Development and Validation of Prognostic Model for Patients with Esophageal Carcinoma after Esophagectomy: A SEER-based Analysis

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Research

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Abstract

Backgrounds: Esophageal carcinoma (EC) is one of the most common cancers worldwide with high morbidity and mortality. While, the prognosis of EC is generally poor because of the relatively late stage for most patients at the time of diagnosis (1), even if a surgery was performed.

Methods: To predict the prognosis of patients with esophageal carcinoma after surgery, we identified 7,215 patients with esophageal carcinoma from the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2016. A total of 5,052 patients were allocated to the training cohort and the remaining 2,163 patients were distributed to the validation cohort using bootstrap resampling.

Results: For the entire cohort, the cancer-specific mortality of 1-year, 3-year, and 5-year were 14.6%, 35.7% and 41.6%, respectively. The nomograms were established and well-calibrated. The C-indexes of the nomograms for predicting overall survival (OS) and cancer-specific survival (CSS) were 0.726 (95% CI: 0.714–0.738) and 0.735 (95% CI: 0.727–0.743) in the training cohort. Meanwhile, the nomograms were well-validated in the validation cohort, with the C-indexes of 0.728 (95% CI: 0.720–0.736) and 0.739 (95% CI: 0.731–0.747) for predicting OS and CSS respectively. In addition, the nomogram showed a higher sensitivity than the tumor node metastasis (TNM) staging system according to the areas under the curves (AUC) of ROC curves.

Conclusion: As a supplement for the current TNM staging system, it would be beneficial to identify the high-risk patients with EC after surgery.

Introduction

Esophageal carcinoma is the eighth leading cause of cancer death, causing 400,000 deaths in 2012 worldwide (2). The poor prognosis is associated with the lymph nodes or distant metastasis and weight loss (3). It was reported that the rate of 5-year survival was less than 20% (4). Surgery is regarded as the most important therapy for the early-stage esophageal carcinoma. With the development of the surgical techniques, the 5-year survival rate after operation increased these years, otherwise, still remaining less than 40% (5, 6). Perioperative chemoradiotherapy was increasingly applied in treatment of esophageal carcinoma in the last few years. A network meta-analysis (7) suggested that neoadjuvant chemoradiotherapy improved OS but might also increase the risk of postoperative mortality. With the data of radiation and chemotherapy available in the SEER database, we wanted to figure out the effect of perioperative chemoradiotherapy on the prognosis of esophageal carcinoma.

The TNM staging system is now widely applied in clinical practice, while some researchers approved other important risk factors should be taken into consideration in predicting cancer survival, such as age, tumor location, tumor size and Perioperative chemoradiotherapy (8–11). The predicting nomograms were developed and used in many types of cancers (12–15), of which some showed a greater benefit than the TNM staging system. However, only OS, using Kaplan–Meier and Cox analyses, was taken into account,

without considering the competing risk model for esophageal carcinoma in previous studies. Therefore, a more accurate clinical nomogram for esophageal carcinoma is urgently needed.

We aimed to develop a clinical predicting model for patients with EC after esophagectomy using nomogram, on the basis of the Surveillance, Epidemiology, and End Results (SEER) database. The OS and CSS of 1-year, 3-year, and 5-year after operation were predicted in the nomograms.

Materials And Methods

Patients

The subjects were derived through SEER*Stat 8.3.6.1 software from the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/), which is a population-based cancer registry. The newly SEER 18 registries research database from 1975 to 2016 was used while the 2017's data was excluded because of lacking of essential data on radiation and chemotherapy. Only patients with first and primary esophageal carcinoma were eligible in the study.

The risk factors of interest included age, gender, race, grade, tumor location, histology, tumor size, TNM stage, radiation, chemotherapy and regional lymph nodes. Lymph node ratio (LNR) was defined as the ratio of regional LN positive and regional LN examined (12). Meanwhile, the outcomes of interest consisted of overall survival and cancer-specific survival.

Eligible criteria

The inclusion criteria were as follows: (1) patients with esophagus cancer (AJCC 7th TNM) in the SEER 18 registries research database of 1975–2016; (2) Adults; (3) primary and first carcinoma; (4) surgery performed.

The exclusion criteria were as follows: (1) patients with missing data on TNM stage; (2) patients without regional lymph nodes examined or with unclear numbers; (3) patients only undergoing endoscopic surgery; (4) patients without data on CSS; (5) patients with incomplete follow up data.

Statistical Analysis

Stata/SE 16.0 (Stata Corp LLC, college station, USA) was applied in processing the primary data from the SEER database. R for windows (version 4.0.0) was implemented to develop and validate the nomogram. The cut-off value of continuous variables, such as tumor size and LNR, was analyzed by X-tile (16) (version 3.6.1; Yale University School of Medicine, USA). Statistical significance was defined as a two-tailed $p < 0.05$.

For the construction of the nomograms, 70% of patients (5,052) were allocated to the training cohort and 30% patients (2,163) were distributed to the validation cohort using bootstrap resampling. Kaplan–Meier

method was conducted in analyzing OS using a log-rank test. Competing risk model (17) was applied in analyzing CSS using Fine and Gray's test, and the cumulative incidence function (CIF) was utilized to show the difference between cancer-specific death and non-cancer-specific death. Multivariate cox regression analysis model was carried out in analyzing the significant factors and constructing nomograms.

