Original Article

Establishment of a prognostic nomogram for evaluating non-adjuvant therapy in patients with stage I to III esophageal cancer: a population-based study

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Background: According to reports from China, esophageal cancer ranked sixth in terms of morbidity and accounted for 6.26% of all cancer cases in China. This study aimed to establish an effective prognostic nomogram for non-adjuvant therapy in patients with stage I to III esophageal cancer.

Methods: We took up cases from 2010 to 2015 from the Surveillance, Epidemiology, and End Results (SEER) database and used R language software to perform Kaplan-Meier survival curve and multivariate Cox regression analysis. Furthermore, we established the nomogram for non-adjuvant therapy patients with stage I to III esophageal cancer to predict 3- and 5-year esophageal cancer-specific survival rate. The prognostic ability of the nomogram was assessed using the C-index, area under the receiver operating characteristic (ROC) curve, and calibration chart.

Results: The esophageal cancer-specific survival rate of cancer in the lower third of the esophagus was significantly higher than that of cancers in the upper-third of the esophagus as per the Kaplan-Meier curve. Based on the multivariate Cox regression analysis, sub variables such as advanced age, stage II and III, squamous cell carcinoma, moderately differentiated (grade II), poorly differentiated (grade III), and undifferentiated (grade IV) cancer significantly increased risk of prognosis in all patients. With a total of 150 points in the nomogram, the 3- and 5-year esophageal cancer-specific survival rates were 50% and 40% respectively. The value of C-index of this model was 0.851 and the value of the area under receiver operating curve projected 1-, 3-, and 5-year esophageal cancer-specific survival rates of 0.884, 0.874, and 0.856, respectively.

Conclusions: The established nomogram had good prediction ability for non-adjuvant therapy patients with stage I to III esophageal cancer.

Keywords: Esophageal cancer; independent prognostic factors; survival analysis; surgical management; Surveillance, Epidemiology, and End Results database (SEER database)

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Introduction

According to reports from China (1), in 2015, esophageal cancer ranked sixth in terms of morbidity, and accounted for 6.26% of all cancer cases in China. Similarly, esophageal cancer ranked fourth in terms of mortality, and accounted for 8.04% of all cancer cases in China. Squamous cell carcinoma is the most common pathological subtype of esophageal cancer globally, although adenocarcinoma remains the most prevalent in Western countries (2,3). The distinction may be related to dietary habits and gastrointestinal disorders—eating hot food and drinking and smoking could be related to squamous cell carcinoma, while obesity and gastrointestinal disorders could be related to adenocarcinoma (4,5). The purpose of this study was to define significant risk factors and to establish an effective nomogram to predict the 3- and 5-year esophageal cancer-specific survival (ECSS) rates for non-adjuvant therapy in patients with stage I to III esophageal cancer. We present this article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1377/rc).

Methods

We screened patients with stage I to III esophageal cancer who had received non-adjuvant therapy, from the Surveillance, Epidemiology, and End Results (SEER) database by SEER*Stat software (8.3.9). The selected patients fulfilled the inclusion and exclusion criteria, and the detailed process is shown in *Figure 1*. The inclusion criteria included: disease diagnosis from 2010–2015, cancer prevalence in the upper, middle, or lower segment of the esophagus, adenocarcinoma or squamous cell carcinoma, stage I to III, without adjuvant therapy, patients still living or dead due to esophageal cancer. The exclusion criteria included: value of variables or sub-variables were unknown or blank, stage III not otherwise specified (NOS), surgery codes were 90 or 99, survival time ≤1 month. Variables such as age, sex, race, subtype, primary site, stage, diagnosis year, differentiation, and treatment method of selected patients were included. Before the statistical analysis, we divided each variable into several sub-variables according to the purpose of study, where each sub-variable was a potential independent prognostic factor that could be defined for esophageal cancer.

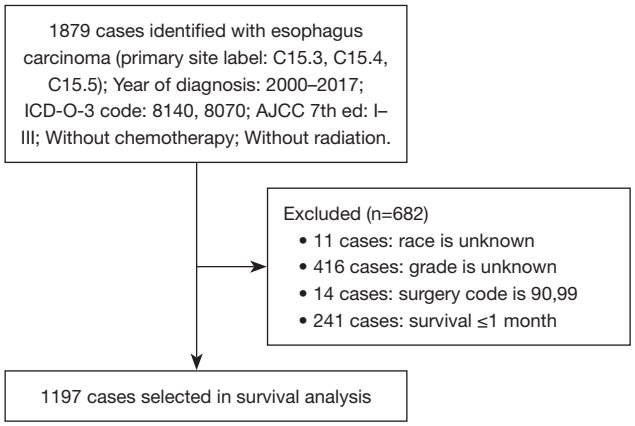

Figure 1 Primary site label C15.3, C15.4, and C15.5 represent the esophagus neoplasm. ICD-O-3 code 8140 and 8070 represent adenocarcinoma and squamous cell carcinoma, respectively. AJCC 7th ed: I–III means esophagus cancer stage I to III. Surgery code 90, 99 means the type of operation is not clear or unknown if surgery performed. AJCC, American Joint Committee on Cancer.

