Original Article

Prognostic prediction model for patients with pathological T1N0 stage esophageal squamous cell carcinoma undergone esophagectomy

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Background: There is a shortage of reliable predictive models to provide valuable prognostic information for early esophageal squamous cell carcinoma (ESCC) without lymph node metastasis (LNM). We aimed to develop and validate a nomogram using the prognostic factors in T1N0 ESCC patients.

Methods: Patients with pathological T1N0 ESCC who underwent esophagectomy between 2014 and 2021 at three institutes were reviewed. The prognostic factors were evaluated by Cox proportional hazards model and a nomogram was developed. Patients were divided into high- and low-risk groups based on cut-off value of total points in the nomogram. Overall survival (OS) was estimated by the Kaplan-Meier method and compared using the log-rank test.

Results: A total of 275 patients were included and split into training (n=180) and external validation (n=95) cohorts. In the training cohort, multivariable analysis showed that the surgical approach, T1 substage, and carcinoembryonic antigen (CEA) level were independent prognostic factors. The developed nomogram had relatively high performance, with the area under the receiver operating characteristic (ROC) curve (AUC) of 0.783, 0.711 and 0.612 for 1-, 3-, and 5-year OS, respectively. The calibration curves showed that the predicted probability was in good agreement with the actual probability. Forty-seven was determined as cut-off value of total points. High-risk group (n=148) showed a significant poor OS than low-risk group (n=127) (P<0.001).

Conclusions: Left surgical approach, stage T1b, and higher CEA were associated with poorer prognosis in T1N0 ESCC patients. The nomogram demonstrated a good performance to predict the individual survival.

Keywords: Esophageal squamous cell carcinoma (ESCC); prognostic factors; lymph node metastasis (LNM); T1 stage

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Introduction

Esophageal cancer (EC) is one of the most common malignant tumors in the world with the morbidity and mortality rank of 7th and 6th in all solid cancers globally (1,2). Despite significant advancements in treatments for EC, the prognosis remains poor with a 5-year survival rate of only 15–25% for all stage diseases due to the lack of obvious symptoms in the early stages, leading to diagnosis in the advanced or late stages (1,3). The causes of poor prognosis might be related to the main characteristics of EC, including tumor progression, lymph node metastases (LNMs), and distant metastases (4). Esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype of EC in Asia, comprising more than 90% of the major pathological types (1).

LNM is also observed in the early stages of ESCC disease, significantly contributing to poor prognosis (5). The rates of LNM in the T1a and T1b stages of ESCC are 0–14% and 5.5–51%, respectively (6). Our previous studies (7,8) have established a nomogram to predict LNM in patients with T1 ESCC, and pointed out that clinicopathological and hematological parameters of tumor differentiation, the T1 sub-stage, the preoperative alanine aminotransferase/aspartate aminotransferase ratio and the high-density lipoprotein cholesterol level are risk factors for LNM in the patients (7). Although esophagectomy is still the gold standard for the treatment of ESCC, endoscopic resection has been shown to be an effective treatment for superficial ESCC and offers the advantage of preserving esophageal function (9,10). However, the presence of LNM in the T1 stage may restrict the applicability of endoscopic therapy (6,11), and endoscopic treatment is only considered for selected T1a stage EC patients (12). For the treatment in clinical T1N0 EC, a large sample study conducted by Semenkovich *et al.* (13) demonstrated that esophagectomy significantly prolonged the survival than local endoscopic therapy and chemoradiation based on National Cancer Database of US. However, it should be noted that 64% of the included patients had adenocarcinoma, and there is a lack of efficacy evaluation for squamous cell carcinoma. Previous study reported that the estimated 5- and 10-year cancer-specific survival probabilities for T1 ESCC patients with LNM were 39.8% and 31.5%, respectively, while they were 72.7% and 65.5% for patients without LNM (14).

