59%), 88 (51.76%), and 64 (37.65%), respectively. There were 63 cases (37.16%) in stage T1a, 107 cases (62.94%) in stage T1b. The average level of CEA was 2.91 ± 2.43 g/L. The average level of SCC was 1.71 ± 1.28 g/L. During the follow-up period, the mean follow-up time was 40.6 ± 18.5 months. By the end of the follow-up period, 34 (20%) of 170 pT1 ESCC patients

had LNM (postoperative pathology). The number of deaths within 5 years was 17 (10%), and the 5-year survival rate was 90% (Tables 1 and 2).

4.2. Survival significance of LNM

Kaplan–Meier survival curves and cumulative risk curves were established by COX analysis to assess the impact of LNM on patient survival. It is not difficult to find that LNM has a statistically significant impact on long-term survival of patients in pT1 EC ($P < .0001$), suggesting that with the extension of survival time, the cumulative risk of LNM increases, the survival probability of patients decreases, and the survival time is shortened (Fig. 1).

4.3. Contribution of the factors to LNM

Univariate logistic regression analysis was used to assess whether each demographic variable and clinical risk factor was associated with LNM. LNM in patients with pT1 EC was found to be positively correlated with smoke, vascular tumor thromboembolus (LVSI), CEA, and tumor differentiation degree. Age, sex, and BMI were not risk factors. In terms of SCC level ($P = 0.61$), tumor location ($P = .45$), and T1 substage ($P = .32$), the results were not statistically significant. The risk factors of postoperative LNM in patients with pT1 EC were brought into multivariate logistic regression analysis. The results suggested that smoke, LVSI, CEA,

Table 1

Main clinical characteristics and parameters of patients with pathological T1 esophageal squamous cell carcinoma.

Subgroup	LNM group (* /170% or σ)	Non-LNM group (* /170% or σ)	<i>P</i> value *
Overall	34 (20)	136 (80)	/
Age (yr)	56.71 (7.15)	59.06 (6.92)	.79
BMI	21.49 (4.48)	26.23 (4.59)	.54
Sex			.48
Male	28 (16.5)	88 (51.76)	/
Female	6 (3.53)	48 (28.42)	/
Smoke	24 (14.1)	93 (54.71)	.04
1 cigarette a few days	3 (1.76)	33 (19.41)	/
1 cigarette a day	1 (0.59)	14 (8.24)	/
2–3 cigarettes a day	1 (0.59)	23 (13.53)	/
4–10 cigarettes a day	2 (1.18)	13 (7.65)	/
10–20 cigarettes a day	4 (2.35)	5 (2.94)	/
More than 20 cigarettes a day	13 (7.65)	5 (2.94)	/
CEA (μ g/L)	3.81 (4.20)	2.69 (2.03)	.03
SCC (μ g/L)	1.96 (1.13)	1.95 (1.32)	.93
Tumor location			.45
Upper	4 (2.35)	16 (9.41)	/
Middle	18 (10.59)	84 (49.41)	/
Lower	12 (7.06)	36 (21.18)	/
LVSI	9 (5.29)	7 (4.12)	.0001
T1 substage			.37
T1a	5 (2.94)	58 (34.12)	/
T1b	29 (17.06)	78 (45.88)	/
Degree of tumor differentiation			.04
G3	10 (5.88)	58 (34.12)	/
G2	18 (10.59)	70 (41.18)	/
G1	6 (3.53)	8 (4.71)	/
Death rate	10 (5.88)	7 (4.12)	.00017

BMI = body mass index, CEA = carcinoembryonic antigen, CI = confidence interval, IQR = interquartile range, LNM = lymph node metastasis, LVSI = vascular tumor thromboembolus, SCC = squamous cell carcinoma antigen.

* Chi-square test or Fisher exact test.

Table 2
Univariable logistic proportional hazards models for the LNM of pathological T1 esophageal squamous cell carcinoma.