Highlight box

Key findings

- The nomogram established in this study had good prediction ability for non-adjuvant therapy patients with stage I to III esophageal cancer.

What is known and what is new?

- Esophageal cancer ranked sixth in terms of morbidity and accounted for 6.26% of all cancer cases in China.
- An effective prognostic nomogram has been established for non-adjuvant therapy in patients with stage I to III esophageal cancer.

What is the implication, and what should change now?

- The nomogram established using several clinical variables has good prognostic ability for non-adjuvant therapy patients with stage I to III esophageal cancer.

Statistical analysis

All variables and sub-variables were included in the statistical analysis conducted using R software (R i386 4.0.5). In our study, survival time was the interval between diagnosis of esophageal cancer and patient being alive, missing, or death due to esophageal cancer, which is referred to as ECSS. The Kaplan-Meier survival curve was used to perform univariate analysis, and log-rank test value was used to determine the significance of difference between sub-variables. In the Kaplan-Meier survival curve,

Table 1 Basic information of all patients

Variables	N (%)
Age, years	
<50	60 (5.0)
50–59	200 (16.7)
60–69	411 (34.3)
70–79	312 (26.1)
≥80	214 (17.9)
Sex	
Male	935 (78.1)
Female	262 (21.9)
Race	
White	1,069 (89.3)
Black	77 (6.4)
Other	51 (4.3)
Subtype	
Adenocarcinoma	922 (77.0)
Squamous cell carcinoma	275 (23.0)
Location	
Upper third of esophagus	48 (4.0)
Middle third of esophagus	204 (17.0)
Lower third of esophagus	945 (78.9)
Stage	
I	875 (73.1)
II	161 (13.5)
III	161 (13.5)
Diagnosis of year	
2010	206 (17.2)
2011	188 (15.7)
2012	193 (16.1)
2013	193 (16.1)
2014	200 (16.7)
2015	217 (18.1)
Grade	
I	221 (18.5)
II	610 (51.0)
III	356 (29.7)
IV	10 (0.8)
Treatment	
No surgery	348 (29.1)
Endoscopic therapy	296 (24.7)
Partial esophagectomy	90 (7.5)
Total esophagectomy	53 (4.4)
Combined operation	392 (32.7)
Esophagectomy	18 (1.5)

the lateral axis represents survival months of ECSS, and the vertical axis represents corresponding survival rate. The variable was viewed as a possible risk factor for esophageal cancer when $P<0.05$. Based on the results of the univariate analysis, all potential risk factors were included in the multivariate Cox regression analysis. The multivariate Cox regression analysis was used to define the independent prognostic sub-variables and eliminate variable interaction. The independent prognostic sub-variables were somewhat significantly impacted in ECSS compared with the basic sub-variables. Hazard ratios (HR) and 95% confidence interval (CI) were also calculated using multivariate Cox regression analysis. The nomogram was formulated based on multivariate analysis. The established model predicted 3- or 5-year ECSS rates using a series of scored sub-variables for stage I to III esophageal cancer patients without adjuvant therapy. The C-index and area under the receiving operating characteristic curve were used to assess the prediction ability of the nomogram. Calibration was used to distinguish between the predicted survival rate and actual survival rate. Finally, we randomly divided all patients into the modeling group and validation group in a 7:3 ratio, to evaluate the accuracy of the nomogram. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Clinical characteristics

A total of 1,197 non-adjuvant therapy cases from the SEER database were included based on the inclusion and exclusion criteria. The clinical information of all patients is displayed in *Table 1*.

