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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Nomogram to Predict Overall Survival for Thoracic Esophageal Squamous Cell Carcinoma Patients After Radical Esophagectomy

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ABSTRACT

Background. Effective tools evaluating the prognosis for patients with esophageal cancer undergoing surgery is lacking. The current study aimed to develop a nomogram to predict overall survival (OS) and provide evidence for adjuvant therapy for patients with esophageal carcinoma after esophagectomy.

Methods. The study retrospectively reviewed patients with pathologic T1N +/T2-4aN0-3, M0 thoracic esophageal squamous cell carcinoma after radical esophagectomy, with or without adjuvant therapy, in one institution as the training cohort (n = 2281). A nomogram was established using Cox proportional hazard regression to identify prognostic factors for OS, which were validated in an independent validation cohort (n = 1437). Area under curve (AUC) values of receiver operating characteristic curves were calculated to evaluate prognostic efficacy.

Results. In the training cohort, the median OS was 50.46 months, and the 5-year OS rate was 47.08%. Adjuvant therapy, sex, tumor location, grade, lymphovascular invasion, removed lymph nodes, and T and N categories were identified as predictive factors for OS. The nomogram showed favorable prognostic efficacy in the training and validation cohorts (5-year OS AUC: 0.685 and 0.744, respectively), which was significantly higher than that of the American Joint Committee on Cancer (AJCC) staging system. The nomogram distinguished OS rates among six risk groups, whereas AJCC could not separate the OS of 2A and 1B, 3C and 3B, or 3A and 2B. Patients with a nomogram score of 72 to 227 were predicted to achieve a 5-year OS increase of 10% or more from adjuvant therapy.

Conclusion. The nomogram could effectively predict OS and aided decision making in adjuvant therapy for patients with thoracic esophageal squamous cell carcinoma after esophagectomy.

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Esophageal cancer is a fatal disease that accounted for 455,784 new cases and 400,169 deaths worldwide in 2012. Nearly half of the cases were in Asia.[1,2] Although neoadjuvant chemoradiation is the standard care for locally advanced esophageal cancer,[3,4] many patients receive surgical excision as their first treatment.

In China, squamous cell carcinoma is the predominant histologic type of esophageal cancer, and surgery is one of the most common treatment methods for patients with esophageal cancer. Despite progress in diagnosis and treatment, the 5-year overall survival (OS) for patients who undergo esophagectomy remains poor, with studies reporting an OS rate of about 25%.[5] The benefit of adjuvant therapy also is debated and inconclusive. Thus, how to evaluate patient prognosis after surgery and provide subsequent treatment options is important.

The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system is widely used to stratify disease risk, predict patient survival outcomes, and make decisions about cancer treatment, but it has limitations. The AJCC staging system is not accurately enough to predict survival for patients with esophageal cancer who received multimodality treatment.[6] In several other cancer types, data suggest that including more prognostic clinical factors in consideration could result in better prognostic accuracy and efficacy.[7–9]

This study aimed to develop a nomogram to predict OS for patients with esophageal squamous cell carcinoma after radical esophagectomy and to validate its reliability in an independent external cohort of patients. The prognostic accuracy and efficacy of the nomogram were compared with those of the AJCC staging system. To the best of our knowledge, these are the largest cohorts ever reported concerning esophageal squamous cell carcinoma after radical surgery.

METHODS AND MATERIALS

Study Population

The training cohort comprised 2281 consecutive patients with thoracic esophageal squamous cell carcinoma who received esophagectomy between January 2004 and December 2012 in the Cancer Hospital Chinese Academy of Medical Sciences. The separately identified validation cohort of 1437 patients received esophagectomy from February 1993 to March 2007 in the Fujian Cancer Hospital.

The inclusion criteria specified patients with no previous anticancer therapy before surgery; pathologic stage T1N + or T2-T4aN0-3, M0; and complete resection of microscopic tumors. Adjuvant therapy was optional. Patients with distant metastasis, secondary malignancies, perioperative mortality, or a follow-up period shorter than 3 months were excluded from the study. The study was approved by the institutional ethics committee.