Subgroup	n (%) or median (IQR)	Hazard ratio (95%CI)	P value
Overall	170 (100)	/	/
Age (yr)	58.59 (54-63)	0.95 (0.90–1.01)	.81
BMI	22.40 (20.22–24.47)	0.97 (0.90–1.04)	.36
Sex	/	0.68 (0.61–0.75)	.31
Male	116 (68.24)	/	/
Female	54 (31.76)	/	/
Smoke	117 (68.82)	3.06 (1.41–6.65)	.01
CEA ($\mu\text{g/L}$)	2.91 (1.50–3.40)	1.96 (1.76–2.15)	.04
SCC ($\mu\text{g/L}$)	1.71 (1.21–2.42)	1.14 (1.01–1.31)	.61
Tumor location	170 (100)	1.27 (0.68–2.36)	.45
Upper	20 (11.76)	/	/
Middle	102 (60)	/	/
Lower	48 (28.24)	/	/
LVSI	16 (9.41)	6.63 (2.26–19.47)	.001
T1 substage	170 (100)	4.09 (0.25–67.13)	.52
T1a	53 (31.76)	/	/
T1b	107 (62.94)	/	/
Degree of tumor differentiation	170 (100)	1.91 (1.04–3.53)	.03
G3	18 (10.59)	/	/
G2	88 (51.76)	/	/
G1	64 (37.65)	/	/
Death rate			
Total death (5 yr)	17 (10)	/	/

BMI=body mass index, CEA=carcinoembryonic antigen, CI=confidence interval, IQR=interquartile range, LNM = lymph node metastasis, LVSI = vascular tumor thromboembolus, SCC = squamous cell carcinoma antigen.

and tumor differentiation degree were independently associated with LNM (Tables 2 and 3).

4.4. Establishment of nomogram

To visualize the logistic proportional hazards models results, the significantly different variables in Table 3, smoking, LVSI, CEA, and tumor differentiation degree, were imported into R library “RMS” for analysis. A nomogram is generated based on the contribution weights of variables. The prediction of postoperative individual risk of LNM and postoperative 3 to 5 years disease free survival probability of patients with pT1 EC was determined by the total score value of each risk factor corresponding to the top of the scale (Figs. 2 and 3).

4.5. Determination of decision point for maximum clinical benefit

Decision analysis and the clinical impact curve were used to determine the optimal decision point. First, the net benefit between the nomogram and each independent risk factor for LNM was assessed by DCA. In this analysis, the nomogram provided a higher net benefit than all other factors, suggesting that the nomogram was superior in predicting the probability of LNM. As more patients are treated under the low-risk threshold, the net benefit tends to increase as the risk threshold is lowered. However, the low-risk threshold led to an increase in false-positive rates and unnecessary interventions. Next, clinical impact curves were generated to analyze the number of patients classified as high risk at

each threshold and the number of patients classified as high risk. As shown in Fig. 4, the difference between the total number of patients considered at high risk for LNM and the actual number of patients who failed is widening as the risk threshold decreases, which means an increase in false-positive rates and an increase in unnecessary treatment. Therefore, we adjusted DCA according to the clinical impact curve to strike a balance between higher net benefits and lower false-positive rates. The calibration results showed that when the risk threshold for postoperative pulmonary venous obstruction was set at 0.3 (Fig. 4), it provided the most significant clinical benefit for the entire included population, with the score falling just above the total score of 85 (Figs. 2 and 4). In other words, radical EC surgery is recommended when the risk score is higher than 85.

4.6. Internal validation

The validation of the prediction model involves 2 key indicators: calibration and discrimination. A good model can not only accurately predict the probability of endpoint events (good calibration), but also distinguish the objects with different probability of endpoint events (good discrimination).

4.6.1. Calibration. The nomogram showed good accuracy in predicting the possibility of LNM, with a C index of 0.869, 95% confidence interval: 0.794–0.914, $P < .0001$.

4.6.2. Discrimination. The predicted value of the correction curve fits well with the actual value, showing good consistency (Fig. 5).

