Original Article

Nomogram model for predicting long-term survival in esophageal cancer patients with metastasis after treatment: a SEER-based study

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Background: There is a large variance in the long-term survival of esophageal cancer (EC) patients with metastasis after treatment. This study was designed to analyze long-term survival of metastatic EC patients after surgery, radiotherapy and chemotherapy.

Methods: A retrospective cohort of EC patients with metastasis received surgery, radiotherapy and chemotherapy from 2004 to 2015 was obtained from the Surveillance, Epidemiology and End Results (SEER) database. Univariate Cox and complete subset regression analyses were performed to select prognostic factors. Nomograms were established to predict 3-, 5-, and 8-year overall survival (OS), and their performance was evaluated by receiver operating characteristic (ROC) curve and calibration curve.

Results: Age at diagnosis [hazard ratio (HR): 1.01; 95% confidence interval (CI): 1.00, 1.02; P=0.04], EC of other sites (HR: 1.78; 95% CI: 1.29, 2.45; P<0.001), lymph node involvement (HR: 1.37; 95% CI: 1.08, 1.37; P=0.009), and poorly differentiated or undifferentiated (grade III or IV) (HR: 1.39; 95% CI: 1.20, 1.76; P=0.006) was the independent risk factors for poor OS in EC patients. Female (HR: 0.58; 95% CI: 0.38, 0.88; P=0.01) showed reduced risks of showing poor OS compared with male population. The established nomograms based on these predictors showed satisfactory discrimination efficacy for predicting 3-, 5-, and 8-year OS in metastatic EC patients after treatment.

Conclusions: The nomograms showed good efficacy in predicting 3-, 5-, and 8-year OS among metastatic EC patients after surgery, radiotherapy and chemotherapy.

Keywords: Esophageal cancer (EC); lymphadenectomy; nomogram; long-term survival; Surveillance, Epidemiology and End Results (SEER)

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Introduction

Esophageal cancer (EC) is the seventh most prevalent malignancy and the sixth leading cause of cancer-related mortality worldwide (1). To date, preoperative and/or postoperative adjuvant therapy combined with surgical resection of the primary tumor and potential metastatic lymph nodes has been considered as the most effective treatment option for locally advanced EC (2). Nevertheless, the overall survival (OS) for EC remains dismal due to the metastasis and recurrence (3,4).

Tumor node metastasis (TNM) classification system, established by the American Joint Committee on Cancer

(AJCC), has been widely used to evaluate tumor progression and risk stratification (5). However, this system is inadequate to predict the OS of EC patients because patients of the same TNM stage may have markedly different survival profiles even after the same treatment (6). Besides, other clinicopathological factors such as age, race, and lymph node ratio (LNR) may also affect the prognosis of EC (7,8). Therefore, a more effective tool is imperative to distinguish the prognosis of EC patients with different risk levels to guide treatment.

Nomogram is a reliable statistical predictive model with a simple intuitive graph that can accurately elucidate the risk of clinical events by incorporating important factors for oncology prognostics (9). It is more effective than the traditional staging systems in predicting the prognosis of the majority of cancers such as gastric (10), breast (11), colorectal (12), and lung (13) cancers. These lead us to investigate the feasibility of establishing a nomogram for predicting the prognosis of metastatic EC after treatment.

The Surveillance, Epidemiology and End Results (SEER) program provides the data of cancer diagnoses, treatment and survival from population-based cancer registries covering approximately 30% of the U.S. population. This makes it a reliable resource for studying the oncology (14). Based on the SEER database [2010–2014], Liu *et al.* developed a nomogram to predict 1- and 2-year OS and cancer-specific survival (CSS) for M1 stage EC (15). Besides, the nomogram constructed by Cao *et al.* with the SEER database between 1988 and 2007 predicted the probabilities of 3- and 5-year survival in EC patients after esophagectomy (16). However, there are limited studies focusing on predicting the long-term survival of metastatic EC patients after surgery, radiotherapy and chemotherapy. The purpose of this study was to establish a nomogram model based on SEER database for predicting 3-, 5-, and 8-year OS of metastatic EC patients after treatment. We present this article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-742/rc).