Diagnosis and Treatment

Pretreatment evaluation included physical examination, routine hematologic and biochemistry profile, pulmonary function test, and electrocardiogram (ECG). Esophagogastroduodenoscopy with pathologically confirmed biopsies was required. The staging procedures were endoscopic ultrasound, neck/chest/abdomen computed tomography (CT) with contrast, cervical/abdominal lymph node ultrasound, barium swallow, radionucleotide bone scan, and brain magnetic resonance imaging (MRI). Positron emission tomography (PET)/CT to rule out suspicious metastasis was optional.

The surgical approaches included left thoracotomy, Ivor-Lewis procedure, three-incision, and minimally invasive esophagectomy. The surgery aimed to achieve radical resection of the primary tumor and dissection of regional lymph nodes. The postoperative treatment options included radiotherapy, concurrent chemoradiation, or chemotherapy initiated 4 to 6 weeks after surgery and determined by a multidisciplinary team or by patient preference. Radiation was delivered by three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT). The total radiation dose was at least 50 Gy with conventional fractions. The chemotherapy regimen typically included platinum, taxane, and fluorouracil.

The patients were followed up every 3 months during the first 2 years, every 6 months in the third and fourth years, and then annually. The follow-up examinations included routine laboratory test, neck/chest/abdomen CT scan, cervical/abdominal lymph node ultrasound, barium swallow, and/or PET/CT. Once suspicious recurrent lesions were found by imaging, biopsy was attempted.

Statistical Analysis

The baseline characteristics of categorical variables between the training and validation cohorts were compared using chi-square test. Overall survival was defined as the time from the date of surgery to the date of death or censor. Cumulative survival rates were estimated using the Kaplan-Meier estimator and compared using the log-rank test. Cox proportional hazard models were used to estimate the association between clinical factors and OS, with additional adjustment for potential confounders. The backward stepwise procedure was used in the multivariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) also were calculated. The proportional hazard assumption was assessed using Cox models that allowed time-dependent HRs combined with a curve of $S(t) \sim \log[-\log(t)]$. A nomogram then was developed to classify patients into subgroups with corresponding 1-, 3-, and 5-year OS values given the selected prognostic factors.

Next, we used internal validation by the bootstrap method to estimate the bias-corrected or overfitting-corrected predictive accuracy of the models, which was presented as a time-dependent receiver operating characteristic (ROC) curve and area under curve (AUC) value. Calibration curves were plotted using the average K–M estimates, calculated on the basis of 1000 bootstrap samples, against the corresponding nomogram for the 5-year OS to evaluate the performance of the predictive models.

Finally, we performed external validation by the nomogram to assess each patient's total score in the validation cohort. In addition, Cox regression analysis was used to derive ROC and calibration plots. The z test and likelihood ratio test were used to compare the time-dependent AUC values and the goodness of fit of the nomogram and AJCC staging system, respectively. All p values were two-sided, and p values lower than 0.05 were considered statistically significant. The analyses were conducted using SPSS Statistics (version 20.0; Chicago, IL) and R (version 3.4.3).

RESULTS

Baseline Characteristics and Survival

The baseline characteristics are summarized in Table 1. There were more men than women, and their median age was 58 years. The median tumor length was 5 cm. More than half of the patients had a primary tumor located in the middle esophagus, and the tumor grade was mostly well to moderate. Lymphovascular invasion was present in 13.99% of the patients. The majority of the patients had more than 16 lymph nodes removed. Most of the patients were staged as T2–3, with more than 50% having node-positive disease, and the majority had locally advanced disease. Adjuvant therapy had been performed for 31.09% of the patients. Except for LVSI, the distribution of demographic and clinical factors differed significantly between the training and validation cohorts.