Scholars have previously examined prognostic factors in lymph node (LN)-positive T1 ESCC patients, including T stage, primary site, and surgery (4,15). However, limited research has been conducted on LN-negative patients with T1 ESCC. Our study aimed to identify prognostic factors in T1N0 ESCC patients and develop an externally validated nomogram for predicting 1-, 3-, and 5-year survival rates. Furthermore, we stratified patients into high- and low-risk groups based on prognostic factors and compared the survival outcomes between these two groups. We present this article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-935/rc).

Highlight box

Key findings

- Left surgical approach, stage T1b, and higher carcinoembryonic antigen (CEA) were associated with poorer prognosis in T1N0 esophageal squamous cell carcinoma (ESCC) patients. The nomogram demonstrated a good performance to predict the individual survival.

What is known and what is new?

- There is a shortage of reliable predictive models to provide valuable prognostic information for early ESCC without lymph node metastasis. Scholars have previously examined prognostic factors in lymph node-positive T1 ESCC patients, including T stage, primary site, and surgery. However, limited research has been conducted on lymph node-negative patients with T1 ESCC.
- Our study aimed to identify prognostic factors in T1N0 ESCC patients and develop an externally validated nomogram for predicting 1-, 3-, and 5-year survival rates. Furthermore, we stratified patients into high- and low-risk groups based on prognostic factors and compared the survival outcomes between these two groups.

What is the implication, and what should change now?

- Left surgical approach, stage T1b, and higher CEA were associated with poorer prognosis in patients with pathological T1N0 ESCC. The nomogram developed by the above prognostic factors demonstrated a good performance in predicting 1-, 3-, and 5-year survival in both the training and validation cohorts. Patients classified as high-risk group with scores higher than 47 in the model showed a poorer prognosis, and therefore, postoperative timely follow-up and interventions are necessary.

Methods

Patient selection

Patients with primary ESCC underwent esophagectomy with two- or three-field lymph node dissection (LND) from January 2014 to January 2021 at three institutions were enrolled. Patients were split into the training

cohort (Affiliated Hospital of North Sichuan Medical College, Nanchong Central Hospital) and the external validation cohort (Suining Central Hospital). Inclusion criteria were as follows: (I) patients with primary ESCC; (II) underwent esophagectomy with two- or three-field LND; (III) T1 stage was confirmed by pathology; and (IV) patients without LNM confirmed by pathology. Exclusion criteria were as follows: (I) patients received any pre-operative adjuvant therapy; (II) with non-R0 resection; (III) with any concurrent primary cancer of other organs; and (IV) complete data were not available. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was registered in the Chinese Clinical Trial Registry (ChiCTR2100051728) and approved by the relevant Ethics Committees and Review Boards (Affiliated Hospital of North Sichuan Medical College: No. 2020ER181-1; Nanchong Central Hospital: No. 2019-041; and Suining Central Hospital: No. LLSNCH20200027). Individual consent for this retrospective analysis was waived.

Treatment procedure

The special preoperative examination included endoscopy with biopsy, upper gastrointestinal contrast, computed tomography of the chest and abdomen, and ultrasonography of the neck. Endoscopic ultrasonography and positron emission tomography are not commonly used in this group of cases. Patients with no contraindications underwent radical esophagectomy via left (Sweet) or right (McKeown or Ivor-Lewis) esophagectomy approaches depending on the tumor location with at least a two-field lymphadenectomy. Pathological results were evaluated by two experienced pathologists (X.G.G. and S.H.J.) according to the 8th edition tumor-node-metastasis (TNM) classification criteria of the American Joint Committee on Cancer (AJCC) & Union for International Cancer Control (UICC).

Variable selection and follow-up

The following variables were extracted from the databases of the three institutions including age at diagnosis, sex, body mass index (BMI), comorbidity, postoperative complications, surgical mode, surgical approach, tumor location, G category, T1 substage, N stage, TNM stage, tumor size, the number of LNs harvested and other laboratory indexes. The primary outcomes were the 1-, 3-, and 5-year overall survival (OS) rates.