Highlight box

Key findings

- A nomogram was established for predicting survival of metastatic esophageal cancer (EC) patients.

What is known and what is new?

- Nomogram is a reliable statistical predictive model with a simple intuitive graph that can accurately elucidate the risk of clinical events by incorporating important factors for oncology prognostics.
- This study established a nomogram model based on the Surveillance, Epidemiology and End Results (SEER) database for predicting 3-, 5-, and 8-year overall survival (OS) of EC patients after treatment.

What is the implication, and what should change now?

- The nomograms showed good efficiency in predicting 3-, 5-, and 8-year OS among EC patients with metastasis after surgery, radiotherapy and chemotherapy.

Methods

Data source

This retrospective study was based on the latest version of SEER database. Data of metastatic EC patients who underwent surgery, radiotherapy and chemotherapy from 2004 to 2015 was retrieved from the SEER database using the SEER*Stat software (version 8.4.2).

Patient population

We selected patients following International Classification Disease for Oncology, 3rd Edition (ICD-O3) topography codes for anatomic location in the esophagus: cervical esophagus (15.0), thoracic esophagus (15.1), abdominal esophagus (15.2), upper third of esophagus (15.3), middle third of esophagus (15.4), lower third of esophagus (15.5), overlapping lesion of esophagus (15.8) and esophageal lesions, not otherwise specified (15.9). We only considered patients over the age of 18 at diagnosis. To minimize bias caused by missing diagnostic and follow-up data, we referred to the following inclusion and exclusion criteria. Inclusion criteria were: (I) those with metastasis after surgery, chemotherapy and radiotherapy for the treatment; (II) data originating from hospitals or treatment centers; (III) complete data; and (IV) clearly classified data. Exclusion criteria were: (I) patients whose information was collected from autopsy and death certificates; and (II) patients with unknown or incomplete information of significant variables such as race, marital status, survival, and TNM stage. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Variables

Demographic and clinicopathological variables collected for each patient included age at diagnosis, gender, race,

marital status, histological type, number of tumors, primary site (inferior esophagus and/or other sites), size of tumor, positive lymph nodes, poorly differentiated or undifferentiated (grade III or IV), T stage, N stage, radiation, and chemotherapy. The histological types included esophageal adenocarcinoma (EAC), esophageal squamous cell carcinoma (ESCC), and others according to ICD-O3. TNM stage classification was based on the AJCC 8th edition. The main outcome of this study was OS, which was defined as the time from diagnosis to death from any cause.

Statistical analysis

Patients included in this study were randomized into the training and the validation cohorts in a ratio of 7:3. Chi-squared test was used to determine the comparability of demographic and clinicopathological characteristics between the training and the validation cohorts. In the training cohort, univariate and complete subset regression analyses were performed to determine the independent predictors of OS. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were used to show the effect of various factors on OS. A nomogram based on independent predictors was established for predicting 3-, 5-, and 8-year OS. The performance of the nomogram was assessed with respects to discrimination and calibration. The discriminative ability of the nomogram model was evaluated with area under the receiver operating characteristic (ROC) curve (AUC). Calibration was visualized by comparing nomogram-predicted versus observed survival probabilities. The survival curves were plotted by Kaplan-Meier method. Data were analyzed using R software (version 4.3.0). Survival analysis was performed using R packages survival, survminer and ggplot2. ROC curve was generated with R package timeROC. Nomogram and calibration curve were plotted using R package rms. The optimal cutoff values calculated by X-tile software (http://www.tissuearray.org/rimmlab) were utilized to stratify the patients into low- and high-risk groups for comparing the OS in different risk groups. A P value of less than 0.05 was considered statistically significant.