The median follow-up period was of 65.38 months (95% CI 63.40–67.36) in the training cohort and 69.80 months (95% CI 65.87–73.73) in the validation cohort. Deaths from any cause occurred for 1204 patients (52.78%) in the training cohort and 743 patients (51.70%) in the validation cohort. The training cohort had a median OS of 50.46 months, with 1-, 3-, and 5-year OS rates of 87.59%, 57.30%, and 47.08%, respectively. The validation cohort had a median OS of 57.10 months, with 1-, 3-, and 5-year OS rates of 88.43%, 61.00%, and 48.91%, respectively.

Prognostic Nomogram Development and Internal Validation

In the univariable analysis, sex, tumor length, tumor grade, LVSI, and T and N categories were prognosis predictors for OS. The multivariable analysis showed that male sex, age older than 60 years, upper and middle esophagus tumor, poor tumor grade, LVSI, fewer than 16 removed lymph nodes, and advanced T and N categories independently predicted poor OS (Table 2).

A prognostic nomogram integrating all the independent predictors for OS was constructed (Fig. 1). Each factor was assigned certain points according to their coefficients. The 1-, 3-, and 5-year OS rates were predicted by the sum of these points. The 1-, 3-, and 5-year AUC values of ROC were respectively 0.706 (95% CI 0.673–0.739), 0.701 (95% CI 0.678–0.723), and 0.685 (95% CI 0.660–0.710) (Fig. 2a). The calibration plot for the probability of the 5-year OS was highly consistent between the predictive and actual survival rates (Fig. 2b).

External Validation

The nomogram was externally validated using an independent validation cohort. The 1-, 3-, and 5-year AUC values of ROC were respectively 0.693 (95% CI 0.650–0.737), 0.730 (95% CI 0.711–0.766), and 0.744 (95% CI 0.715–0.774) (Fig. 2c). The calibration plot also indicated a good correlation between the nomogram-predicted and observed survival (Fig. 2d).

Comparison of Nomogram with the 7th and 8th AJCC Staging Systems

The prognostic efficacy of the nomogram was compared with that of the 7th and 8th AJCC staging systems for patients with esophageal cancer. The 5-year AUC values of ROC for the 7th AJCC were 0.643 (95% CI 0.618–0.669) for the training cohort (Fig. S1A), and 0.721 (95% CI 0.706–0.751) for the validation cohort (Fig. S1B), which were significantly lower than those of the nomogram ($p < 0.001$). A similar result was obtained for the 8th AJCC. The 5-year AUC value of ROC was 0.620 (95% CI 0.593–0.646) in the training cohort (Fig. S1C) and 0.679 (95% CI 0.653–0.712) in the validation cohort ($p < 0.001$) (Fig. S1D).

We further divided the patients into six risk groups according to their accumulated nomogram scores (< 70, 70–119, 120–139, 140–169, 170–199, and > 200). The