To evaluate the discrimination ability of nomograms, Harrell's concordance indexes (C-indexes) and calibration curves (18, 19) were carried out, meanwhile the ROC curves were also conducted to compare the accuracy of prediction between the prognostic nomograms and TNM staging system.

Result

Characteristics of Patients

We identified a total of 7,215 patients from the database eventually. The selecting flow diagram was presented in Fig. 1 and the characteristics of the patients was showed in Table 1.

Table 1
Characteristics of Patients with Esophageal Carcinoma after Surgery

Whole cohort (n = 7284)		Training cohort (n = 5100)		Validation cohort (n = 2184)			
Variables		N	%	N	%	N	%
Age	< 50	683	9.5	479	9.5	204	9.4
	50–59	1948	27.0	1349	26.7	599	27.7
	60–69	2841	39.3	2003	39.6	838	38.7
	70–79	1491	20.7	1055	20.9	436	20.2
	≥ 80	252	3.5	166	3.3	86	4.0
Gender	Female	1129	15.6	809	16.0	320	14.8
	Male	6086	84.4	4243	84.0	1843	85.2
Race	White	6496	90.0	4560	90.3	1936	89.5
	Black	397	5.5	278	5.5	119	5.5
	Others	322	4.5	214	4.2	108	5.0
Site	Upper	131	1.8	97	1.9	34	1.6
	Middle	977	13.6	679	13.4	298	13.7
	Lower	5656	78.4	3958	73.3	1698	78.5
	Overlapping	226	3.1	164	3.3	62	2.9
	Unknown	225	3.1	154	3.1	71	3.3
Histology	ESCC	1359	18.8	958	18.9	401	18.5
	EAC	5357	74.3	3743	74.1	1614	74.6
	Others	499	6.9	351	7.0	148	6.9
Grade	Well	478	6.6	336	6.6	142	6.6
	Moderately	2798	38.8	1974	39.1	824	38.1
	Poorly	3104	43.0	2153	42.6	951	44.0
	Undifferentiated	94	1.3	66	1.3	28	1.3
	Unknown	741	10.3	523	10.4	218	10.0
TNM stage	I	1509	20.9	1086	21.5	423	19.6
	II	2367	32.8	1633	32.3	734	33.9
	III	2638	36.6	1854	36.7	784	36.2

Whole cohort (n = 7284)		Training cohort (n = 5100)		Validation cohort (n = 2184)			
	IV	701	9.7	479	9.5	222	10.3
Radiation	No	2524	35.0	1787	35.4	737	34.1
	Yes	4691	65.0	3265	64.6	1426	65.9
Chemo	No	2121	29.4	1484	29.4	637	29.5
	Yes	5094	70.6	3568	70.6	1526	70.5
LNR	0	4492	62.2	3187	63.1	1305	60.3
	< 0.05	264	3.7	169	3.3	95	4.4
	0.05–0.3	1602	22.2	1090	21.6	512	26.7
	> 0.3	857	11.9	606	12.0	251	11.6
Size	0–20 mm	1373	19.0	995	19.7	378	17.5
	21–50 mm	2769	38.4	1945	38.5	824	38.1
	> 50 mm	1628	22.6	1100	21.8	528	24.4
	UNK	1445	20.0	1012	20.0	433	20.2

In general, 6,086 patients (84.4%) were male, and 4,584 patients (63.5%) were more than 60 years old. compared with other sites, the lower esophagus was the most common site. The white race made up 90% of the entire cohort. More than half of the study population received perioperative radiation (65.0%) and chemotherapy (70.6%). Of all the histology types, EAC accounted for the largest proportion (74.3%). Nearly half of the patients were in advanced stages (III, IV) at the time of diagnosis. There were 2,723 patients (37.8%) with regional LN positive, with 2,459 patients (34.1%) LNR higher than 0.05.

A total of 3,983 deaths occurred, including 3,209 cancer-specific deaths and 774 deaths from other causes during a follow-up period of up to 155 months. The mean follow-up period was 39.8 months. The cancer-specific mortalities of 1-year, 3-year, and 5-year were 14.6%, 35.7%, 41.6%, and the competing mortalities were 3.2%, 6.2%, and 7.8% respectively

The corresponding CIF curves of competing risk model were presented in Fig. 2. For males, the cumulative mortality of EC was significantly higher than females while it did not show statistic difference as for competing causes. Compared with EAC, ESCC and other histology types had a higher cancer-specific mortality but it was inapplicable for death of competing causes. Greater cumulative mortality of EC was observed when patients presented with older age, worse differentiation, greater tumor size, later the TNM stage, later histology stage, and more positive LN. In addition, higher probability of death from competing causes was shown in other all risk factors except gender, grade, and T stage.

The OS survival curves of risk factors above were presented in **Supplement** Fig. 1. It was demonstrated that greater survival probability was associated with younger age, female, well differentiation (grade I), smaller tumor size, earlier TNM stage, EAC histology type, earlier histology stage, absent or less positive LN, and lower LNR.