Results

Characteristics of the EC patients

Initially, 46,685 EC patients were screened, among which 14,491 showed metastasis (M1 stage). Among these cases, 860 patients received surgery, 587 underwent radiotherapy, and 561 underwent chemotherapy for the treatment, respectively. Finally, a total of 557 eligible EC patients underwent surgery, radiotherapy and chemotherapy were included in our analyses after excluding four cases with unknown N stage. Patients were randomly allocated into the training cohort (N=390) and the validation cohort (N=167) based on a ratio of 7:3. The demographic and clinicopathological characteristic of all patients are summarized in *Table 1*. The proportions of EAC, ESCC and other histological types were 71.63%, 15.62% and 12.75%, respectively. In terms of primary sites, lower portion of EC accounted for the highest proportion (83.84%), followed by others (13.29%), and overlapping lesion of esophagus (2.87%). A total of 61.58% of patients showed lymph node involvement. The vast majority (82.59%) of patients showed single tumor lesion.

Identification of predictors in training cohort

Univariate and complete subset regression analyses were performed to investigate the correlation between variables and OS in the training cohort (*Table 2*). Univariate Cox analysis showed that age at diagnosis (P=0.04), female (HR: 0.62; 95% CI: 0.41, 0.94; P=0.02), primary malignant site (P=0.004), lymph node involvement (P=0.02), stage III or IV (P=0.002) was the potential predictors for OS. In complete subset regression analysis, age at diagnosis (HR: 1.01; 95% CI: 1.00, 1.02; P=0.04), EC of other sites (HR: 1.78; 95% CI: 1.29, 2.45; P<0.001), lymph node involvement (HR: 1.37; 95% CI: 1.08, 1.37; P=0.009), and stage III or IV (HR: 1.39; 95% CI: 1.20, 1.76; P=0.006) were the independent risk factors for poor OS. Female (HR: 0.58; 95% CI: 0.38, 0.88; P=0.01) showed reduced risk of poor OS compared with male population.

Construction and evaluation of the nomogram for OS

A nomogram was constructed based on the independent predictors identified by the univariate and complete subset regression analyses, including age at diagnosis, male, EC of other sites, lymph node involvement, and stage III or IV. The 3-, 5-, and 8-year OS were predicted using the constructed nomogram (*Figure 1*). The time-dependent ROC was used to evaluate the discriminative ability of the nomogram. In the training cohort, the AUC values of the nomogram in predicting the 3-, 5-, and 8-year OS were

Table 1 Baseline demographic and clinicopathological characteristics of the patients with esophageal cancer

Name	Whole cohort (n=557)	Training cohort (n=390)	Validation cohort (n=167)	P value
Age (years)	60.08±9.56	59.61±9.73	61.20±9.07	0.07
Sex, female	62 (11.13)	40 (10.26)	22 (13.17)	0.39
Marital				0.21
Married	405 (72.71)	277 (71.03)	128 (76.65)	
Single	59 (10.59)	47 (12.05)	12 (7.19)	
Others	93 (16.70)	66 (16.92)	27 (16.17)	
Number of tumors, 2 or more	97 (17.41)	65 (16.67)	32 (19.16)	0.56
Primary site				0.77
EC, lower portion of esophagus	467 (83.84)	329 (84.36)	138 (82.63)	
Other sites	74 (13.29)	51 (13.08)	23 (13.77)	
Overlapping lesions	16 (2.87)	10 (2.56)	6 (3.59)	
Size (mm)	50.71±22.77	50.74±23.43	50.65±21.21	0.97
Lymph node involvement	343 (61.58)	231 (59.23)	112 (67.07)	0.10
III and IV grade	335 (60.14)	234 (60.00)	101 (60.48)	0.99
T stage				0.85
T1	51 (9.16)	37 (9.49)	14 (8.38)	
T2	57 (10.23)	42 (10.77)	15 (8.98)	
T3	356 (63.91)	247 (63.33)	109 (65.27)	
T4	65 (11.67)	43 (11.03)	22 (13.17)	
Tx	28 (5.03)	21 (5.38)	7 (4.19)	
N stage, N1	347 (62.30)	243 (62.31)	104 (62.28)	>0.99
Histology				0.36
ESCC	87 (15.62)	64 (16.41)	23 (13.77)	
EAC	399 (71.63)	281 (72.05)	118 (70.66)	
Others	71 (12.75)	45 (11.54)	26 (15.57)	