Statistical analysis

Continuous variables were described as mean ± standard deviation or median (range). Categorical variables were described as frequency with percentage. OS was estimated by the Kaplan-Meier method and compared using the log-rank test among the groups. Univariate and multivariate Cox proportional hazards regression analyses were used to determine the independent prognostic factors. Variables with P<0.1 were included in multivariate analysis. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. A nomogram model based on the results of multivariate analysis was developed to predict 1-, 3-, and 5-year OS. Model performance was evaluated both in the training cohort and external validation cohort by receiver operating characteristic (ROC) curves with area under the curve (AUC) and calibration curves. The predicted total point for each patient were calculated according to the established nomogram. The cut-off of the ROC curve for each patient's predicted total points was regarded as a critical point, then the patients were divided into high-risk group and low-risk group. The effectiveness of risk stratification was demonstrated by the difference in survival between the two groups. A P value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 26.0 (version 25.0 Inc., Chicago, IL, USA) and the R programming language (version 4.0.2, Vienna, Austria).

Results

Patient characteristics

From 2014 to 2021, a total of 2,493 patients underwent esophagectomy with lymphadenectomy at three institutions, of which 362 cases were pathologically confirmed as T1N0 EC. After excluding those who received neoadjuvant treatment (30 cases), had other primary malignancies (4 cases), had incomplete case data (47 cases), or died within one month after surgery (6 cases), a total of 275 cases were ultimately included in the study, with 180 patients in the training cohort and 95 patients in the external validation cohort (*Figure 1*).

There were 199 (72.4%) male and 76 (27.6%) female with a median age of 65 years (range, 40–83 years). Preoperative comorbidities and postoperative complications were suffered in 168 (61.1%) and 135 (49.1%) cases, respectively. Common preoperative comorbidities included hypertension (34 cases), chronic obstructive pulmonary