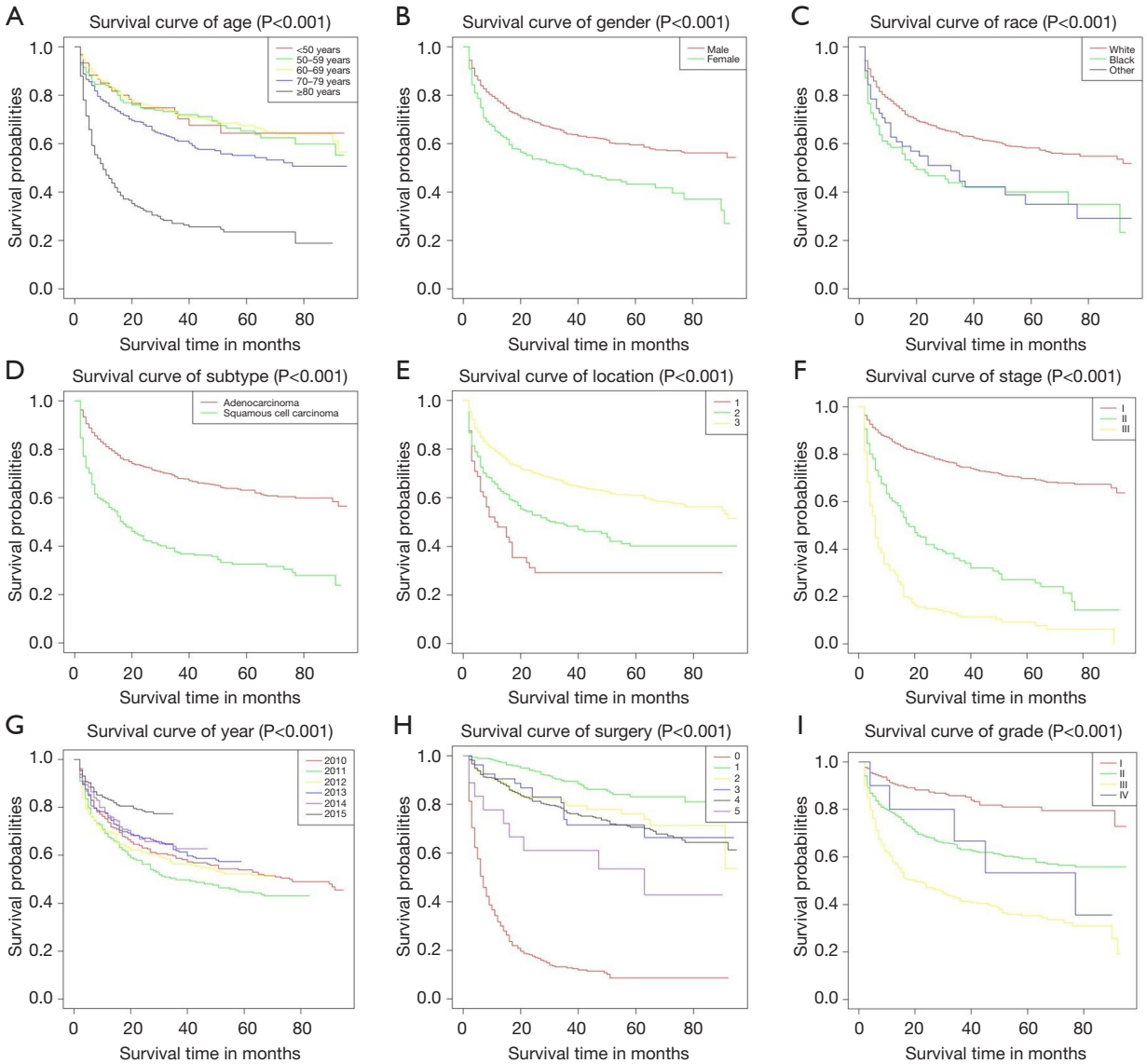

Figure 2 The Kaplan-Meier curve of nine variables (A-I). In (E), 1, 2, and 3 represent cancer in the upper, middle, and lower segment of the esophagus, respectively. In (H), code 0 represents no surgical therapy, and other codes are different surgical therapy methods. 1, 2, 3, 4, 5 represent endoscopic therapy, partial esophagectomy, total esophagectomy, combined operation, and esophagectomy, respectively.

Kaplan-Meier analysis

After the primary statistical analysis, all variables were included in the Kaplan-Meier curve to conduct the univariate analysis. All sub-variables depicted in the Kaplan-Meier curve were significantly different from each other, and the value of the log-rank test was less than 0.05. The outcome of the Kaplan-Meier curve illustrated that every sub-variable was a potential impact factor for esophageal cancer prognosis. Patients aged 70–79 or ≥80 years had lower long-term survival probabilities than patients of other age groups, based on the Kaplan-Meier curve (*Figure 2A*). The 3- and 5-year ECSS rates were 71.6% and 66.7% in patients aged <70 years, and 47.2% and 41.8% in patients aged ≥70 years, respectively. The mean ECSS was 68.1 and 47.0 months for patients aged <70 and ≥70 years, respectively. Male patients had a significantly longer ECSS than female patients in terms of both, short and long-term survival (*Figure 2B*). The 3- and 5-year ECSS rates were 63.9% and 59.5% in male patients and 50.3% and 43.2%