Data are presented as mean ± standard deviation or n (%) unless otherwise stated. EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

0.676, 0.687 and 0.717, respectively (*Figure 2A*). In the validation cohort, the AUC values of the nomogram in predicting 3-, 5-, and 8-year survival were 0.653, 0.635, and 0.629, respectively (*Figure 2B*). These together indicated the well discriminative ability of the nomogram. The 3-, 5-, and 8-year calibration curves of the nomogram for the prediction of OS demonstrated a good consistency in training cohort (*Figure 3A-3C*) and validation cohort (*Figure 3D-3F*).

Performance of the nomogram in risk stratification

The risk scores of all EC patients were calculated. The cutoff point calculated by X-tile software was 0.5 for OS. Based on the cutoff point of OS in the training cohort, 321 cases were stratified into the low-risk group and 69 patients were stratified into high-risk group (*Figure 4A*). Kaplan-Meier curves for OS predicted by the nomogram were significantly distinct among low- and high-risk EC patients (P<0.001).

Table 2 Univariate Cox and complete subset regression analysis for the training cohort

Name	Dead (n=308)	Alive/censored (n=82)	Univariate Cox regression		Complete subset regression	
			HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	59.98±9.36	58.18±10.95	1.01 (1.00, 1.02)	0.04	1.01 (1.00, 1.02)	0.04
Sex, female	25 (8.12)	15 (18.29)	0.62 (0.41, 0.94)	0.02	0.58 (0.38, 0.88)	0.01
Marital						
Married	222 (72.08)	55 (67.07)	–	–	–	–
Single	35 (11.36)	12 (14.63)	0.83 (0.58, 1.18)	0.29	–	–
Others	51 (16.56)	15 (18.29)	0.99 (0.73, 1.35)	0.96	–	–
Number of tumors, 2 or more	53 (17.21)	12 (14.63)	0.84 (0.63, 1.13)	0.26	–	–
Primary site						
EC, lower portion of esophagus	256 (83.12)	73 (89.02)	–	–	–	–
Other sites	45 (14.61)	6 (7.32)	1.61 (1.17, 2.21)	0.004	1.78 (1.29, 2.45)	<0.001
Overlapping lesions	7 (2.27)	3 (3.66)	1.18 (0.56, 2.50)	0.67	1.04 (0.48, 2.24)	0.93
Size (mm)	51.54±24.46	47.73±18.89	1.00 (1.00, 1.01)	0.24	–	–
Lymph node involvement	192 (62.34)	39 (47.56)	1.31 (1.04, 1.66)	0.02	1.37 (1.08, 1.73)	0.009
III and IV grade	192 (62.34)	42 (51.22)	1.45 (1.15, 1.83)	0.002	1.39 (1.20, 1.76)	0.006
T stage						
T1	29 (9.42)	8 (9.76)	–	–	–	–
T2	32 (10.39)	10 (12.20)	0.76 (0.46, 1.26)	0.29	–	–
T3	197 (63.96)	50 (60.98)	0.93 (0.63, 1.38)	0.72	–	–
T4	34 (11.04)	9 (10.98)	0.85 (0.52, 1.39)	0.51	–	–
Tx	16 (5.19)	5 (6.10)	1.06 (0.57, 1.95)	0.86	–	–
N stage: N1	199 (64.61)	44 (53.66)	1.14 (0.90, 1.44)	0.26	–	–
Histology						
ESCC	48 (15.58)	16 (19.51)	–	–	–	–
EAC	228 (74.03)	53 (64.63)	1.06 (0.78, 1.45)	0.70	–	–
Others	32 (10.39)	13 (15.85)	0.98 (0.63, 1.54)	0.95	–	–

Data are presented as mean ± standard deviation or n (%) unless otherwise stated. EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; HR, hazard ratio; CI, confidence interval.