Multivariate Cox Regression Analysis

Multivariate cox regression analysis of training cohort was conducted to identify significant risk factors, presenting in Table 2. Age, race, gender, tumor location, histology, grade, TNM stage, tumor size, radiation, chemotherapy, LN positive, LNR were taken into consideration. Perioperative radiation (HR = 1.07, 95%CI: 0.96–1.19) was not included in the nomograms because of not presenting statistical significance. Compared with the white, although the black patients suffered a higher risk of death (HR = 1.28, 95% CI: 1.12–1.46), race was not included in the nomograms because racial information was not widely applicable. Moreover, the number of positive LNs showed significant difference in predicting survival of EC after surgery, whereas it was also excluded to avoid multicollinearity.

Table 2
Multivariate Cox Analysis of the Training Cohort

Variables Overall Survival					
		HR	95% CI		P value
Age	< 50	Ref			
	50–59	1.19	1.05	1.35	0.005*
	60–69	1.33	1.18	1.50	< 0.001*
	70–79	1.79	1.57	2.03	< 0.001*
	≥ 80	2.31	1.92	2.79	< 0.001*
Gender	Female	Ref			
	Male	1.21	1.09	1.32	< 0.001*
Site	Upper	Ref			
	Middle	0.87	0.69	1.10	0.241
	Lower	0.75	0.60	0.94	0.013*
	Overlapping	0.83	0.63	1.09	0.187
	Unknown	0.78	0.59	1.05	0.105
Histology	ESCC	Ref			
	EAC	0.88	0.80	0.97	0.012*
	Others	0.99	0.86	1.14	0.947
Grade	Well	Ref			
	Moderately	1.19	1.00	1.41	0.025*
	Poorly	1.36	1.15	1.62	< 0.001
	Undifferentiated	1.43	1.01	2.01	0.022*
	Unknown	1.07	0.87	1.33	0.896
TNM stage	I	Ref			
	II	1.73	1.49	2.03	< 0.001*
	III	2.23	1.87	2.66	< 0.001*
	IV	2.06	1.65	2.58	< 0.001*

HR: Hazard ratio; CI: Confidence interval; TNM stage: tumor node metastasis stage; LNR: lymph node ratio.

Variables Overall Survival					
Size	0–20 mm	Ref			
	21–50 mm	1.15	1.04	1.27	0.006*
	> 50 mm	1.27	1.14	1.43	< 0.001*
	Unknown	1.12	0.98	1.25	0.102
Radiation	No	Ref			
	Yes	1.07	0.96	1.19	0.234
Chemo	No	Ref			
	Yes	0.67	0.60	0.75	< 0.001*
LNR	0	Ref			
	< 0.05	1.01	0.84	1.21	0.906
	0.05–0.25	1.51	1.39	1.65	< 0.001*
	> 0.25	2.47	2.24	2.71	< 0.001*

HR: Hazard ratio; CI: Confidence interval; TNM stage: tumor node metastasis stage; LNR: lymph node ratio.

Construction and Validation of Nomograms for OS and CSS

The training cohort consisted of 70% of patients. For the training cohort, the nomograms of OS and CSS were presented in Fig. 3 and Fig. 4. Of all risk factors, age, gender, tumor site, histology, grade, TNM stage, tumor size, chemotherapy, and LNR were included. The 1-, 3-, and 5 years of predicted OS and CSS were lined at the bottom. The C-indexes of prognostic nomograms were 0.748 (95% CI: 0.738–0.758) for OS, and 0.795 (95% CI: 0.785–0.804) for CSS, which suggested a good discrimination ability for predicting OS and CSS of EC after surgery. In addition, a total of 2,184 patients (30%) were assigned into the validation cohort. The C-indexes of the nomograms were 0.752 (95% CI: 0.738–0.765) for OS and 0.804 (95% CI: 0.790–0.817) for CSS.

The efficiency of nomograms was also evaluated by calibration plots in both training cohort and validation cohort. The calibration plots of 1-, 3-, and 5-years survival probabilities were shown in **Supplement** Fig. 2**(A-F)** for the OS, and in **Supplement** Fig. 3**(A-F**) for the CSS. Calibration plots of training cohort demonstrated the optimal agreement between the prediction by nomogram and actual observation

in the probability of 1-, 3-, and 5-year OS and CSS. Meanwhile, it suggested a high agreement between the predicted and actual survival in the validation cohort.

Comparison of Nomogram and TNM system

The ROC curves were carried out to compare the difference of discriminatory accuracy between the established nomograms and TNM staging system, presenting in Fig. 5. The AUC values of ROC curves for predicting 1-, 3-, and 5-year OS and CSS were calculated (Table 3). The AUC values of 1-, 3-, and 5-year OS were 0.703, 0.731, 0.736 respectively, with 0.628, 0.677, 0.688 for TNM stage. Similarly, it demonstrated that the AUC values of established nomograms were higher than the TNM staging system in terms of CSS.

Table 3
Comparison of the AUC values between nomograms and TNM stages.