5. Discussion

In recent years, endoscopic therapy has made a breakthrough in the treatment of early EC. It is safe and effective in the treatment of esophageal mucosal cancer with a good long-term prognosis. It has become the standard treatment of esophageal mucosal cancer. Perioperative mortality, complications related to radical esophagectomy, and LNM are the key factors affecting the treatment plan. Esophageal anatomical studies have shown that the longitudinal lymphatic vessels in the esophageal submucosa were obvious and the incidence of LNM increases significantly after tumors invade the submucosa through the mucosal layer.^[8–10] Endoscopic treatment is acceptable for patients with LNM negative and EC stage T1a.^[6] However, whether it is suitable for high-risk patients with LNM and T1b diseases remains controversial. Previous studies have reported that the submucosa is divided into SM1, SM2, and SM3, and the risk of LNM in each layer is evaluated to confirm the application of endoscopic resection in patients with T1b.^[2,6,11] However, the preoperative examination is suitable for patients with T1a and T1b, so it is difficult to further distinguish the T1b subphase.^[12,13] In addition, the submucosa is thin and there is no absolute safety zone for endoscopic resection.^[4]

Some scholars advocate surgical resection for T1b EC. Gamboa et al^[6] advocated that after strict endoscopic and imaging monitoring, local endoscopic resection can be regarded as an alternative to surgical treatment in patients with early esophageal adenocarcinoma with a relatively low risk of LNM. However, the pathological type of EC in China is mainly squamous cell carcinoma.^[14] There is still a lack of large sample research on LNM and risk factors of T1b squamous cell carcinoma. And for patients with T1a EC, the low rate of LNM does not mean that there