TABLE 1 Baseline characteristics of the training and validation cohorts

Characteristics	All patients (n = 3718) n (%)	Training cohort (n = 2281) n (%)	Validation cohort (n = 1437) n (%)	p value
Sex				< 0.001
Male	2916 (78.43)	1858 (81.46)	1058 (73.63)	
Female	802 (21.57)	423 (18.54)	379 (26.37)	
Age (years)				< 0.001
< 60	1995 (53.66)	1100 (48.22)	895 (62.28)	
≥ 60	1723 (46.34)	1181 (51.78)	542 (37.72)	
Median (IQR)	58 (52–65)	60 (54–66)	56 (49–63)	
Tumor length (cm)				0.006
< 5	1511 (40.64)	967 (42.39)	544 (37.86)	
≥ 5	2207 (59.36)	1314 (57.61)	893 (62.14)	
Median (IQR)	5 (4–6)	5 (4–6)	5 (4–6)	
Tumor location				< 0.001
Upper	347 (9.33)	117 (5.13)	230 (16.01)	
Middle	2199 (59.14)	1130 (49.54)	1069 (74.39)	
Lower	1172 (31.52)	1034 (45.33)	138 (9.60)	
Grade				< 0.001
Well	701 (18.85)	387 (16.97)	314 (21.85)	
Moderate	2101 (56.51)	1231 (53.97)	870 (60.54)	
Poor	916 (24.64)	663 (29.07)	253 (17.61)	
LVSI	520 (13.99)	325 (14.25)	195 (13.57)	0.562
Removed lymph nodes				< 0.001
< 16	674 (18.13)	549 (24.07)	125 (8.70)	
≥ 16	3044 (81.87)	1732 (75.93)	1312 (91.30)	
Median (IQR)	23 (17–30)	22 (16–30)	24 (19–31)	
T stage				< 0.001
T1	107 (2.88)	89 (3.90)	18 (1.25)	
T2	738 (19.85)	449 (19.68)	289 (20.11)	
T3	2655 (71.41)	1644 (72.07)	1011 (70.35)	
T4a	218 (5.86)	99 (4.34)	119 (8.28)	
N stage				< 0.001
N0	1678 (45.13)	1085 (47.57)	593 (41.27)	
N1	1129 (30.37)	691 (30.29)	438 (30.48)	
N2	668 (17.97)	376 (16.48)	292 (20.32)	
N3	243 (6.54)	129 (5.66)	114 (7.93)	
Stage (AJCC 7th)				< 0.001
1B	136 (3.66)	117 (5.13)	19 (1.32)	
2A	658 (17.70)	454 (19.90)	204 (14.20)	
2B	1126 (30.29)	684 (29.99)	442 (30.76)	
3A	902 (24.26)	539 (23.63)	363 (25.26)	
3B	503 (13.53)	282 (12.36)	221 (15.38)	
3C	393 (10.57)	205 (8.99)	188 (13.08)	
Stage (AJCC 8th)				< 0.001
1B	98 (2.64)	54 (2.37)	44 (3.06)	
2A	938 (25.23)	659 (28.89)	279 (19.42)	
2B	687 (18.48)	436 (19.11)	251 (17.47)	
3A	216 (5.81)	120 (5.26)	96 (6.68)	
3B	1466 (39.43)	849 (37.22)	617 (42.94)	

TABLE 1 continued

Characteristics	All patients (n = 3718) n (%)	Training cohort (n = 2281) n (%)	Validation cohort (n = 1437) n (%)	p value
4A	313 (8.42)	163 (7.15)	150 (10.44)	
Treatment method				< 0.001
Surgery alone	2562 (68.91)	1536 (67.34)	1026 (71.40)	
Adjuvant radiation	874 (23.51)	463 (20.30)	411 (28.60)	
Adjuvant chemoradiation	217 (5.84)	217 (9.51)	0	
Adjuvant chemotherapy	65 (1.75)	65 (2.85)	0	

IQR interquartile range, *LVSI* lymphovascular invasion, *AJCC* American Joint Committee on Cancer

5-year OS rate decreased significantly as the score increased as follows: respectively 75.58%, 62.61%, 46.16%, 34.12%, 19.41%, and 8.73% in the training cohort ($p < 0.05$ between each two score groups, Fig. S2A) and respectively 87.26%, 69.62%, 54.44%, 37.20%, 23.98%, and 11.88% in the validation cohort ($p < 0.05$ between each two score groups, Fig. S2B).

The 7th AJCC staging system could not separate 2A and 1B (HR, 1.19; 95% CI 0.83–1.71; p = 0.352) or 3C and 3B (HR, 1.08; 95% CI 0.87–1.32; p = 0.496) in the training cohort (Fig. S2C), nor 2A and 1B (HR, 0.62; 95% CI 0.27–1.45; p = 0.271), 2B and 1B (HR, 0.85; 95% CI 0.38–1.92; p = 0.694), 3A and 1B (HR, 1.77; 95% CI 0.79–3.98; p = 0.168), or 3C and 3B (HR, 1.23; 95% CI 0.99–1.53; p = 0.067) in the validation cohort (Fig. S2D).