	Overall survival			Cancer-specific survival		
	1 year	3 year	5 year	1 year	3 year	5 year
Nomogram	0.703	0.731	0.736	0.718	0.745	0.753
TNM Stage	0.628	0.677	0.688	0.645	0.687	0.700

Discussion

In this study, we established prognostic nomograms of OS and CSS for patients with esophageal carcinoma after surgery. The predicting risk factors included age, gender, histology, grade, TNM stage, tumor size, chemotherapy, and LNR. The C-indexes of the nomograms showed a satisfactory accuracy for predicting the OS and CSS. Meanwhile, calibration plots confirmed the optimal agreement between the predicted probabilities and actual probabilities. In addition, ROC curves also demonstrated better predicting efficiency than TNM staging system based on higher AUC values.

Except gender and tumor differentiation grade, the other risk factors demonstrated statistical significance in competing mortality. This result was similar to that of He et.al (9). Of those, age was recognized as a quite important factor in competing death in some researches (20–23). With age increasing, older patients are more likely to die of heart failure, respiratory failure, stroke, falls and other causes compared with the younger.

Whether perioperative chemoradiotherapy was beneficial to patients remained unclear. Huang et.al (24) reported that findings for preoperative chemotherapy followed by surgery (CTS) and preoperative radiotherapy followed by surgery (RTS) did not differ for 5-year survival, compared with surgery alone. In this study, perioperative chemotherapy suggested the protective effect (HR = 0.67, 95% CI: 0.60–0.75) for

patients with esophageal carcinoma after surgery while not for perioperative radiotherapy (HR = 1.07, 95%CI: 0.96–1.19). It might be caused by the differences in the sequence of radiation and surgery and due to selection bias. Therefore, a subgroup analysis of radiotherapy was needed to identify the role of radiation.

Several nomograms for esophageal carcinoma had been developed (10, 25, 26), while there was still no best prognostic model widely applied in clinical practices for EC after surgery. Du et.al (26) and Cao et.al (27) constructed the nomograms based on the SEER database. While, only OS was taken into account in the study of Cao et.al, and only CSS is considered in the study of Du et.al. Additionally, chemotherapy and radiation were not considered in the study of Du et.al.

Compared with the previous researches, this study had several advantages. Primarily, cancer-specific death and non-cancer specific death were thought as important competitive factors, which meant that competing risk model should be considered in predicting survival of cancers. Competing risk model based on Fine's and Grays's test was conducted in this study, and the results suggested that all factors other than gender and grade were statistically significant in the cause of competitive death. Moreover, the discrimination ability of the nomogram was better than previous ones (0.735 vs 0.710 (26); 0.726 vs 0.716 (27)). Besides, we defined LNR as the ratio of regional LN positive and regional LN examined. The number of positive LN was a powerful prognostic factor for esophageal carcinoma, with the prognosis declining when lymph nodes increasing. Considering both the number of LN examined and the positive number, LNR was reported as an independent predictor in previous studies (28, 29). LNR was selected in this study because the N stage was determined by the number of positive LNs and lymph node stations. Compared with LNR 0, 0-0.05 and > 0.05 presented a statistical significance. When LNR was divided into five subgroups as: 0%, 0–25%, 26–50%, 51–75%, 76–100%, Hazard ratio (HR) increased with the increase of LNR. In addition, ROC curves were applied in comparing the nomograms and TNM staging system, which demonstrated that the AUC values of nomograms were higher than TNM, suggesting a better predicting accuracy. Moreover, more patients were identified in this study based on data from 2004–2016 in the SEER database.

Several shortcomings also existed in this study. Firstly, although the SEER database is population-based and internal validation was conducted, multi-center external validation are needed in order to confirm the accuracy of this prognostic model (30). Secondly, some risk factors influencing the prognosis of the EC such as body mass index (BMI), postoperative complications, nutritional conditions were not available in the SEER database. It was reported that BMI adjusted by preoperative weight loss (PWL) had an independent prognostic impact on OS in patients with ESCC (31). There was not much research about postoperative complications and EC survival. In the study of Yamamoto M et.al (32), pulmonary complications significantly influence the OS of patients undergoing R0 esophagectomy. In terms of the nutritional condition, enteral feeding access was considered to be associated with improved short-term survival (33). Thirdly, esophageal carcinoma was divided into various histologic types, of which ESCC and EAC were most common. Further analysis of histological type subgroups should be performed.

Conclusion

In summary, we developed and validated the prognostic nomograms to estimate the cumulative incidences of OS and CSS for patients with EC after surgery based on the SEER database. Showing a better accuracy than the TNM classification in predicting the EC survival, the calibrated nomograms might be applied to identify the high-risk patients in clinical practices.

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent for participate

This research is based on the public SEER database (https://seer.cancer.gov/), in which all data of patients were anonymized. Thus, informed consent was not needed. The approval of the institutional review board was waived for this retrospective and non-interventional study, according to local regulations.

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Competing interests:

None declared.

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Authors' contributions:

Conceptualization: Chao Zheng, xiao-Kun Li, Yang Xu;

Methodology: Chao Zheng, Yang Xu;

Data extraction: Chao Zheng, Zhuangzhuang Cong;

Data analysis: Chao Zheng, Yong Qiang;

Writing: Chao Zheng, Yi Shen.