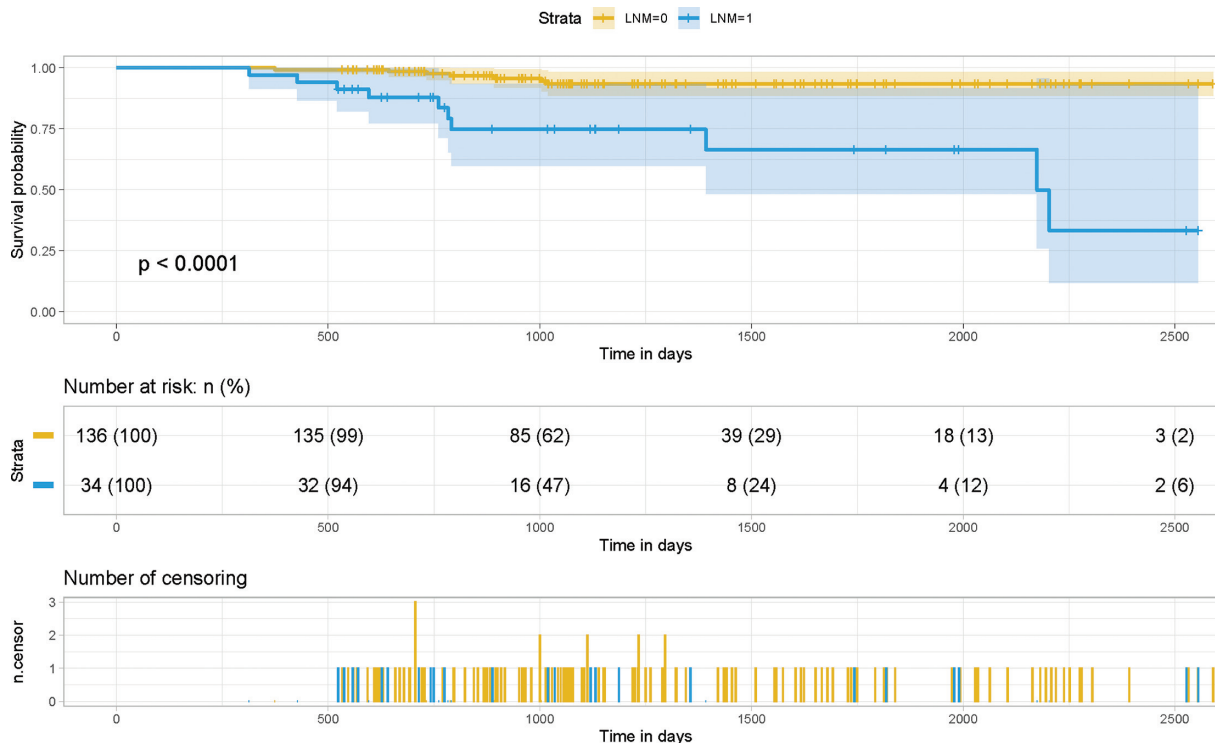


Figure 1. Kaplan–Meier and cumulative risk curves (effect of LNM on postoperative survival in patients with pathological T1 esophageal squamous cell carcinoma and the cumulative risk) (log-rank test). The above figure can be divided into 3 parts: upper, middle, and lower. The x-axis and y-axis represent the postoperative follow-up time (d) and survival probability respectively [in yellow (LNM=0, negative), the line represents the survival curve, and the width of the yellow bar represents the cumulative risk (the larger the width, the higher the cumulative risk). In blue (LNM=1, positive), the line represents the survival curve, and the width of the blue bar represents the cumulative risk (the greater the width, the higher the cumulative risk).] The x-axis and y-axis in the below picture represent the number of survival cases and the postoperative follow-up time, respectively. LNM = lymph node metastasis.

is no possibility of LNM. Our population-based data analysis showed that the prevalence of LNM was relatively high: about 20% of all T1 ESCC patients who underwent surgical resection had LNM. We found that the frequency of LNM in patients with intramucosal carcinoma was 10.87% (5/46), similar to that reported by Tanaka et al.^[15] This study showed that the incidence of LNM in the T1b ESCC stage was 27.10% (29/107). A retrospective study of 295 patients undergoing surgery and/or ESD/endoscopic mucosal resection showed that the LNM rate of T1b ESCC was 34.3% (35/102).^[8] This result may be partly due to studies focusing on lymph node resection and evaluation of postoperative pathological sections, resulting in a high LNM rate. However, Shen et al.^[16] the LNM rate in T1b ESCC patients was 16.7% (5/30). The difference between the 2 results may be due to the large sample size of our study and the fact that patients underwent 3-field lymphadenectomy.

Studies have shown that the worse the differentiation of ESCC, the higher the LNM rate. Our results showed that the LNM rates of G1, G2 and G3 tumors were 9.4% (6/64), 20.5% (18/88), and 55.6% (10/18), respectively. Shen et al.^[16] reported that the LNM rates of G1, G2, and G3 tumors were 6.1% (3/49), 17.2% (17/99), and 45.2% (33/73), respectively, and Tian et al.^[17] reported that the LNM rates of G1, G2, and G3 tumors were 13.0% (12/92), 17.7% (23/130), and 52.4% (11/21), respectively, which was similar to the values obtained in our study. In our study, there were fewer patients with poorly differentiated tumors, but we still found that patients with tumor differentiation into G3 had a significantly higher risk of LNM. We also found that the LNM rate of G3 tumors was 2 to 6 times higher than that of G1 to G2 tumors.

Previous studies suggested that smoking might be the main factor of EC. Through epidemiological investigation, it is found that smoking is quite common among residents in some areas with a high incidence of EC. Many studies have shown that tobacco is a carcinogen, and its harm to the human body is multi-effect.^[18] Carcinogens in tobacco may act directly with saliva or food swallowing to the esophagus or act on the esophagus after being absorbed by the human body, causing cancer. It has been found that cigarette smoke and tar contain a variety of carcinogens, such as benzoic acid α pyrene and other polycyclic aromatic hydrocarbons, epoxides, lactones, peroxides, and haloethers, and also contains a variety of nitroso compounds, such as nitrosopyrrolidine, dimethylnitrosamine, nitroso-dimethyl nicotine or nitrosodenonicotine. In addition, there are

Table 3
Multivariable model for risk factors associated with the LNM of pathological T1 esophageal squamous cell carcinoma.

Subgroup	B	OR (95%CI for OR)	P value
Smoke	0.78	2.16 (0.93–5.02)	.046
G. stage	0.79	2.20 (1.12–4.39)	.022
LVSI	1.73	5.66 (1.70–18.85)	.005
CEA	0.15	1.12 (0.98–1.28)	.038

B=regression coefficient, CEA = carcinoembryonic antigen, CI=confidence interval, G. stage=degree of tumor differentiation, LNM = lymph node metastasis, LVSI = vascular tumor thromboembolus, OR=odds ratio.