The 8th AJCC staging system could not separate 3A and 2B (HR, 1.23; 95% CI 0.92–1.63; p = 0.158) in the training cohort (Fig. S2E) nor 2A and 1B (HR, 1.49; 95% CI 0.72–3.10; p = 0.286) or 3A and 2B (HR, 1.42; 95% CI 0.99–2.03; p = 0.056) in the validation cohort (Fig. S2F).

Defined Subgroups Benefited From Adjuvant Therapy

According to the nomogram, a specific predicted 5-year OS rate was assigned for each total score. The treatment method was the only factor that could be determined by clinicians or patients. We assumed that patients underwent surgery alone (which meant the total score started from 34), and then plotted a curve showing the increase in the 5-year OS rate from reception of adjuvant therapy corresponding to each total score (Fig. 3). The patients with a total score ranging from 72 to 227 were estimated to achieve a 5-year OS rate increase of at least 10% from adjuvant therapy.

DISCUSSION

Our study developed a nomogram to estimate the probability of OS for patients with T1N +/T2-4aN0-3, M0 esophageal squamous cell carcinoma who received radical esophagectomy with or without adjuvant therapy. The nomogram showed high prognostic efficacy and good reproducibility when validated using an external cohort. The nomogram showed a better performance in both the training and validation cohorts than the AJCC staging system. The nomogram could divide patients into six different groups based on accumulated risk scores. As the score increased, the patients were predicted to have a significantly worse OS. By contrast, the AJCC staging system could not completely separate all the subgroups. A total nomogram score of 72 to 227 indicated an increased benefit from adjuvant therapy. The nomogram provided a possible criterion for evaluating the prognosis of patients with esophageal carcinoma who received radical esophagectomy as their first treatment.

Despite the lack of consensus on adjuvant therapy after radical esophagectomy, evidence indicated that more than 50% of the patients experienced recurrence after surgery, and the median time to recurrence was within 2 years.[10–12] A locoregional recurrence rate as high as 35.7% to 41.8% accounted for the major failure pattern in esophageal cancer.[12–14] Moreover, the probability of systemic metastasis was approximately 14% to 19.8%,[11,15] which increased according to the numbers of positive lymph nodes.[16]

Studies investigating adjuvant radiation or chemotherapy for esophageal carcinoma reported promising results. Retrospective data indicated that adjuvant radiation improved the median survival time by 4 to 6 months and the 3-year OS rate by 2.9% to 3.3%.[17–19] In a prospective trial of 495 patients, adjuvant radiation significantly improved the 5-year OS rate by 22% for stage 3 patients. Notably, although it did not reach statistical significance, a potential 3-year OS benefit of 8% was observed for stage 2A disease.[20]

In a recent propensity score-matched study, adjuvant radiation demonstrated its survival benefits for patients with T3N0 esophageal carcinoma, increasing the OS rate from 58.8 to 75.7% after matching.[21] For adjuvant chemotherapy, improved survival outcomes also have been observed.[22–24] However, the value of adjuvant therapy after radical surgery is not well recognized, partly because of

TABLE 2 Multivariable analysis of clinical factors associated with overall survival in the training cohort

Characteristics	Multivariable analysis		
	HR	95% CI	*p* Value
Sex			
Female	Ref		
Male	1.34	1.15–1.57	< 0.001
Tumor location			
Lower	Ref		
Middle	1.22	1.08–1.37	0.001
Upper	1.56	1.21–2.01	0.001
Grade			
Well	Ref		
Moderate	1.10	0.93–1.30	0.277
Poor	1.36	1.13–1.63	0.001
LVSI			
None	Ref		
Present	1.27	1.08–1.48	0.003
Removed lymph nodes			
≥ 16	Ref		
< 16	1.29	1.13–1.47	< 0.001
T			
T1	Ref		
T2	1.27	0.91–1.76	0.157
T3	1.76	1.30–2.38	< 0.001
T4a	1.96	1.34–2.87	0.001
N			
N0	Ref		
N1	2.21	1.91–2.56	< 0.001
N2	3.07	2.58–3.64	< 0.001
N3	4.55	3.58–5.77	< 0.001
Treatment method			
Adjuvant therapy	Ref		
Surgery alone	1.67	1.50–1.90	< 0.001