in female patients, respectively, and the mean ECSS was 62.0 and 46.8 months for males and females, respectively. Caucasians had a longer ECSS compared to Black or people of other races in long-term survival, as illustrated in the Kaplan-Meier curve, whereas the survival distinction was not obvious between Black and people of other races (*Figure 2C*). The mean ECSS were 60.8, 42.5, and 43.3 months for Caucasian, Black, and people of other races, respectively. Patients with confirmed adenocarcinoma had higher survival probabilities than patients with confirmed squamous cell carcinoma (*Figure 2D*). The 3- and 5-year ECSS rates were 68.0% and 63.1% in patients with adenocarcinoma and 37.3% and 32.6% in patients with squamous cell carcinoma, respectively. The mean ECSS was 65.1 and 37.6 months for patients with confirmed adenocarcinoma or squamous cell carcinoma, respectively. Patients with cancer in the lower segment of the esophagus had higher survival probabilities than patients with cancer in the upper or middle segment of the esophagus in terms of long-term survival (*Figure 2E*). The 3- and 5-year ECSS rates were 29.2% and 29.2% in the upper segment, 48.3% and 40.2% in the middle segment, and 65.3% and 60.9% in the lower segment, respectively. The mean ECSS rates were 32.3, 47.2, and 62.7 months in patients with esophageal cancer in the upper, middle, and lower segments, respectively. The prognosis of patients with stage I to III followed the staging prescribed in the American Joint Committee on Cancer Staging System (*Figure 2F*). The 3- and 5-year ECSS rates were 74.7% and 69.8% in patients with stage I, 35.1% and 25.6% in patients with stage II, and 11.4% and 7.8% in patients with stage III, respectively. The mean ECSS rates were 71.2, 33.9, and 15.6 months for patients with stage I, stage II, and stage III, respectively. As for the year of diagnosis, the value of the log-rank test was significantly different between all sub-variables, however, the Kaplan-Meier curve did not depict obvious differences between sub-variables (*Figure 2G*). Patients who had surgery had a significantly longer ECSS than those who did not have surgery ($P<0.05$). The mean ECSS rates were 75.8 and 17.1 months for patients who had or did not have surgery. Patients who underwent an esophagectomy or did not have a surgery had the poorest survival probabilities as per the Kaplan-Meier curve, while conversely, patients who underwent endoscopic therapy had the best prognosis (*Figure 2H*). The mean ECSS rates were 82.0 months for patients who had undergone endoscopic therapy. The 3- and 5-year ECSS rates were 89.5% and 83.2% for patients who had undergone endoscopic therapy, respectively. The mean ECSS rates were 72.4 months for patients who had undergone partial, total or combination surgery. The 3- and 5-year ECSS rates were 76.5% and 71.6% for patients who had undergone partial, total or combination surgery, respectively. The mean ECSS rates were 52.5 months for patients who had undergone esophagectomy. The 3- and 5-year ECSS rates were 53.5% and 42.8% for patients who had undergone esophagectomy, respectively. There were no significant differences in patients with partial, total esophagectomy, or combination surgery as per the Kaplan-Meier curve. The prognosis gradually became poorer in patients with esophageal cancer from grade I to III (*Figure 2I*). Based on the results of the Kaplan-Meier curve, all variables were included in the multivariate Cox multiple regression analysis.

Multivariate Cox regression analysis and nomogram

Multivariate Cox regression analysis was used to compare every sub-variable with baseline sub-variables to discover independent prognostic factors. Different from the results of the Kaplan-Meier analysis, only advanced age (≥80 years), stage II or III, squamous cell carcinoma, late diagnosis, surgical therapy, grade II, III, or IV were independent prognostic factors for non-adjuvant therapy patients with stage I to III esophageal cancer (*Table 2*). Sub-variables such as advanced age, stage II or III, squamous cell carcinoma and grade II, III, or IV were poor prognostic factors for non-adjuvant therapy patients with stage I to III esophageal cancer, whereas patients who underwent various surgeries or had late diagnosis had good prognosis. The nomogram was established based on the results of the multivariate Cox regression analysis (*Figure 3*). The nomogram revealed that sub-variables such as non-surgery, grade IV, stage III were the most influential factors for non-adjuvant therapy patients with esophageal cancer stage I–III. The effects of some independent factors including squamous cell carcinoma were the same as with non-independent factors including patients aged 70–79 years in esophageal cancer prognosis. The estimated 3- and 5-year ECSS rates were 50% and 40%, respectively when they received 150 points in the nomogram. Compared with endoscopic therapy, partial, total or combination surgeries have similar moderate risk scores. The risks of non-surgical treatment and esophagectomy are the highest, with the former being approximately 1.5 times higher than the latter, approximately 100 points.