In the validation cohort, the number of patients stratified into low- and high-risk groups was 126 and 41, respectively. Similarly, patients in the high-risk group were more likely to show a significantly reduced survival time compared with the low-risk group (P=0.002, *Figure 4B*).

Discussion

In the present study, we constructed a nomogram to predict 3-, 5-, and 8-year OS of EC patients with metastasis after surgery, radiotherapy and chemotherapy based on large-population SEER databases. Through univariate and complete subset regression analyses, we identified age at diagnosis, male, primary site, lymph node involvement and poorly differentiated or undifferentiated (grade III or IV) as independent prognostic factors. The nomogram established using these predictors were eventually proved to show good efficacy in predicting the 3-, 5-, and 8-year OS of these

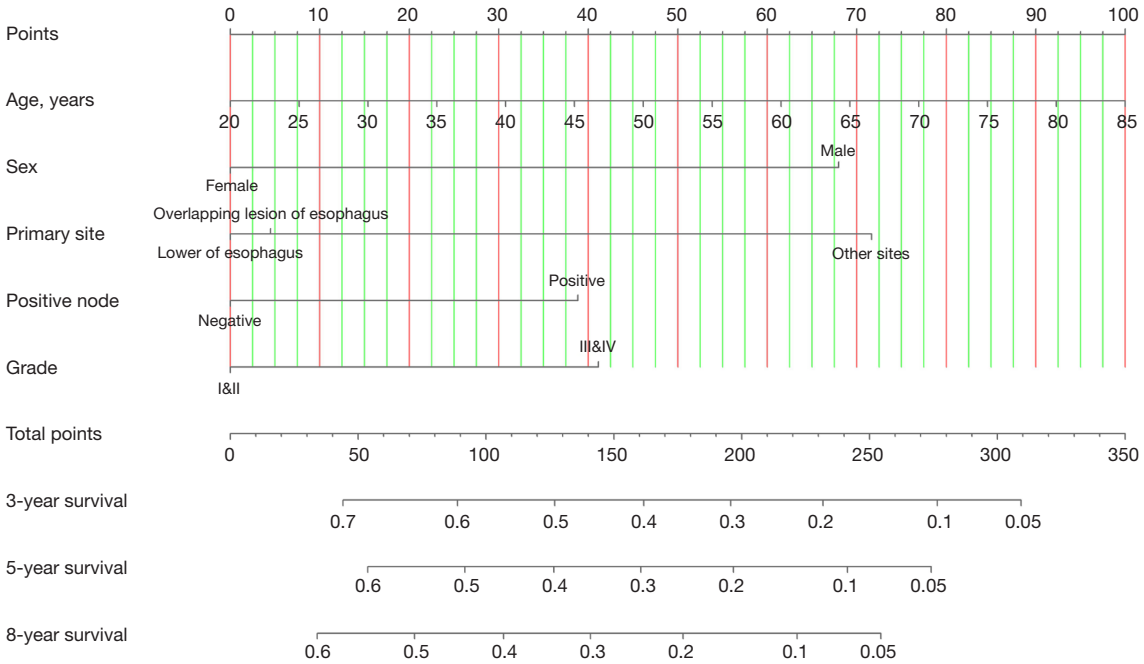

Figure 1 Nomograms for 3-, 5-, and 8-year OS in training cohort. OS, overall survival.