HR hazard ratio, *CI* confidence interval, *LVSI* lymphovascular invasion

small sample sizes or lack of validation. According to our nomogram developed from 2281 patients, adjuvant therapy was identified as a protective treatment compared with surgery alone. The role of adjuvant therapy should be taken into consideration in future clinical practice.

Sex was reported to be an independent survival predictor for patients with esophageal cancer.[25,26] An analysis of 26,848 patients with locoregional esophageal cancer in the Surveillance, Epidemiology, and End Results (SEER) database showed that women had a 4% longer 5-year esophageal cancer-specific survival than men, especially in squamous cell carcinoma.[27]

A previous study indicated that lower esophageal cancer tends to have better survival outcomes.[28] The analysis of worldwide esophageal cancer collaboration (WECC) found that OS increased together with a more distal location of the tumor.[29] Tumor differentiation grade was incorporated into a staging system by Dickson et al.[30] decades ago. Based on their research, 3-year OS rates decreased from well-differentiated (33.3%) to moderately differentiated (28.9%), and finally to poorly differentiated tumors (15.9%). Survival disparities among different tumor grades also were observed in node-negative patients.[31,32]

Lymphovascular invasion (LVSI), considered to increase the risk of micrometastasis, is associated with unfavorable survival outcomes in various cancer types.[33,34] In esophageal cancer, LVSI is related to aggressive pathologic characteristics, such as close circumferential resection margin, poor tumor invasion, and greater depth of invasion, or increased involvement of node metastasis.[35,36] In addition, LVSI has been identified as an independent adverse prognostic factor for OS, disease-free survival (DFS), and disease-specific survival (DSS).[36–38] Based on the SEER database, Groth et al.[39] found that patients who had more than 12 lymph nodes examined showed significantly improved survival, especially those who had more than 30 lymph nodes examined. A WECC report indicated that a greater extent of lymphadenectomy was associated with increased survival for patients with pN0M0 moderately or poorly differentiated and pN + cancer.[40]

Besides T and N categories, six clinicopathologic factors were added in our nomogram. The nomogram showed favorable stratification for survival. Compared with the AJCC staging system, it distinguished between lower-risk groups (< 70 vs 70–119) and higher-risk groups (170–199 vs > 200). Meanwhile, AJCC could not separate between 1B and 2A, 3B and 3C, or 3A and 2B.

The nomogram also served as a reference for treatment strategy. From the visualized plot, it was convenient to predict OS rate according to the clinicopathologic features of a specific patient. We even presented a plot showing 5-year OS benefits from adjuvant therapy corresponding to the nomogram total score. Patients with a total score of 72 to 227 were estimated to achieve an increase in their 5-year OS rate of at least 10%. Those who had a total score below 72 (too low risk) or higher than 227 (too high risk) benefited less from adjuvant therapy.

Nomograms predicting survival outcomes for patients with esophageal cancer after radical esophagectomy have been reported.[41,42] Compared with these studies, we used a larger sample with independent external validation, resulting in desirable generalization of the nomogram in different populations. We also included patients who received adjuvant therapy, which allowed the direct comparison of survival benefits from adjuvant therapy.