Table 2 Cox multivariate regression analysis results

Variable	HR (95% CI)	P value
Age, years		
<50	Reference	
50–59	0.99 (0.59–1.65)	0.96
60–69	0.91 (0.56–1.48)	0.70
70–79	1.31 (0.81–2.13)	0.28
≥80	1.90 (1.16–3.08)	<0.001
Sex		
Male	Reference	
Female	1.10 (0.88–1.36)	0.40
Race		
White	Reference	
Black	1.09 (0.79–1.51)	0.60
Other	1.18 (0.81–1.73)	0.38
Subtype		
Adenocarcinoma	Reference	
Squamous cell carcinoma	1.47 (1.14–1.88)	0.003
Location		
Upper third of esophagus	Reference	
Middle third of esophagus	0.79 (0.53–1.19)	0.26
Lower third of esophagus	0.77 (0.51–1.15)	0.20
Stage		
I	Reference	
II	1.93 (1.52–2.47)	<0.001
III	2.65 (2.10–3.34)	<0.001
Diagnosis of year		
2010	Reference	
2011	1.00 (0.76–1.33)	0.99
2012	0.89 (0.66–1.18)	0.41
2013	0.95 (0.70–1.28)	0.73
2014	0.82 (0.60–1.11)	0.19
2015	0.46 (0.32–0.66)	<0.001
Grade		
I	Reference	
II	2.30 (1.64–3.24)	<0.001
III	2.69 (1.89–3.82)	<0.001
IV	4.48 (1.73–11.63)	0.002
Treatment		
No surgery	Reference	
Endoscopic therapy	0.11 (0.07–0.15)	<0.001
Partial esophagectomy	0.15 (0.10–0.24)	<0.001
Total esophagectomy	0.21 (0.13–0.37)	<0.001
Combined operation	0.18 (0.14–0.23)	<0.001
Esophagectomy	0.48 (0.24–0.95)	<0.04

CI, confidence interval; HR, hazard ratio.

Assessment of model ability

The value of C-index of this model was 0.851 (95% CI: 0.837–0.865), which indicated middle levels for predicting prognosis of esophageal cancer. The area under curve (AUC) values of the receiver operating characteristic (ROC) curve were 0.884, 0.874, and 0.856 for the projected 1-, 3- and 5-year ECSS rates, respectively (*Figure 4A-4C*). The calibration curve for the probability of 1-, 3- and 5-year ECSS rates showed an optimal agreement between prediction by nomogram and actual observations (*Figure 5A-5C*). All patients were randomly divided into the modeling group and validation group in a 7:3 ratio. The modeling group and validation group were used to establish two series of clinical prognostic models for esophageal cancer to validate the accuracy of the primary nomogram. The values of C-index were 0.846 (95% CI: 0.828–0.864) and 0.880 (95% CI: 0.856–0.904) in the modeling group and validation group, respectively. The AUC values of 1-, 3- and 5-year ECSS rates were 0.870, 0.864, and 0.848 in the modeling group (*Figure 4D-4F*), and 0.921, 0.899, and 0.878 in the validation group (*Figure 4G-4I*), respectively. The calibration curve for the probability of 1-, 3- and 5-year ECSS rates showed an optimal agreement between prediction by nomogram and actual observations both in the modeling group (*Figure 5D-5F*) and the validation group (*Figure 5G-5I*). The primary nomogram had good prognostic ability for non-adjuvant therapy patients with stage I to III esophageal cancer.

Discussion

Globally, the morbidity and mortality of esophageal cancer are two to three higher for males compared to females,

