Original Article

Nomogram predicting cancer-specific mortality in patients with esophageal adenocarcinoma: a competing risk analysis

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Background: Many factors are reported to be related to the prognosis of patients with esophageal adenocarcinoma (EAC), but few reliable and straightforward tools for clinicians to estimate individual mortalities have been developed. This study aimed to evaluate the probability of cancer-specific death for patients with EAC and to build nomograms for predicting long-term cancer-specific mortality and overall mortality for EAC patients.

Methods: Between 2004 and 2013, a total of 20,623 patients were identified from the surveillance, epidemiology, and end results (SEER) database and randomly divided into training (N=14,436) and validation (N=6,187) cohorts. The cumulative incidence functions (CIFs) of EAC-specific death and other causes were evaluated at the 1st, 3rd, and 5th year after diagnosis. We integrated the significant prognostic factors to construct nomograms and subjected them to internal and external validation.

Results: The CIFs of EAC-specific survival at 1, 3, and 5 years after diagnosis were 60.9%, 37.1%, and 31.3%, respectively. Predictors for cancer-specific mortality for EAC comprised tumor grade, tumor extension, the involvement of lymph nodes, distant metastasis, surgery of primary site, insurance recode, and marital status. For overall mortality, it also included the predictor of age at diagnosis. The nomograms were well-calibrated and had good discriminative ability with concordance indexes (c-indexes) of 0.733, 0.728, and 0.728 for 1-, 3- and 5-year prognosis prediction of EAC-specific mortality respectively, and 0.726, 0.720, 0.719 for 1-, 3-, and 5-year prognosis prediction of overall mortality respectively.

Conclusions: We proposed and validated the effective and convenient nomograms to predict cancer-specific mortality and the overall mortality for patients with EAC, which only require the basic information available in clinical practice.

Keywords: Esophageal adenocarcinoma (EAC); surveillance, epidemiology, and end results (SEER); nomogram; mortality

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Introduction

The incidence of esophageal adenocarcinoma (EAC) has dramatically increased in Western countries (1). It is characterized by several epidemiologic features, including male gender, white race, high body mass index, and age (2,3). Most patients with EAC present with symptoms of dysphagia from late-stage tumors, but only a portion of them are identified by screening and surveillance (4). Accurate prognosis estimates based on clinic pathologic factors play a vital role in determining therapeutic strategies in the shortest possible time.

Esophageal squamous cell carcinoma has been widely investigated in a significant amount of research (5-7), while EAC, as the other subtype of esophageal cancers, has been less studied. It has been previously reported that *TP53* gene mutations were related to reduced overall survival of patients with EAC (8). Although four genes were demonstrated to be prognostic for EAC (9), none of them are easy to obtain in routine clinical work. Elevated BMI in early adulthood and substantial cumulative smoking history were suggested to be associated with the mortality risk of EAC patients in one study in North America (10). A study using the surveillance, epidemiology, and end results (SEER) database with data from 1973 to 2003 showed that patients who were older and did not undergo esophagectomy had a worse overall survival (11). At the same time, the older and obese population constituted a larger proportion of patients with EAC (1,12), but their mortalities were likely increased due to other causes such as metabolic syndrome and cardiovascular diseases (13). Therefore, competing causes of death should be taken into account when evaluating the prognosis of this disease.

A competing risk is an event whose occurrence precludes the critical event of interest. Competing risk analysis is time-to-event analysis that considers all kinds of fatal or non-fatal events which potentially alter or prevent subjects from experiencing the interest endpoint (14,15). Thus, when predicting the incidence of the outcome of disease, competing risk analysis can provide a more accurate and less biased estimate for clinicians to make individual therapy strategies (16).

The nomogram visualizes the complex regression equation, making the results of the prognostic model more readable and convenient for the evaluation (17). Therefore, the nomogram is intuitive and easy to understand having been gradually applied to medical research and clinical practice.

In this study, we conducted a competing-risk analysis for EAC in the SEER database using cumulative incidence function (CIF) instead of Kaplan-Meier survival function when estimating the crude incidence of endpoint event (16,18). A competing risk nomogram model to predict individual long-term cancer-specific mortality for EAC and a nomogram model to predict overall mortality were constructed and validated.