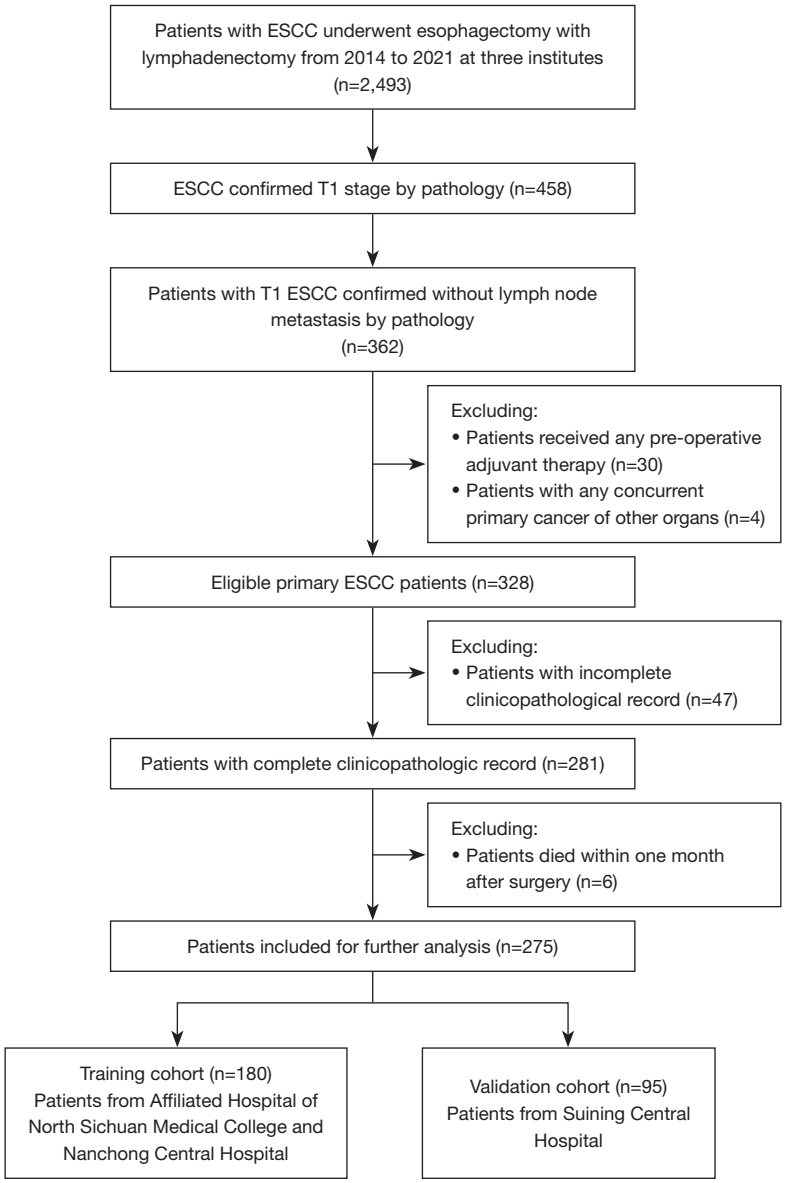

Figure 1 Flow chart of patient enrollment and data analysis. ESCC, esophageal squamous cell carcinoma.

disease (31 cases), diabetes (16 cases), and coronary artery disease (5 cases). The majority of patients (176, 64%) underwent minimally invasive video-assisted thoracic surgery (VATS). The right surgical approach was performed in more than half of the cohorts (212, 77.1%). The majority of tumors originated from the middle portion of the esophagus (166, 60.4%), followed by the lower portion (61, 22.2%). There were 96 (34.9%) patients with T1a stage and 179 (65.1%) patients with T1b stage. There were 73 (26.5%), 179 (65.1%), and 23 (8.4%) cases with G1, G2 and G3 differentiation, respectively. Tumor size was measured by maximum diameter with a mean of 2 cm (range, 0.5–7.0 cm). The average number of LNs harvested was 11.97±8.46. The average level of carcinoembryonic antigen (CEA), white blood cell (WBC), neutrophilic granulocyte and lymphocyte was 2.39±1.35 μg/L, 6.09±1.69 $\times 10^9$/L, 3.80±1.84 $\times 10^9$/L and 1.63±0.55 $\times 10^9$/L, respectively. The detailed clinical characteristics are shown in *Table 1*.

Independent prognostic factors

In the univariate analysis, surgical approach (HR, 0.463; 95%

Table 1 Clinical characteristics of pathological T1N0 ESCC patients

Variables	Whole cohort (n=275)	Training cohort (n=180)	External validation cohort (n=95)
Age (years)	65 [40–83]	64 [40–81]	64 [44–83]
Sex			
Male	199 (72.4)	124 (68.9)	75 (78.9)
Female	76 (27.6)	56 (31.1)	20 (21.1)
BMI (kg/m^2)	22.85±2.76	22.65±2.95	23.22±2.35
Comorbidity			
No	107 (38.9)	72 (40.0)	35 (36.8)
Yes	168 (61.1)	108 (60.0)	60 (63.2)
Postoperative complications			
No	140 (50.9)	81 (45.0)	59 (62.1)
Yes	135 (49.1)	99 (55.0)	36 (37.9)
Surgical mode			
Open	99 (36.0)	72 (40.0)	27 (28.4)
VATS	176 (64.0)	108 (60.0)	68 (71.6)
Surgical approach			
Left	63 (22.9)	50 (27.8)	13 (13.7)
Right	212 (77.1)	130 (72.2)	82 (86.3)
Tumor location			
Upper	48 (17.5)	23 (12.8)	25 (26.3)
Middle	166 (60.4)	114 (63.3)	52 (54.7)
Lower	61 (22.2)	43 (23.9)	18 (18.9)
T1 substage			
T1a	96 (34.9)	54 (30.0)	42 (44.2)
T1b	179 (65.1)	126 (70.0)	53 (55.8)
Differentiation			
G1	73 (26.5)	50 (27.8)	23 (24.2)
G2	179 (65.1)	120 (66.7)	59 (62.1)
G3	23 (8.4)	10 (5.5)	13 (13.7)
The number of lymph nodes harvested	11.97±8.46	11.98±9.05	11.97±7.24
Tumor size (cm)	2 [0.5–7.0]	2 [0.5–7.0]	2.40 [0.7–6.0]
White blood cell (10^9/L)	6.09±1.69	6.01±1.97	6.24±0.92
Neutrophilic granulocyte (10^9/L)	3.80±1.84	3.68±2.00	4.04±1.47
Lymphocyte (10^9/L)	1.63±0.55	1.66±0.57	1.58±0.52
Carcinoembryonic antigen (μg/L)	2.39±1.35	2.24±1.34	2.67±1.33