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Figures

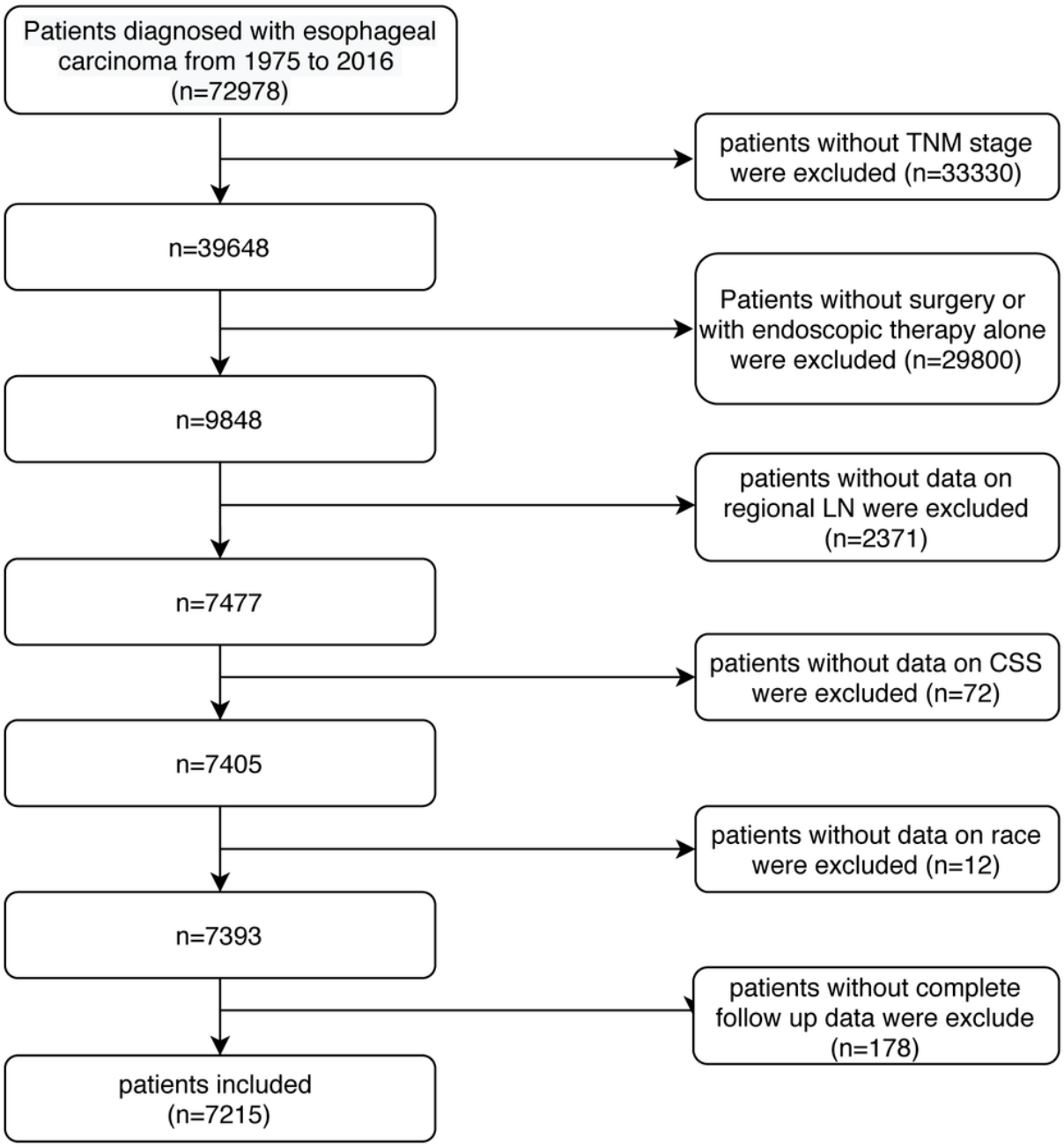

Figure 1

Selecting flow diagram. TNM: tumor node metastasis; LN: lymph node; CSS: cancer-specific survival.