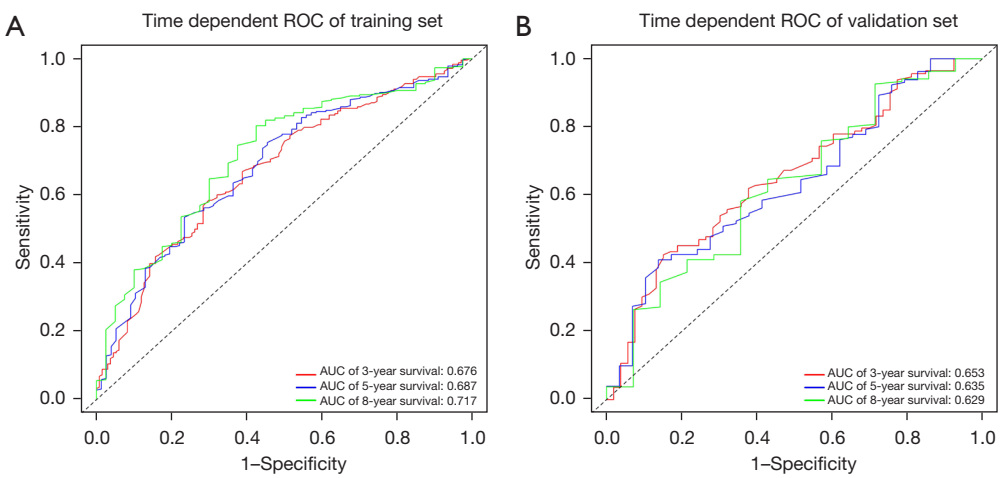

Figure 2 Time-dependent ROC curves and AUC for 3-, 5-, and 8-year OS in training cohort (A) and validation cohort (B). ROC, receiver operating characteristic; AUC, area under the ROC curve; OS, overall survival.

patients after surgery, radiotherapy and chemotherapy.

A handful of studies have shown that the survival of EC patients worsens with increasing age (16-18). Consistently, we found that the patients over 65 years old had a higher risk score than younger patients, which may be attributed to the poor nutritional status, decreased body resistance, and difficulty in recovering from surgery (19). In a previous study, based on univariate and multivariate analyses, Chen *et al.* reported that individuals aged 60 years or more and male sex were negative prognostic factors for OS in squamous cell carcinoma esophagus (SCCE) (20). Besides, in a study focused on the prognosis of EC patients with stage I–III, male sex and aged over 60 years mostly showed a poor prognosis (21). In this study, increasing age and male