Continuous variables were described as mean ± standard deviation or median [range]; categorical variables were described as frequency (%). ESCC, esophageal squamous cell carcinoma; BMI, body mass index; VATS, video-assisted thoracic surgery.

Table 2 Univariate and multivariable analysis of predictive factors for T1N0 ESCC patients

Variables	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex	0.576 (0.265–1.251)	0.16		
Age	1.019 (0.979–1.060)	0.35		
BMI	0.942 (0.839–1.056)	0.31		
Comorbidity	1.252 (0.654–2.399)	0.50		
Tumor location	1.077 (0.634–1.829)	0.79		
Surgical approach	0.463 (0.247–0.865)	0.02*	0.430 (0.230–0.804)	0.008*
Postoperative complications	0.860 (0.460–1.609)	0.64		
The number of lymph nodes harvested	0.993 (0.959–1.029)	0.71		
Tumor size	0.972 (0.725–1.302)	0.85		
G stage	0.634 (0.363–1.109)	0.11		
T1 substage	2.426 (1.072–5.491)	0.03*	2.499 (1.104–5.655)	0.03*
White blood cell	1.095 (0.943–1.271)	0.24		
Neutrophilic granulocyte	1.124 (0.985–1.282)	0.08#	1.096 (0.961–1.251)	0.17
Lymphocyte	1.141 (0.648–2.010)	0.65		
Carcinoembryonic antigen	1.298 (1.085–1.552)	0.004*	1.315 (1.091–1.585)	0.004*

#, 0.05≤P<0.1; *, P<0.05. ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; BMI, body mass index.

CI: 0.247–0.865; P=0.02), T1 substage (HR, 2.426; 95% CI: 1.072–5.491; P=0.03), neutrophilic granulocyte (HR, 1.124; 95% CI: 0.985–1.282; P=0.08) and CEA (HR, 1.298; 95% CI: 1.085–1.552; P=0.004) were associated with OS (P<0.1). No associations were found in age, sex, BMI, comorbidities, postoperative complications, tumor location, differentiation, tumor size, the number of LNs harvested, WBC level, or lymphocyte level (P>0.1). The multivariate analysis showed that the surgical approach (HR, 0.430; 95% CI: 0.230–0.804; P=0.008), T1 substage (HR, 2.499; 95% CI: 1.104–5.655; P=0.03) and CEA (HR, 1.315; 95% CI: 1.091–1.585; P=0.004) were independently associated with OS (*Table 2*).

Establishment and validation of nomogram

To visualize the Cox proportional hazards models results, independent factors including surgical approach, T1 substage, and CEA were incorporated to establish the nomogram model based on the contribution weights of variables (*Figure 2*). The prediction of individual postoperative OS was determined by the total score value of each risk factor corresponding to the top of the scale.

The ROC curves performed well in both training and validation sets. The AUC values in the training cohort were 0.783 (95% CI: 0.646–0.920), 0.711 (95% CI: 0.616–0.807), and 0.612 (95% CI: 0.455–0.771) for 1-, 3-, and 5-year OS, respectively. In the external validation cohort, the AUC values were 0.860 (95% CI: 0.755–0.965), 0.775 (95% CI: 0.663–0.886), and 0.821 (95% CI: 0.702–0.941) for 1-, 3-, and 5-year OS, respectively (*Figure 3*).