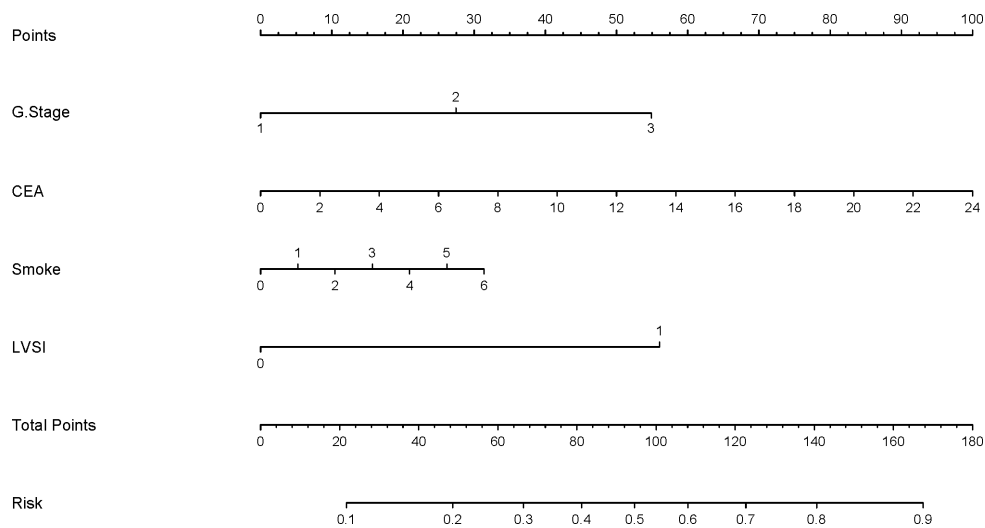


Figure 2. A nomogram for prediction of LNM risk for patients in pathological T1 esophageal squamous cell carcinoma. The percentage of weight, the variable which had the largest coefficients absolute value was set as reference whose scale range was from 0 to 100. Instructions for use of the nomogram: First, obtain the points of each characteristic of the patients by drawing a vertical line from each variable to the scale above (ie, S smoking, LVSI, CEA, and tumor differentiation degree). Total points would be summed. The total score could be converted to the LNM risk by the alignment of the “total point” bar and the “probability of failure” axis, or vice versa. CEA=carcinoembryonic antigen, G. stage=degree of tumor differentiation, LNM = lymph node metastasis, LVSI = vascular tumor thromboembolus.

lot of alkanes and alkoxy free radicals generated by the reaction of nitric oxide, nitrogen dioxide, and hydrocarbons in the smoke, which can directly attack cell fat, protein, nucleic acid, and other components, causing cell damage and carcinogenesis.^[19–23] Several chemical substances in tobacco were added

into drinking water and fed to Fisher rats for 30 weeks. The results showed that 12/20 cases of EC occurred in rats treated with nitroso-dimethyl nicotine, among which 3 cases were EC, which further confirmed the relationship between tobacco and EC.^[24]

Relevant epidemiological studies have also reached similar conclusions,^[25] suggesting that overall survival is significantly associated with smoking in ESCC patients. For ESCC patients who smoke, a higher smoking index is associated with worse clinical outcomes. Therefore, smoking may be used as a predictive indicator for pretreatment evaluation and adjustment of the treatment regimen. This is consistent with the results of our study, which shows that smoking is independently correlated with LNM of EC, suggesting that smoking increases the LNM probability of EC.

In relevant studies at home and abroad, some clinical indicators have been proved to be of great significance in evaluating tumor prognosis and diagnosis. In particular, LVSI has been proved to be an independent risk factor for LNM in ESCC patients.^[3,16,26–29] Tumor cells are isolated from tumor aggregates at the primary focus and then spread through lymphatic vessels or blood vessels. In this process, they may invade lymphatic vessels or blood vessels,^[30] which is considered to be the initial step of LNM and distant metastasis.^[31] Endoscopic ultrasonography and other imaging techniques can partially predict the infiltration depth and regional distribution of LNM, but LVSI can only be detected after endoscopic mucosal resection or surgery. If LVSI is detected in specimens resected after, additional lymph node dissection and surgical treatment should be considered.^[32,33] Hsu et al^[34] reported that the 5-year overall survival rates of the LVSI positive group and LVSI negative group were 28.2% and 61.1%, respectively. This suggests that postoperative treatment should be the focus of improving the prognosis of LVSI patients. In addition, hematoxylin–eosin staining and immunohistochemical detection of LVSI may provide more reliable