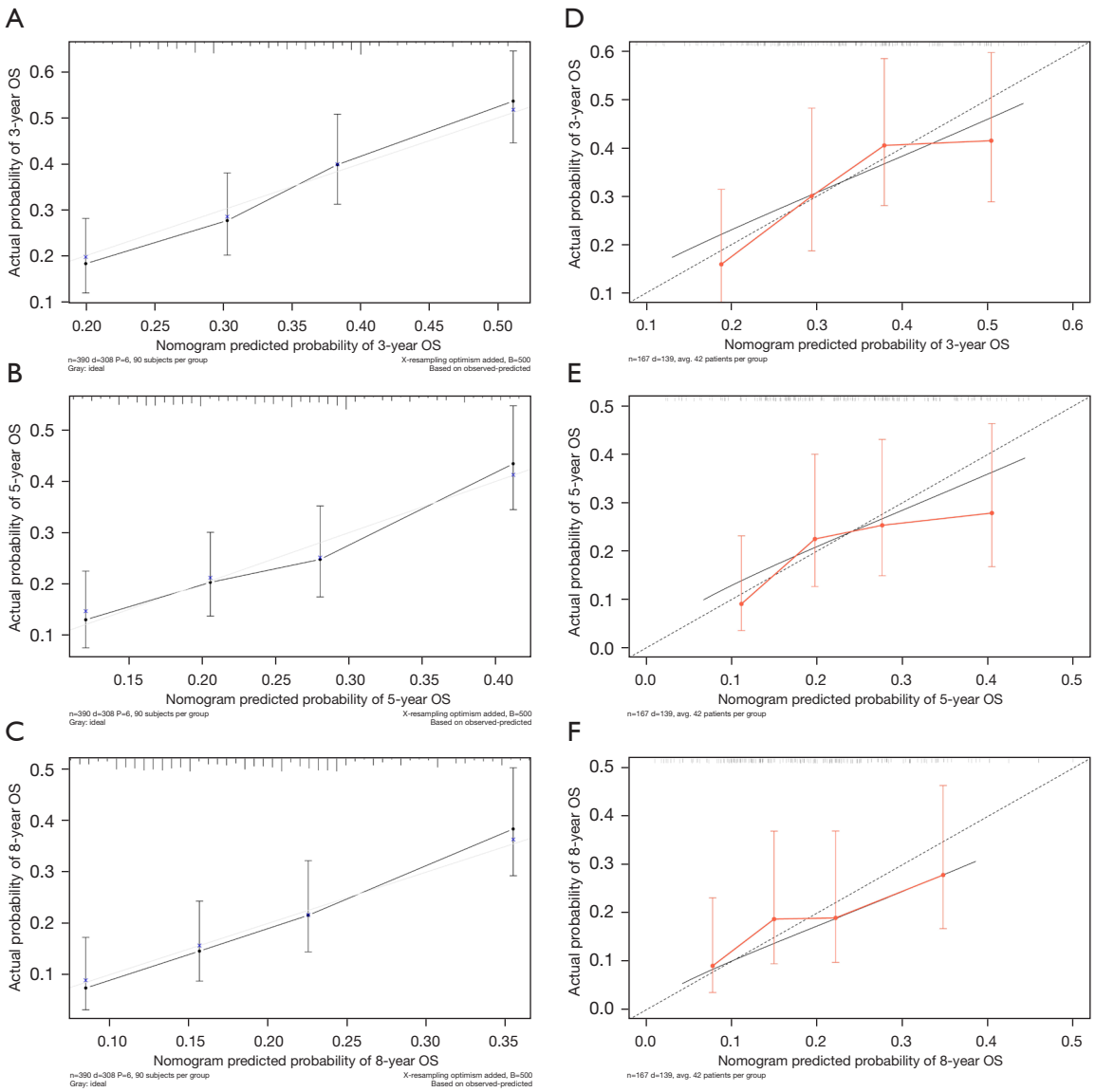

Figure 3 Calibration curves of 3-, 5-, and 8-year OS in the training cohort (A-C) and the validation cohort (D-F), respectively. OS, overall survival.

sex were confirmed to be independent risk factors for poor prognosis among EC patients with distal metastasis after surgery, radiation and chemotherapy.

The primary sites for EC are localized in the esophagus, while those with metastasis would show in the other sites demonstrating distal metastasis (22). Therefore, these patients would show a poor prognosis even after treatment. In this study, multiple site involvement (multiple distal metastasis) was identified as an independent risk factor for poor prognosis, which would induce an increased risk of poor prognosis (1.78-fold).

Selection of therapeutic strategies for patients is still a major challenge for clinicians as prognosis of EC patients remains poor, especially in advanced settings (23). In EC patients of stage III or IV, the cancer cells spread to distant lymph nodes or to other distant organs. Indeed, the worst outcome was noticed in cancer patients of stage III (HR: 1.35, 95% CI: 1.23–1.49, P<0.01) and stage IV (HR: 2.12, 95% CI: 1.94–2.32, P<0.01) (24). In this study, EC patients of stage III or IV were validated to be associated with increased risk of poor prognosis after treatment. Therefore, it is adopted as a predictor in the nomogram.