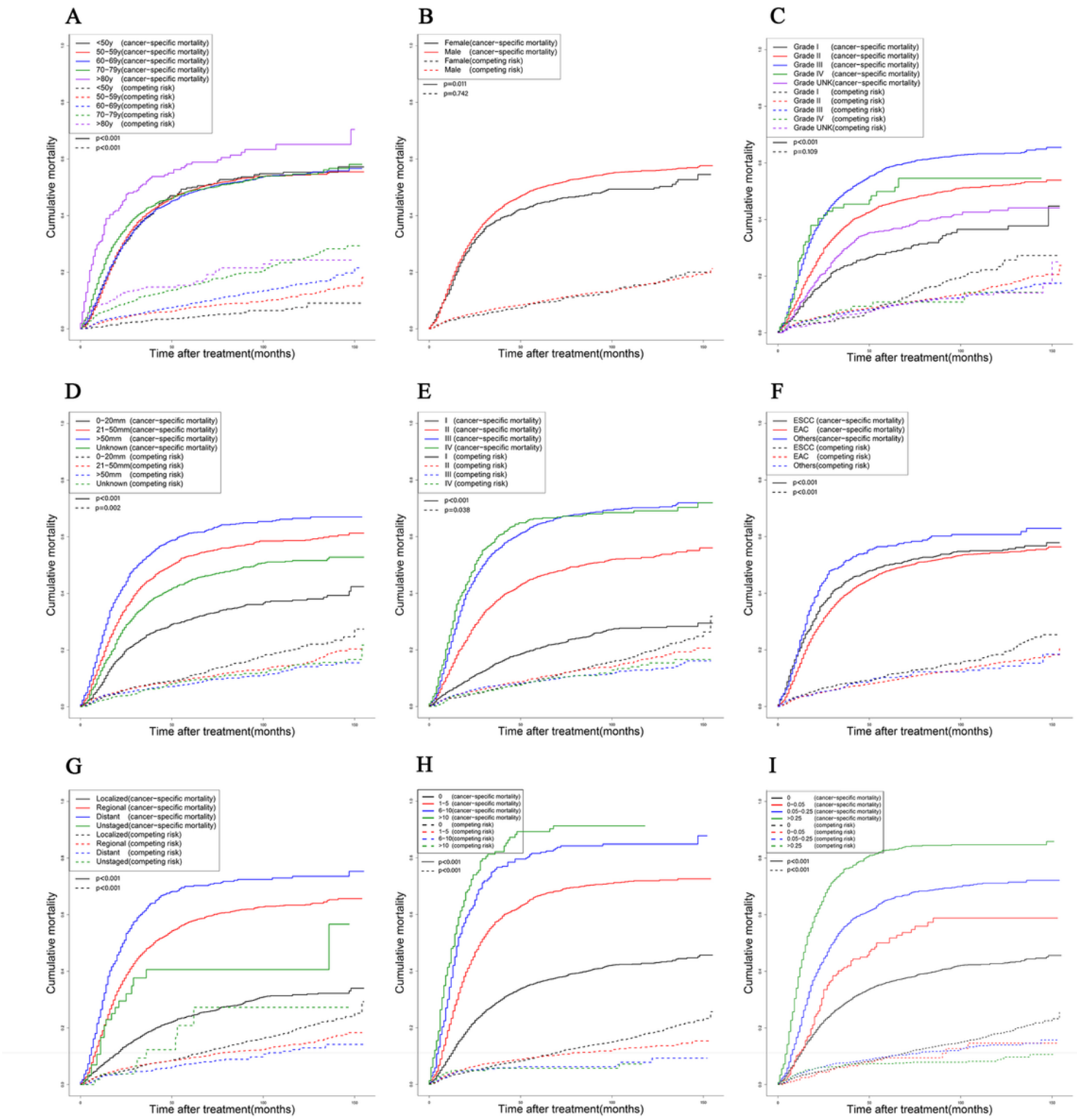

Figure 2

Cumulative mortality rates of cancer-specific death and competing death stratified by patient characteristics: (A) Age; (B) Gender; (C) Grade; (D) Size; (E) T stage; (F) Histology; (G) Histology stage; (H) LN positive; (I) LNR. LN: lymph node; LNR: lymph node ratio.