The calibration curves of the nomogram for 1-, 3-, 5-year OS indicated that the predicted survival probabilities of the training and external verification cohorts were in good agreement with the actual observed survival probabilities (Figure S1).

Risk stratification

In order to classify individual risk-stratify, all patients were devoted to the predict model to calculate the points. The optimal threshold of the total points ROC curve was 0.398, with the AUC value of 0.770 (Figure S2). By calculating the Youden index, its corresponding score of 47 points was used as the cut-off value. All patients were divided into a high-

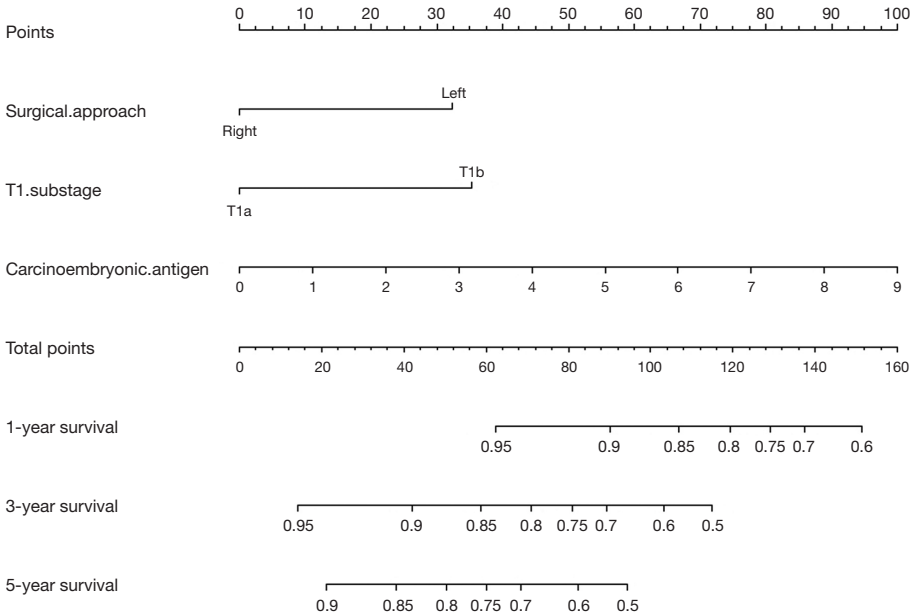

Figure 2 Nomogram for individually predicting the survival.

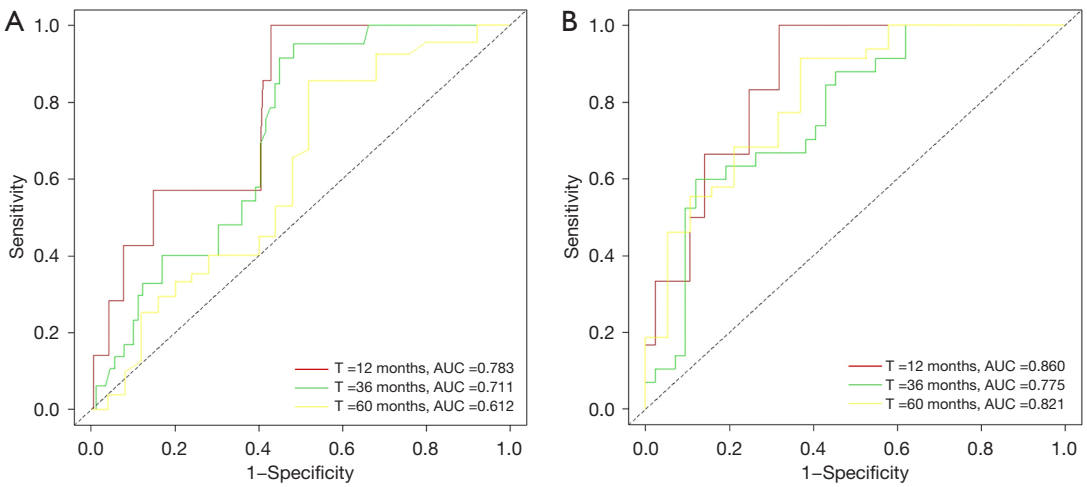

Figure 3 The ROC and the AUC of the training cohort (A) and the external validation cohort (B). AUC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic; T, time.

risk group (n=148) and a low-risk group (n=127) based on a cut-off value of 47 points. The high-risk group showed a significantly poor survival in the Kaplan-Meier curve (P<0.001, *Figure 4*).