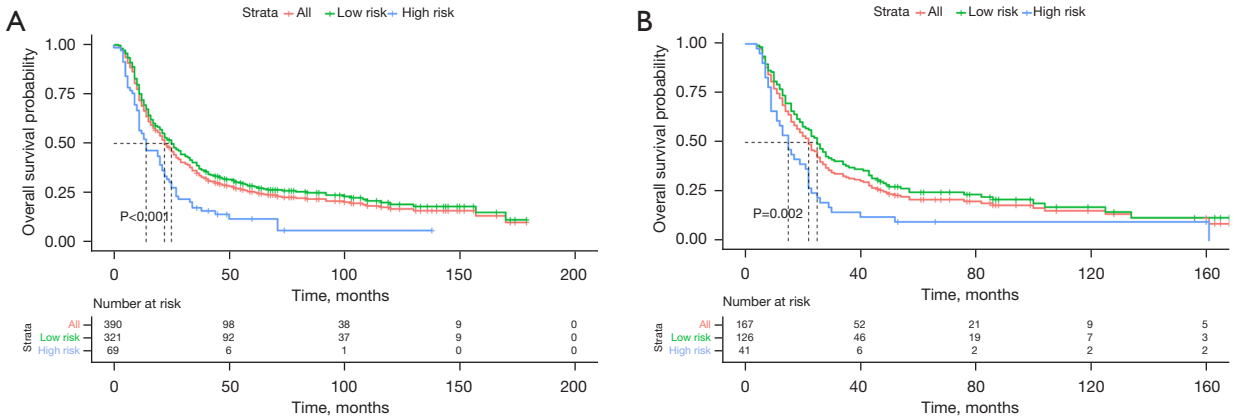

Figure 4 Kaplan-Meier OS curves of the low- and high-risk EC patients stratified by nomograms in the training cohort (A) and validation cohort (B). EC, esophageal cancer; OS, overall survival.

Lymph node status has been considered as the most important single prognostic factor for EC, and thereby detection of involved lymph nodes is crucial. Many studies have attempted to investigate the lymph node involvement in EC patients, with most of them performed in squamous cell carcinoma merely. For instance, stratification of lymph node metastasis could improve the diagnostic efficacy of EC, thereby improving the prognosis after treatment (25). In addition, extracapsular lymph node involvement was reported as a negative prognostic factor for locally advanced EC after neoadjuvant chemotherapy (26). Consequently, these patients showed poor prognosis even after treatment. In this study, lymph node involvement was identified as an independent risk factor for poor prognosis, and thereby was adopted into the nomogram.

Discrimination and calibration of the nomogram are assessed to avoid overfitting and to ensure the general application of the nomogram (9,27). Discrimination has usually been evaluated using ROC, and calibration is assessed by comparing the predicted survival probabilities from the nomogram with the actual survival probabilities. In our study, the AUC values of the nomograms to predict 3-, 5-, and 8-year OS revealed a well discrimination of the nomogram. The calibration plots showed acceptable agreement between the prediction probabilities and actual observations, which ensured the reliability and repeatability of the constructed nomogram. Furthermore, EC patients were divided into low-and high-risk groups based on the nomogram risk score. The Kaplan-Meier survival analysis suggested that the nomogram could help us accurately stratify the risk of EC patients.

Our study was hindered by several limitations. First, the retrospective nature of the SEER database may introduce the possibility of selection bias. Second, we could not collect the data from SEER since 2015 in this study even though there have been significant changes since that year. This was mainly associated with the limitations of data collection years and coding, and the coding was not uniform in the data after 2015. Third, the SEER database lacks some important clinical information that would confound our findings, such as specific regimens and timing of chemotherapy and radiotherapy, which are critical to the prognosis of EC patients. Fourth, the nomogram models were only internally validated, and external validation in other independent cohorts is needed to improve the accuracy and generalizability of the models. Finally, in this study, we could not compare the prediction efficacy of the nomogram with the real-world data (RWD) and the artificial intelligence (AI). Indeed, there are a few studies utilizing the application of AI and RWD to predict the risk of prognosis in cancer patients (28), or the integration of nomogram with the AI techniques for predicting the OS in tongue cancer (29). In the future, we will focus on their combination or their comparison in predicting the prognosis.

Conclusions

The nomograms based on these predictors showed satisfactory discrimination and calibration for predicting 3-, 5-, and 8-year OS. The nomograms could accurately stratify the risk of EC patients. Our findings may guide survival prediction and personalized treatment for EC patients after lymphadenectomy with different risk levels.

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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-24-742/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-742/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).

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