Methods

Patient selection

The SEER database (https://seer.cancer.gov/) was used in this study. Patients who were clinically or pathologically diagnosed with EAC (based on the histologies stage table of the collaborative stage data set with the ICD-O-3 codes 8050, 8140–8147, 8160–8162, 8170–8175, 8180–8221, 8250–8507, 8514–8551, 8571–8574, 8576, 8940–8941 from SEER database) between 2004 and 2013 were included, among whom subjects without recorded survival time were omitted. The specific process is shown in *Figure S1*. Tumors were classified according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual (19).

Construction of the nomogram

Variables that achieved a significance value of $P<0.05$ in univariate Cox analysis were selected for multivariate Cox analysis. On this basis, a total of seven independent clinic pathological prognostic factors were integrated into the nomogram which predicted 1-, 3- and 5-year EAC-specific mortality after diagnosis. In addition to these variables, a factor of age was included to build a nomogram which predicted 1-, 3- and 5-year overall mortality.

The CIFs of mortality were plotted to depict trends over time among the different T, M, and N subgroups of the training cohort and the validation cohort. The calibration plots graphically displayed the relationship between the predicted and observed risk for the outcomes of the nomogram.

Receiver operating characteristic curve and decision curve analysis (DCA)

The time-dependent receiver operating characteristic (td-ROC) curve analysis was adopted to evaluate the predictive capacity of the nomograms for EAC-specific

mortality and overall mortality. DCA was used to compare the potential net benefit of the established models.

Statistical analysis

Statistical analysis was performed using SPSS 23 and R version 3.4.4. Univariate and multivariate Cox regression analyses were completed by SPSS. R software was used for building the nomogram. "Rms" and "survival" packages were used for survival analysis, and "Hmics", "timeROC", and "rmda" were used for the performance evaluation. All P values resulted from two-sided statistical testing. All calculations of CIFs of EAC-specific survival were carried out using SPSS.

Results

Demographic and clinical characteristics of patients at diagnosis

From 2004 to 2013, we gathered data on 20,623 patients with EAC who met the inclusion criteria from the SEER database. All of the patients were randomly distributed into the training cohort (N=14,436) or the validation cohort (N=6,187). *Table 1* shows the demographic and clinical characteristics of patients of the two cohorts at diagnosis, and every cohort was divided into subgroups of death of EAC and other causes.

At diagnosis in the training cohort, the median age of all patients was 67.00 years, whereas patients of cancer-specific death and patients of death from other causes had a significant difference (65.00 *vs.* 73.00 years). The majority of patients were men (86.2% *vs.* 84.6%) and of white race (94.7% *vs.* 94.7%). A considerable proportion of patients had tumors with T1 (23.4% *vs.* 32.3%) or T3 (29.4% *vs.* 24.9%) category, no lymph node involvement (32.3% *vs.* 46.2%), and no distant metastasis (55.5% *vs.* 74.2%). Most of the cohorts had not received surgical treatment (77.2% *vs.* 73.1%) at the primary site. The number of patients who were administered by radiotherapy (57.0% *vs.* 51.4%) slightly outnumber those who were not. Most patients had

Table 1 Patients' demographics, clinical characteristics at diagnosis

Variable	Training cohort (N=14,436)						Validation cohort (N=6,187)					
	All patients (n=14,436)		Cancer-specific death (n=7,482)		Death from other causes (n=3,014)		All patients (n=6,187)		Cancer-specific death (n=3,198)		Death from other causes (n=1,297)	
	No.	%.	No.	%	No.	%	No.	%.	No.	%	No.	%
Age, years (median)	67.00		65.00		73.00		67.00		65.00		73.00	
Gender												
Male	12,427	86.1	6,450	86.2	2,551	84.6	5,370	86.8	2,792	87.3	1,127	86.9
Female	2,009	13.9	1,032	13.8	463	15.4	817	13.2	406	12.7	170	13.1
Race												
White	13,670	94.7	7,088	94.7	2,853	94.7	5,871	94.9	3,031	94.8	1,232	95.0
Black	366	2.5	183	2.4	91	3.0	174	2.8	90	2.8	44	3.4
Other	344	2.4	187	2.5	64	2.1	120	1.9	67	2.1	21	1.6
Unknown	56	0.4	24	0.3	6	0.2	22	0.4	10	0.3	0	0
Tumor grade												
1	705	4.9	251	3.4	150	5.0	298	4.8	113	3.5	60	4.6
2	4,657	32.3	2,293	30.6	978	32.4	2,001	32.3	974	30.5	430	33.2
3	6,188	42.9	3,653	48.8	1,239	41.1	2,634	42.6	1,560	48.8	538	41.5
4	179	1.2	102	1.4	32	1.1	79	1.3	42	1.3	13	1.0
Unknown	2,707	18.8	1,183	15.8	615	20.4	1,175	19.0	509	15.9	256	19.7