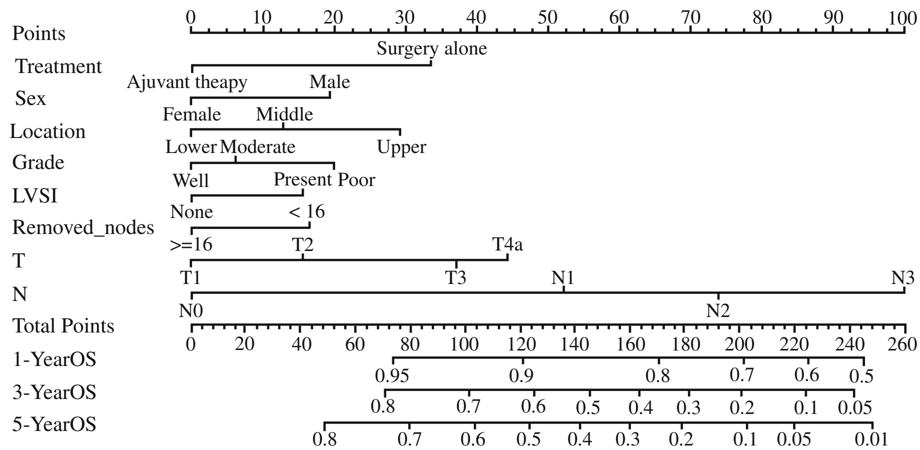

FIG. 1 Nomogram for overall survival developed from the training cohort

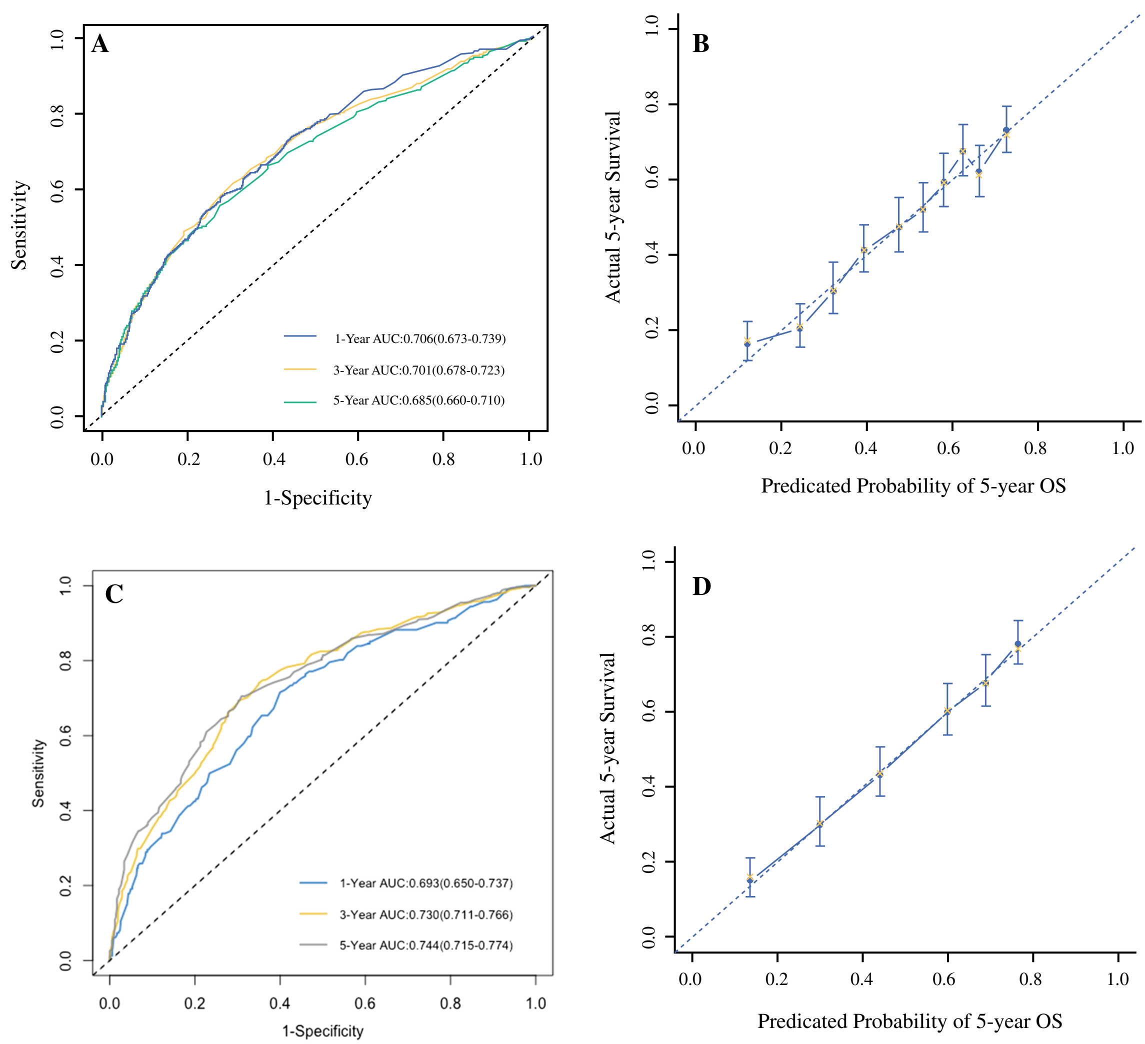

FIG. 2 **a** Receiver operating characteristic (ROC) curves for 1-, 3-, and 5-year overall survival (OS) according to the nomogram for the training cohort: area under curve (AUC): *blue line* (1-year OS ROC curve), *yellow line* (3-year OS ROC curve), *gray line* (5-year OS ROC curve). **b** Calibration plot for 5-year OS prediction according to the nomogram for the training cohort. **c** ROC curves for 1-, 3-, and 5-year OS according to the nomogram for the validation cohort: AUC: *blue line* (1-year OS ROC curve), *yellow line* (3-year OS ROC curve), *gray line* (5-year OS ROC curve). **d** Calibration plot for 5-year OS prediction according to the nomogram for the validation cohort

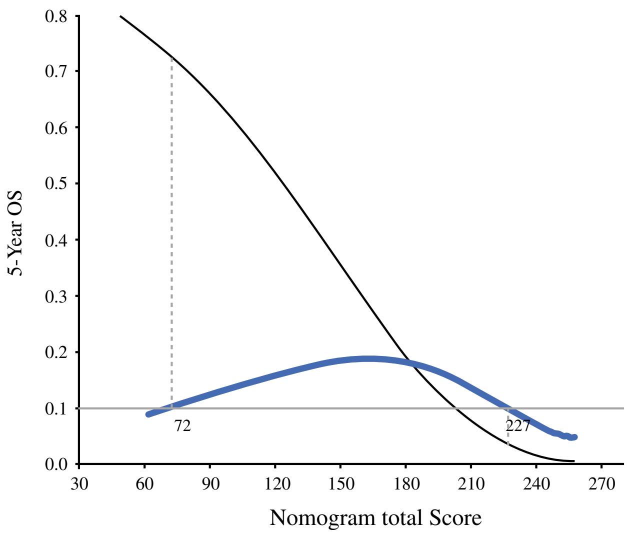

FIG. 3 The 5-year overall survival (OS) rate increase from adjuvant therapy corresponding to the nomogram total score [*purple line* (5-year OS rate increase from adjuvant therapy corresponding to the nomogram total score), *black line* (5-year OS rate corresponding to nomogram total score)]

Our model also had several limitations. First, it was established using a retrospective database, and treatment bias was unavoidable in this study population. Patients with more advanced disease tended to have more lymph nodes removed or to receive adjuvant therapy. However, we used an independent validation cohort from an external institution to validate the nomogram, and both cohorts showed better AUC values than the AJCC staging system. Second, the prognostic factors we included were restricted to common characteristics, and potential features of radiomics or biomarkers could be considered in combination.

In conclusion, we have developed and validated a nomogram to predict OS for patients with esophageal squamous cell carcinoma after esophagectomy with favorable prognostic accuracy and efficacy. The nomogram showed better risk stratification ability than the AJCC staging system. The nomogram is a reliable tool for clinical decision making, but further validation is required to determine whether it could be applied to broader populations.

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