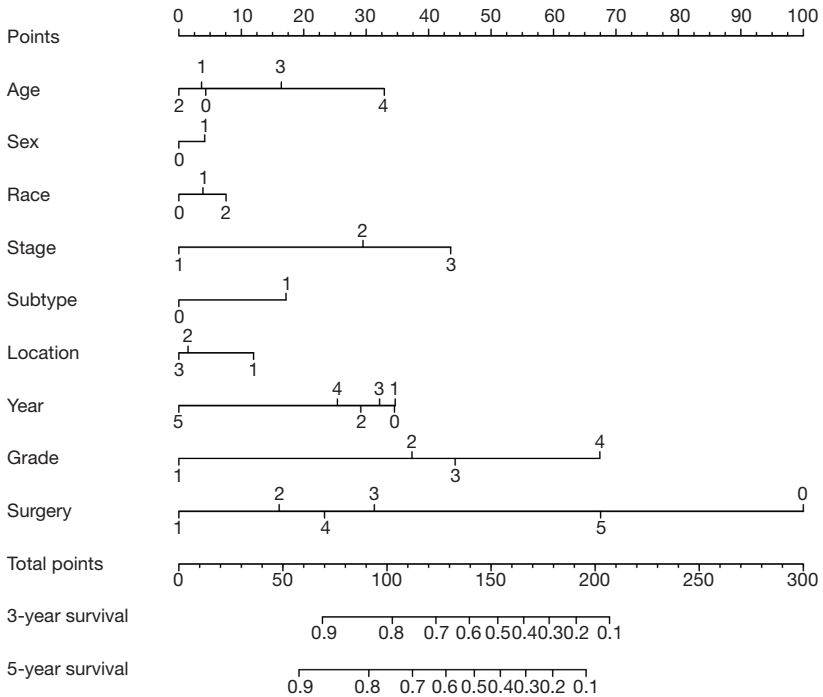

Figure 3 The upper number axis represents the scores of each sub variable and the lower axis represents total scores, which also corresponds to 3- and 5-year survival probability. In the age variable, the numbers represent <50, 50–59, 60–69, 70–79, and ≥80 years. In the sex variable, 0 represents male and 1 represents female. In the race variable, the numbers represent Caucasian, Black, and others sequentially. In the subtype variable, 0 and 1 represent adenocarcinoma and squamous cell carcinoma, respectively. In the location variable, code 1, 2, and 3 represent cancer in the upper, middle, and lower segment of the esophagus, respectively. In the year variable, the numbers sequentially represent 2010 to 2015. In the surgery variable, the numbers sequentially represent no surgery, endoscopic therapy, partial esophagectomy, total esophagectomy, combined operation, and esophagectomy.

and 70% of patients with esophageal cancer are male (6). Male patients had nine times higher morbidity and significantly shorter survival time than female patients (7). Qiu *et al.* proposed that there was a higher incidence of esophageal cancer in males in the United States, however, the gender was not a risk factor for patients with esophageal cancer (8). The difference in incidence between males and females is related to the etiology of esophageal cancer (4,5). Some scholars believe that old age is a high risk of poor prognosis for patients with esophageal cancer (7,8). The results of this study demonstrated that patients with advanced age had significantly poorer prognosis than patients aged ≤50 years (P<0.05). The development of social economy has significantly influenced the prognosis of advanced age patients with esophageal cancer (7,8). With improvement in social economy, ECSS has improved (9). Some scholars believe that the prognosis of esophageal cancer is poor in Black people when compared with other races (10,11). Most scholars believe that the primary site of esophageal cancer is not significantly related to survival time (8,12). Chen *et al.* proposed that the survival distinction of different esophageal segments was significant in univariate analysis, but not so in multivariate regression analysis (13). The prognosis of esophageal cancer gradually became worse from the lower to the upper segment as illustrated by the Kaplan-Meier curve, and the distinction of ECSS was significant between each esophageal segment (P<0.05). Excluding treatment methods, the multivariate regression analysis indicated that the ECSS distinction of each esophageal segment was significant (P<0.05). Another multivariate regression analysis that established endoscopic therapy as baseline sub-variables, showed that all treatment modalities except partial esophagectomy were significantly different from endoscopic therapy (P<0.05). As for tumor cell subtype, Qiu *et al.* believed that only patients with stage I esophageal adenocarcinoma