Discussion

In this study, we determined the independent prognostic factors in patients with pathological T1N0 ESCC and developed a nomogram model for OS prediction. Furthermore, patients were stratified into high- and low-risk groups based on the nomogram scores, and their survival outcomes were compared. The findings were revealed in our current study as follows: (I) surgical approach, T1 substage and CEA were independent prognostic factors in patients with pathological T1N0 ESCC; (II) the nomogram model developed by incorporating demographic and clinical characteristics showed a favorable ability of prognostic

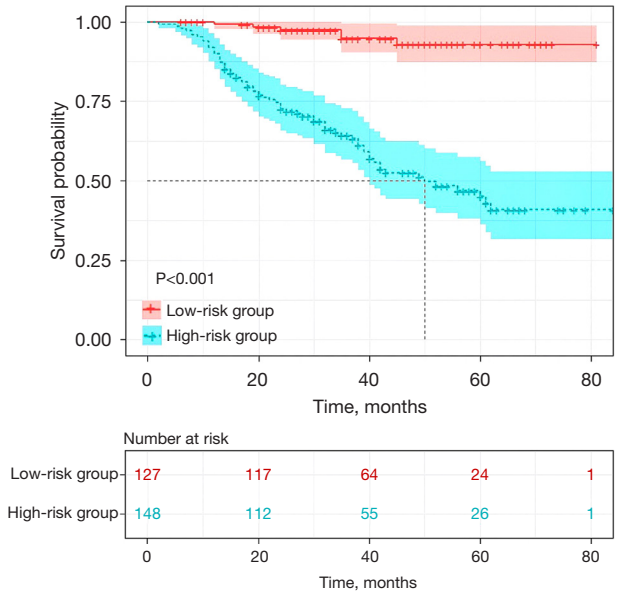

Figure 4 Kaplan-Meier survival curves for high- and low-risk groups.

prediction, which was validated externally; (III) patients in the low-risk group exhibited longer survival time compared to the high-risk group.

In recent years, right-sided approach in esophagectomy has gradually become the preferred surgical technique for achieving more thorough LND (16,17). Compared to the left approach, the right approach in performing complete thoracic and abdominal lymphadenectomy or three-field LND can reduce the postoperative LN recurrence rate in the cervical and thoracic regions, leading to a significant improvement in the OS and disease-free survival (18,19). Interestingly, the current study demonstrated a similar trend even in patients with pathological T1N0 ESCC, where those who underwent the right thoracic approach showed better OS. This could be attributed to the thorough lymphadenectomy reducing the risk of potential positive LN. However, Li *et al.* (18) suggested that the benefits of the right-sided approach in patients with EC were primarily observed in those with LN involvement and/or positive surgical margins, while it did not apply to patients without LN involvement and negative surgical margins. Zheng *et al.* (20) also concluded that there was no significant difference in postoperative survival and recurrence between patients undergoing left- and right-sided approaches in the absence of LNM in the upper mediastinal region. Comprehensive consideration of multiple factors is crucial for selecting the surgical approach, and it is essential to carefully assess the prognosis of patients with different surgical approaches.

T staging, representing tumor depth of infiltration, is positively correlated with the higher risk of LNM and negatively correlated with prognosis. Patients with deeper infiltration and potential LNM may undergo preoperative neoadjuvant therapy to achieve tumor reduction and eliminate metastasis (21). Consistent with previous studies, our research also demonstrated that patients with T1b stage have a poorer prognosis (9). However, Yu *et al.* (4) found that in patients with positive LN, the prognosis of T1b stage was better than that of T1a stage. This difference may be attributed to the fact that T1b patients with LNM are more likely to receive adjuvant therapy, achieving in improved clinical outcomes. However, it should be noted that our study included patients without LNM, and thus was not influenced by this factor.