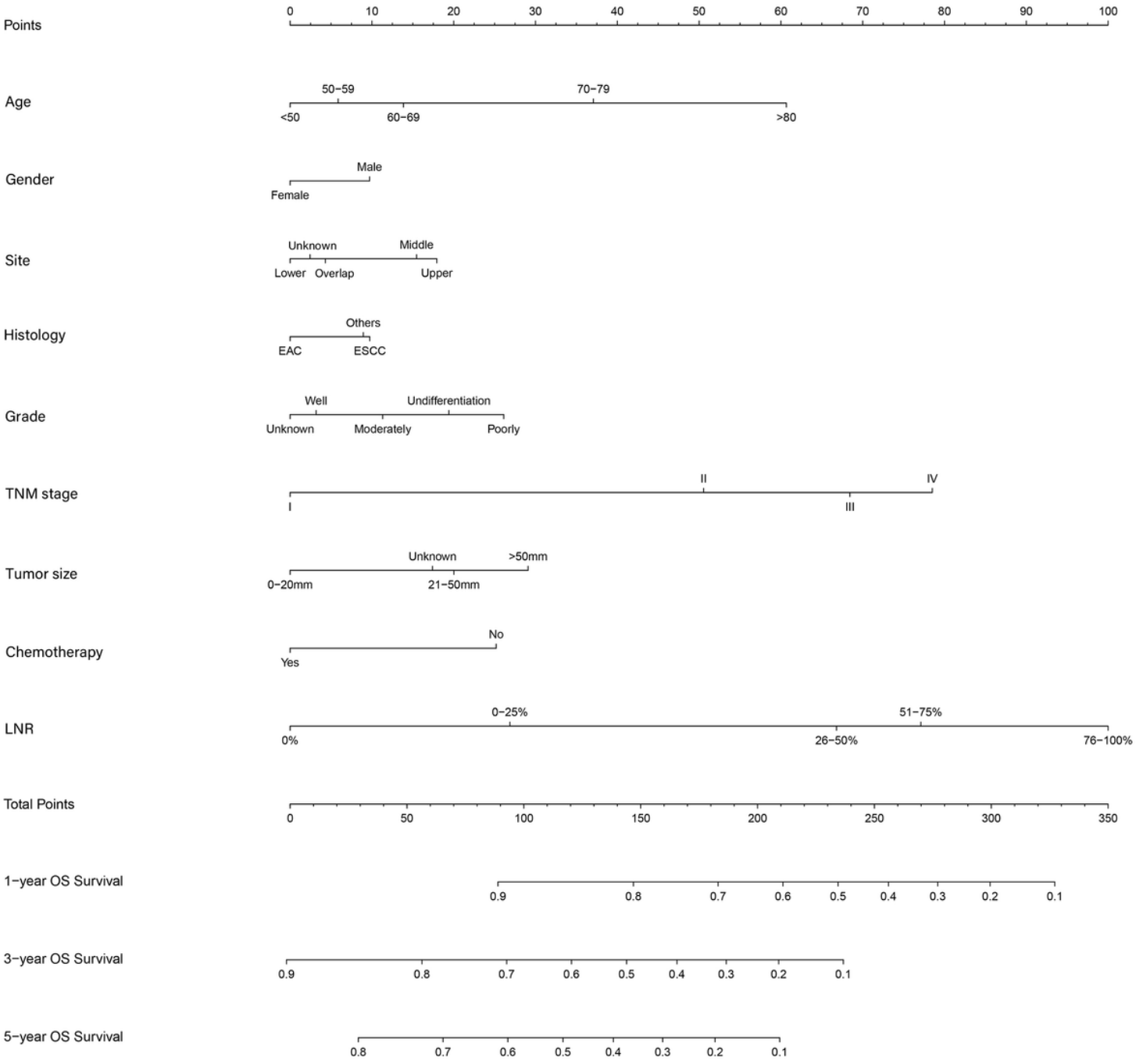

Figure 3

Nomogram predicting overall survival (OS) of patients with esophageal carcinoma after surgery.