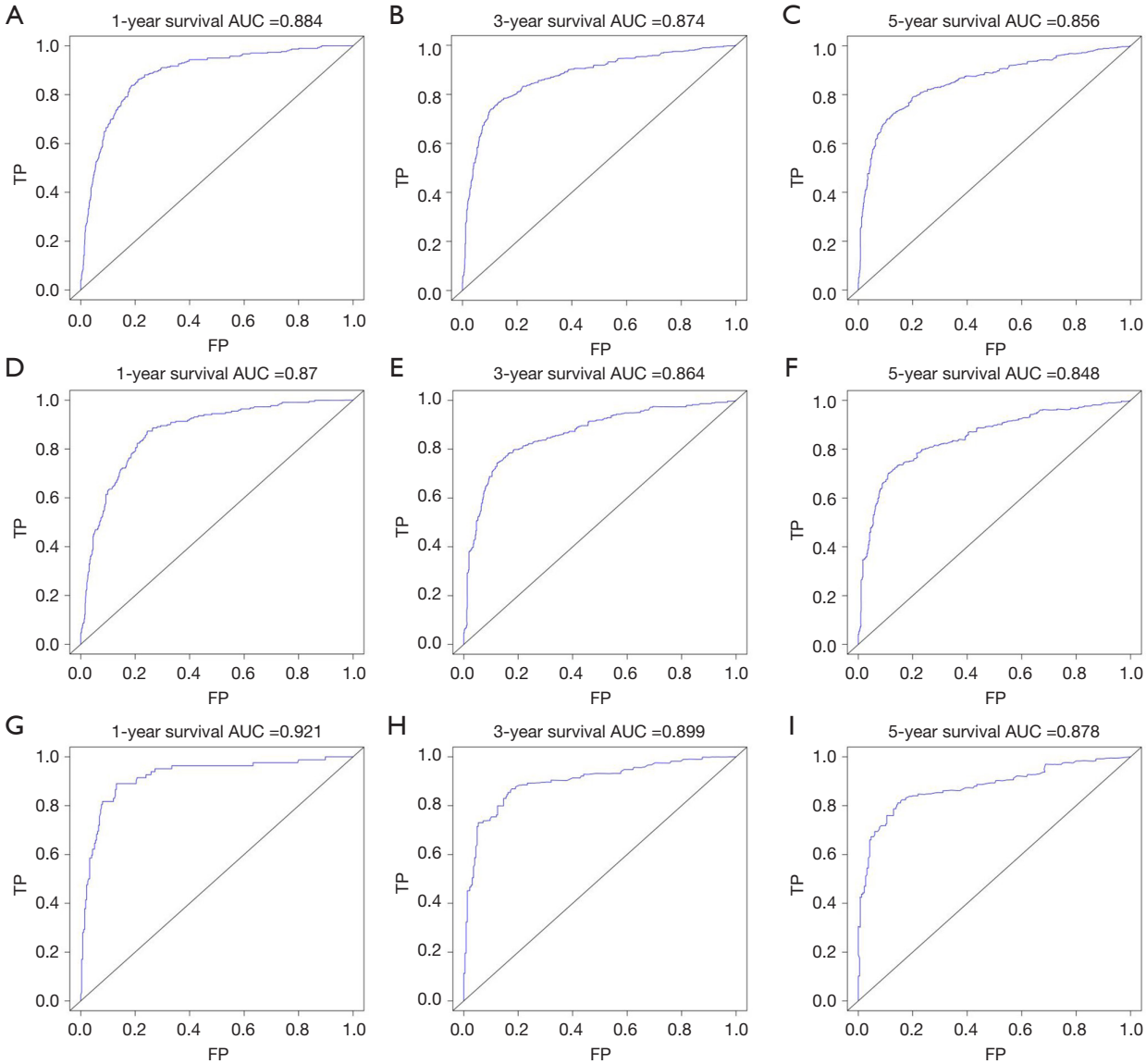

Figure 4 The ROC curves for the three prognostic models used to predict 1-, 3- and 5-year survival rates. (A-C) Primary prognostic model (all patients). (D-F) Modeling group. (G-I) Validation group. AUC, area under curve; FP, false positive; ROC, receiver operating characteristic; TP, true positive.

had significantly better prognosis than patients with stage I esophageal squamous cell carcinoma, but this was not seen in patients with stage II or III esophageal cancer (8). Gertler *et al.* believed that the prognosis of patients with esophageal adenocarcinoma is significantly better than patients with esophageal squamous cell carcinoma (12), which is consistent with the results of our study. The results of the established nomogram illustrated that patients with esophageal squamous cell carcinoma had nearly the same ECSS as patients aged between 70–79 years. Within the past decade, phase III trials investigating the curative potential of chemotherapy alone have challenged the idea that surgery is an indispensable part of curative therapy (14-16). The team of Qiu and Chen believe that surgical therapy is the main curative therapy for patients with esophageal cancer (7,8). Similarly, the prognosis of patients with surgery was significantly better than those without surgery in our study (P<0.05). Martin-Richard *et al.* believed