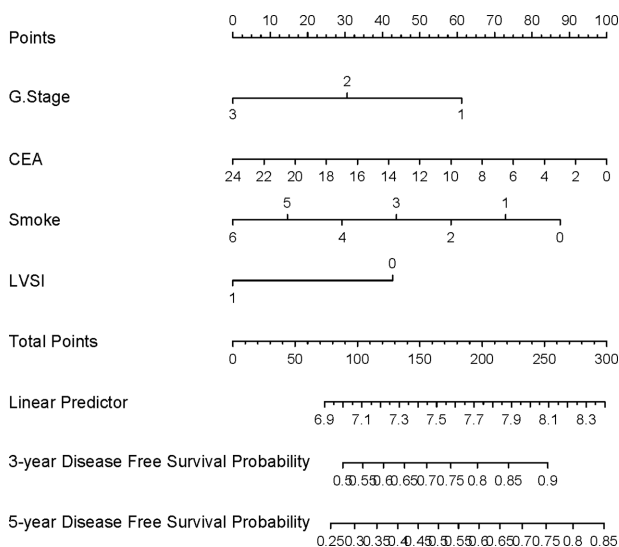


Figure 3. A nomogram for prediction of 3-year and 5-year disease free survival rates for patients in pathological T1 esophageal squamous cell carcinoma. The percentage of weight, the variable which had the largest coefficients absolute value was set as reference whose scale range was from 0 to 100. Instructions for use of the nomogram: first, obtain the points of each characteristic of the patients by drawing a vertical line from each variable to the scale above (ie, smoking, LVSI, CEA, and tumor differentiation degree). Total points would be summed. Total score could be converted to the 3-year and 5-year disease free survival rates by the alignment of the “total point” bar and the “probability of failure” axis, or vice versa. CEA=carcinoembryonic antigen, G. stage=degree of tumor differentiation, LVSI = vascular tumor thromboembolus.