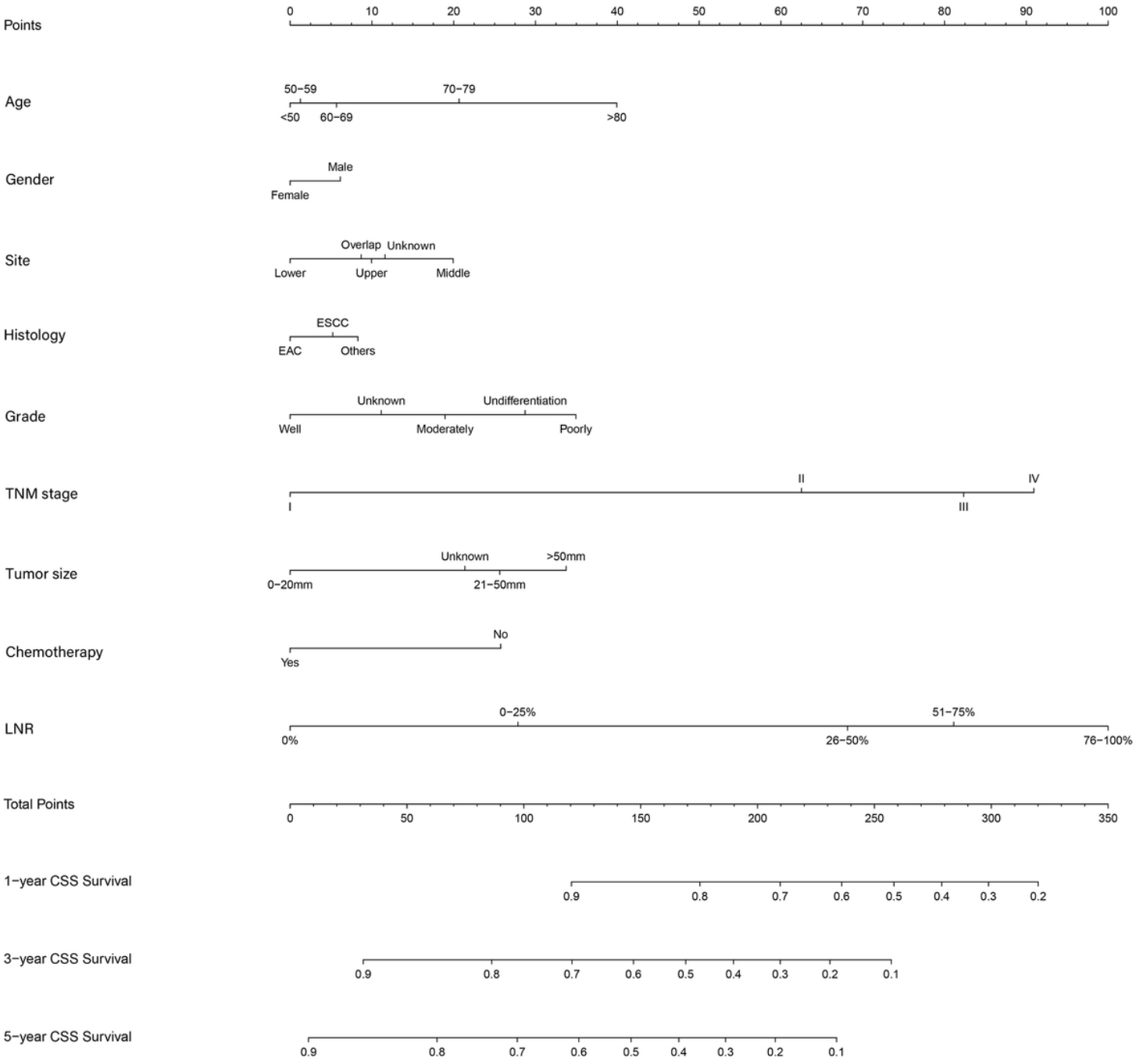

Figure 4

Nomogram predicting cancer-specific survival (CSS) of patients with esophageal carcinoma after surgery.

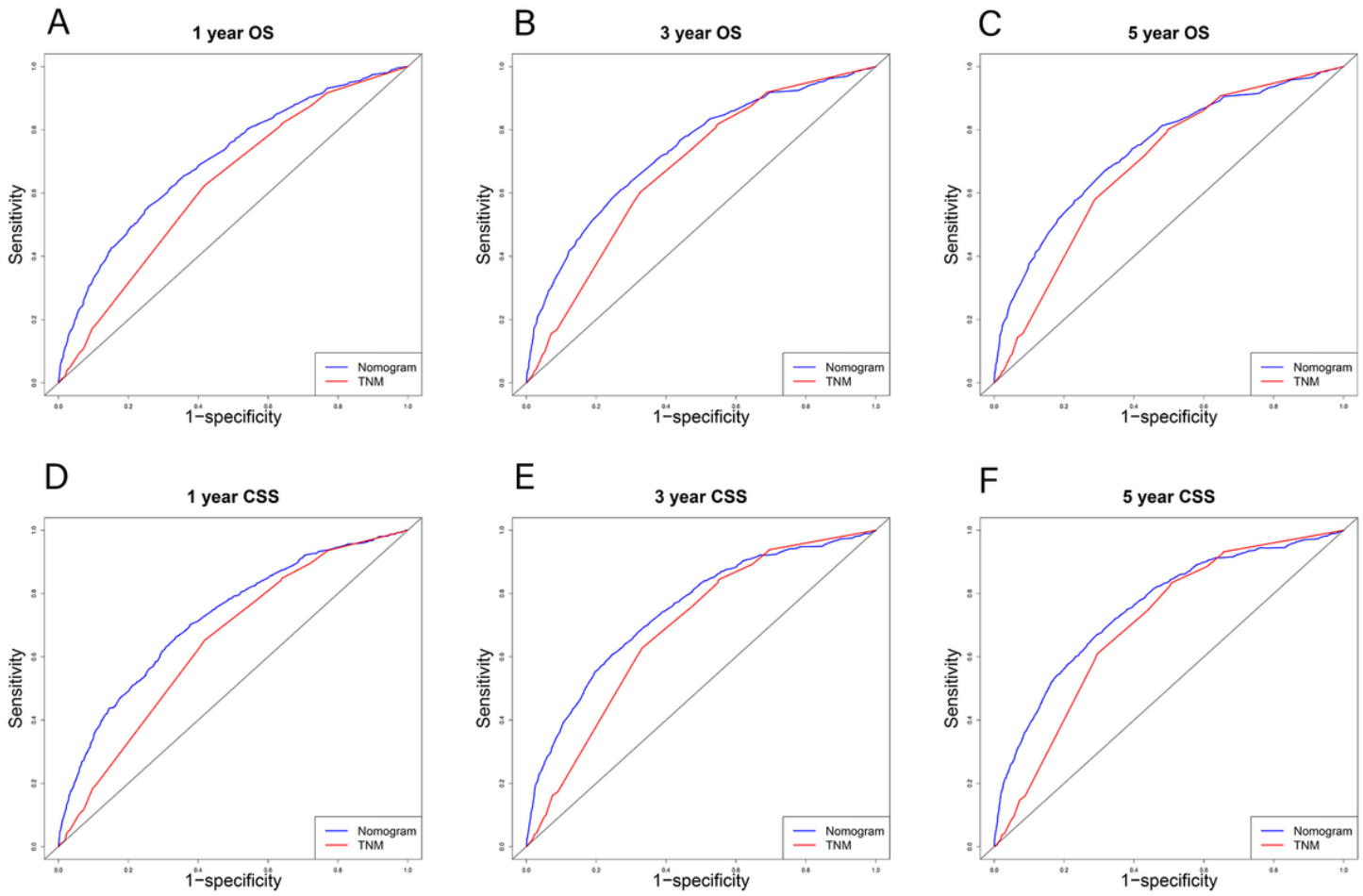

Figure 5

ROC curves of the nomogram and TNM stage for 1-, 3-, and 5-year OS prediction (A–C) and CSS prediction (D–F)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementFigure1.tif
- SupplementFigure3.tif
- SupplementFigure2.tif