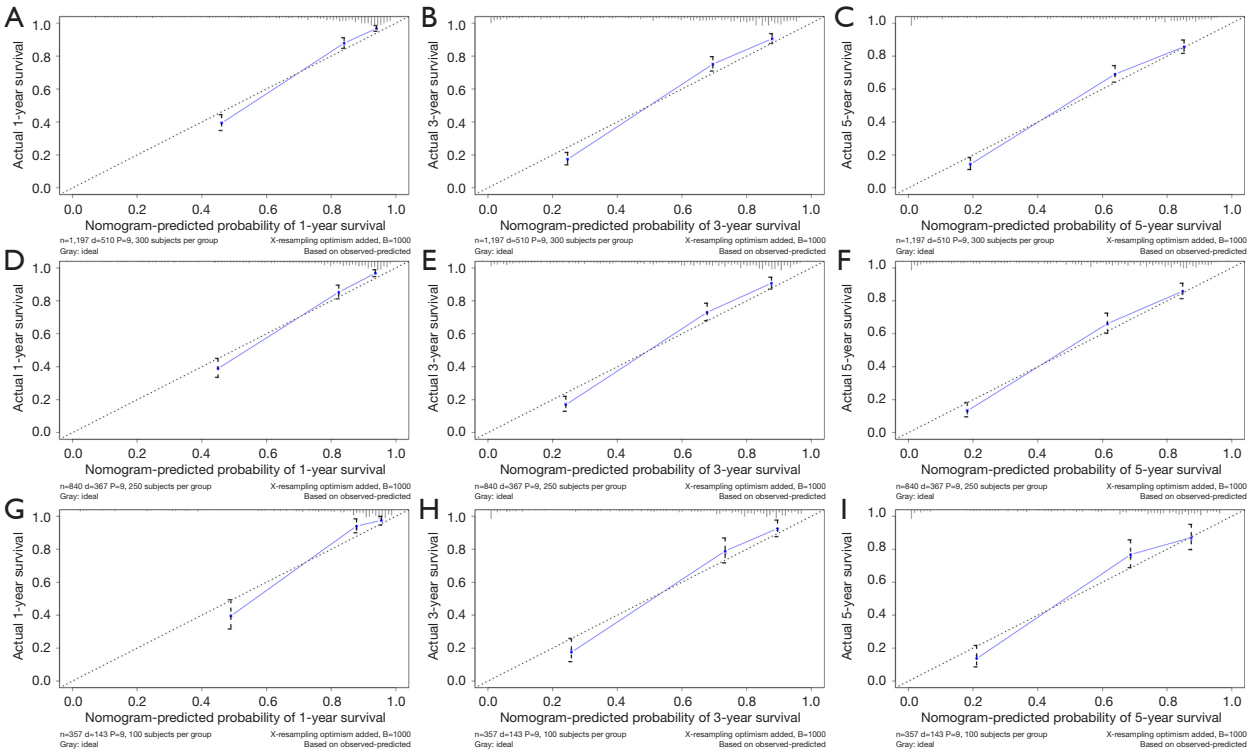

Figure 5 The differences between the three prognostic models and actual situation with respect to the predicted 1-, 3-, and 5-year survival rates. (A-C) Primary prognostic model (1,197 cases). (D-F) Modeling group (840 cases). (G-I) Validation group (357 cases). The dotted line represents the ideal state, that is, no difference between the predicted value and the actual value.

that endoscopic therapy was only suitable for patients with esophageal carcinoma *in situ* or stage T1a. For patients with esophageal cancer at stage T1b, primary surgery was still esophagectomy, and endoscopic therapy was only suitable for patients with bad status. Furthermore, they also believed that the good prognosis of patients with endoscopic therapy was inherent (17).

There are several limitations to this study. Firstly, this is a retrospective study, and its accuracy is inferior to large-scale clinical randomized trials and lacks external validation. Secondly, the surgery modalities of esophageal cancer varied, and it may have involved various other body parts such as the neck, thorax, and abdomen. Hence, absolute resection of the tumor and pathological confirmation was not easy. Thirdly, due to the rigid inclusion and exclusion criteria, there were few patients who met all conditions. Lastly, due to the advancement of the modern social medical environment and access to a variety of medical care, the chemoradiotherapy records in the SEER database may be different from the actual situation.

We have significant shortcomings in the lack of close clinical connection, factors like surgical techniques, operative time, conversion to open rate, number of excised or positive lymph nodes, surgical complications, and surgical approach, which may affect the survival of patients.

Conclusions

The nomogram established using several clinical variables has good prognostic ability for non-adjuvant therapy patients with stage I to III esophageal cancer. Advanced age, squamous cell carcinoma, poor tumor differentiation, late diagnostic time, and surgery modalities were independent prognostic factors for non-adjuvant therapy patients with stage I to III esophageal cancer. The clinical application of this nomogram needs further validation.

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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-24-1377/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-24-1377/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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