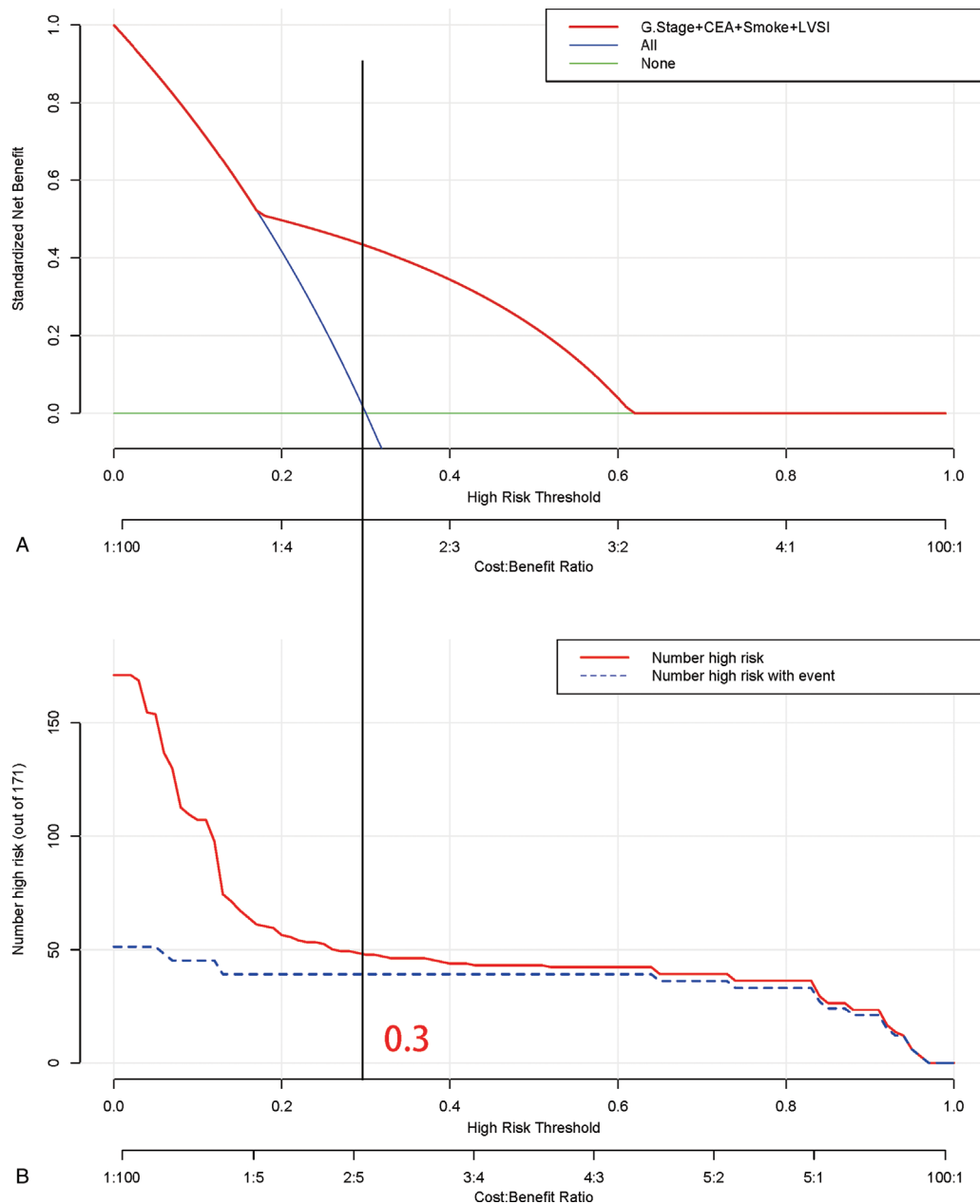


Figure 4. Determination of decision point via decision curve analysis and clinical impact curve (A), decision curve for the prediction model. The decision curve analysis graphically shows the clinical usefulness of the nomogram based on a continuum of potential thresholds for pulmonary venous obstruction (PVO) (x-axis) and the net benefit of using the nomogram to stratify patients (y-axis). Net benefit curves are plotted across probability thresholds for 3 options: “all” assume all patients have PVO, “none” assume no patients have PVO. Net benefit = (true positives/N) – (false positives/N) × (weighting factor). Weighting factor = threshold probability/(1 – threshold probability). (B) Clinical impact curve for EC-score. The red line shows the total number who would be deemed as high risk of PVO for each risk threshold. The blue line shows how many of those would be true positive (implantation failure). The vertical brown lines across subparts A and B showed the alignment of the DCA and the clinical impact curve to achieve the balance between the higher net benefits and lower false-positive rates, in which the threshold is set at 0.3, falling at 85 points in total at Fig 2. CEA=carcinoembryonic antigen, EC = esophageal cancer, LVSI = vascular tumor thromboembolus.

results.^[35] In our study, LVSI remains an independent prognostic risk factor.

It is well known that compared with esophagectomy, endoscopic therapy has the advantages of less invasion, fewer postoperative complications, and better quality of life.^[9,36,37] Ishihara et al^[37] reported that the mortality rate of endoscopic treatment for superficial EC was almost zero, and the incidence rate was very low. However, endoscopic therapy may reduce the survival rate of these patients^[38,39] because of the possibility of

LNM. For patients with early EC with LNM, radical esophagectomy and lymph node dissection should be performed to obtain survival benefits. In this study, we developed a nomogram model to individually predict the risk of LNM before the operation, make a statistical balance between surgical trauma and clinical benefit, and find the best benefit decision point. As previously mentioned, relevant indicators have been confirmed to be closely related to the incidence of EC. The advantage of this model is to provide a quantifiable basis for