Clinical serum tumor biomarkers, which are biological or biochemical substances produced by abnormal tumor cells or stimulated by tumor cells, have been demonstrated to be valuable in evaluating tumor prognosis and aiding in the diagnosis process (22,23). Tumor progression affects the levels of these tumor markers and shows a worse prognosis. Serum CEA, one of the extensively expressed tumor markers in cancer cells, is an independent prognostic factor in T1N0 ESCC patients in this study. It is closely associated with tumor invasion depth, LNM, and prognosis in patients with ESCC (24). Elevated levels of CEA and cancer antigen 19-9 (CA19-9) were significantly associated with worse median recurrence time and median OS. Furthermore, patients with elevated levels of both markers prior to treatment have a 10-fold increased risk of early treatment failure (25). Our study showed a negative correlation between CEA levels and 1-, 3- and 5-year survival for patients, which is consistent with the results of their study. Another study has shown that elevated CEA level is an independent prognostic predictor for patients with ESCC undergoing concurrent chemoradiotherapy (26). These elevated levels are associated with tumor invasion of the lymphatic system and an increased risk of tumor recurrence (26,27).

LNM has a significant impact on the treatment strategies, surgical approaches, and survival for early-stage ESCC (28). For patients with early-stage ESCC without LNM (T1aN0), endoscopic treatment has shown comparable efficacy to surgical procedures, with the added advantages of minimal invasiveness and quicker recovery, resulting in a 5-year survival rate exceeding 80% (10,29). In their study, Yu *et al.* (4) included T1 ESCC patients with LN involvement, incorporating a total of eight variables

to construct a nomogram model. Despite the data solely derived from the Surveillance, Epidemiology, and End Results (SEER) database, the nomogram model underwent rigorous validation through multiple methods, leading to its high accuracy and substantial clinical utility. However, there is currently a lack of relevant prognostic prediction models for early-stage disease without LN involvement. We have developed a prognostic prediction model for pathological T1N0 ESCC patients based on three variables, of which surgical approach and T1 stage were recognized as the factors with a greater impact on prognosis, followed by the effect of CEA. The model demonstrated good predictive performance and acceptable accuracy. In addition, we stratified patients into high- and low-risk groups based on the cutoff value of 47 points. The survival curves showed a significant difference, with patients in the low-risk group exhibiting longer survival time compared to those in the high-risk group.

There are several limitations in this study. Firstly, this study design was retrospective, and there was some inevitable selection bias. A further prospective randomized controlled trial could be considered for future investigations. Secondly, while the prediction model demonstrated favorable calibration and discrimination, further evaluation of its clinical usefulness is warranted. Thirdly, despite the multicenter nature of the study and an adequate sample size, the diversity of collected variables was limited, which restricted the scope of our analysis. In future follow-up studies, if more valuable prognostic risk characteristics can be included, conducting internal validation will enhance the robustness and reliability of our model.

Conclusions

In conclusion, left surgical approach, stage T1b, and higher CEA were associated with poorer prognosis in patients with pathological T1N0 ESCC. The nomogram developed by the above prognostic factors demonstrated a good performance in predicting 1-, 3-, and 5-year survival in both the training and validation cohorts. Patients classified as high-risk group with scores higher than 47 in the model showed a poorer prognosis, and therefore, postoperative timely follow-up and interventions are necessary.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-935/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-935/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-935/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-935/coif). The authors have no conflicts of interest to declare.

Ethical Statement: 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the relevant Ethics Committees and Review Boards (Affiliated Hospital of North Sichuan Medical College: No. 2020ER181-1; Nanchong Central Hospital: No. 2019-041; and Suining Central Hospital: No. LLSNCH20200027). Individual consent for this retrospective analysis was waived.

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