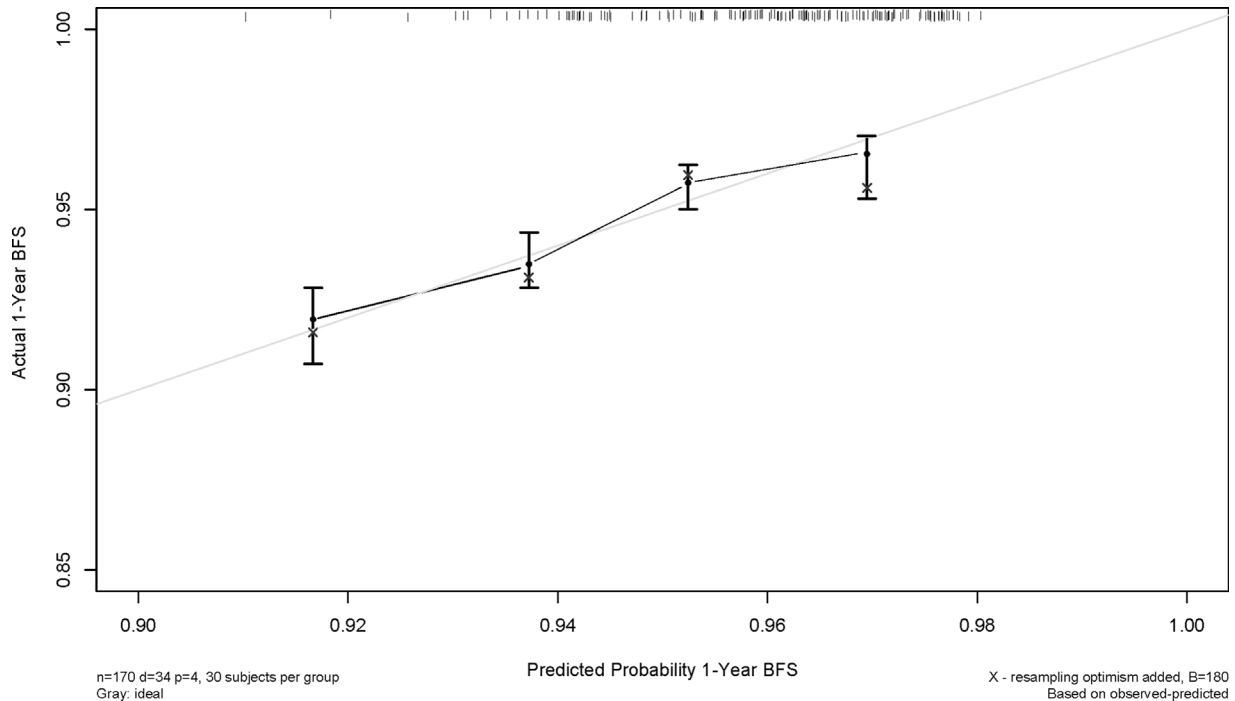


Figure 5. Calibration curve of nomogram model (1-year overall survival of this population). The x-axis and y-axis represent the predicted 1-year survival probability and the actual survival probability of the nomogram model, respectively.

radical surgery for EC. All patients included in the study were patients undergoing radical surgery for EC, and some patients did not find LNM. Because it is impossible to predict the status of LNM and the principle of blind radical resection, patients need to bear huge surgical trauma, and the benefit of surgery is not high. Therefore, the advantage of this study is that all patients with early-stage EC can undergo endoscopic treatment before radical surgery to obtain the data we need to predict the risk of LNM. Only high-risk patients need further radical EC resection and lymph node dissection surgery.

However, some limitations need to be acknowledged. First, this study was limited by retrospective analysis, so further studies are needed to verify this before expanding the clinical application of the nomogram. In addition, this study only included single-center samples, so it should be carefully checked and confirmed when applied in other populations and medical centers. Finally, although this is a large study, the sample size is still small, which hinders us from conducting a more meaningful subgroup analysis. In future studies, a more representative multicenter sample is needed to further refine the value of the risk assessment of the nomogram.

6. Conclusion

In conclusion, the nomogram based on smoking, LVSI, CEA, and tumor differentiation degree realized individual risk assessment and prognosis guidance for LNM in patients with pT1 EC, providing an objective and preliminary reference for clinical decision making and prognosis guidance for pT1 EC. Patients with pT1 EC has a possibility to individually and quantitatively evaluate the risk of LNM after endoscopic surgery, and then decide whether to further choose radical surgery with greater surgical trauma.

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