Table 1 (*continued*)

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Variable	Training cohort (N=14,436)						Validation cohort (N=6,187)					
	All patients (n=14,436)		Cancer-specific death (n=7,482)		Death from other causes (n=3,014)		All patients (n=6,187)		Cancer-specific death (n=3,198)		Death from other causes (n=1,297)	
	No.	%.	No.	%	No.	%	No.	%.	No.	%	No.	%
Tumor extension												
Tis	188	1.3	22	0.3	49	1.6	68	1.1	5	0.2	14	1.1
1	4,275	29.6	1,750	23.4	974	32.3	1,859	30.0	730	22.8	416	32.1
2	1,395	9.7	626	8.4	265	8.8	568	9.2	234	7.3	142	10.9
3	4,136	28.7	2,199	29.4	750	24.9	1,810	29.3	1,014	31.7	313	24.1
4	593	4.1	364	4.9	89	3.0	266	4.3	135	4.2	46	3.5
Unknown	3,849	26.7	2,521	33.7	887	29.4	1,616	26.1	1,080	33.8	366	28.2
Involvement of lymph nodes												
0	6,002	41.6	2,420	32.3	1,392	46.2	2,590	41.9	1,027	32.1	588	45.3
1	3,550	24.6	1,837	24.6	575	19.1	1,525	24.6	798	25.0	262	20.2
2	443	3.1	258	3.4	60	2.0	207	3.3	120	3.8	35	2.7
3	379	2.6	246	3.3	57	1.9	140	2.3	90	2.8	23	1.8
Unknown	4,062	28.1	2,721	36.4	930	30.9	1,725	27.9	1,163	36.4	389	30.0
Distant metastasis												
No	9,862	68.3	4,152	55.5	2,237	74.2	4,200	67.9	1,785	55.8	943	72.7
Yes	4,276	29.6	3,115	41.6	719	23.9	1,856	30.0	1,315	41.1	333	25.7
Unknown	298	2.1	215	2.9	58	1.9	131	2.1	98	3.1	21	1.6
Surgery of primary site												
Yes	4,980	34.5	1,703	22.8	810	26.9	2,100	33.9	693	21.7	350	27.0
No	9,456	65.5	5,779	77.2	2,204	73.1	4,087	66.1	2,505	78.3	947	73.0
Radiotherapy												
Yes	7,905	54.8	4,268	57.0	1,549	51.4	3,403	55.0	1,847	57.8	683	52.7
No	6,531	45.2	3,214	43.0	1,465	48.6	2,784	45.0	1,351	42.2	614	47.3
Insurance recode												
Yes	9,796	67.9	4,736	63.3	1,869	62.0	4,185	67.6	1,973	61.7	830	64.0
No	273	1.9	165	2.2	31	1.0	121	2.0	83	2.6	11	0.8
Unknown	4,367	30.3	2,581	34.5	1,114	37.0	1,881	30.4	1,142	35.7	456	35.2
Marital status												
Married	8,825	61.1	4,497	60.1	1,801	59.8	3,796	61.4	1,914	59.8	773	59.6
Unmarried	4,821	33.4	2,627	35.1	1,043	34.6	2,074	33.5	1,146	35.8	445	34.3
Unknown	790	5.5	358	4.8	170	5.6	317	5.1	138	4.3	79	6.1

insurance records (63.3% *vs*. 62.0%) and were married (60.1% *vs*. 59.8%).

CIFs of EAC-specific survival

There were 1-, 3- and 5-year CIFs of EAC-specific survival in the training patients estimating by age at diagnosis, gender, tumor grade, tumor extension, the involvement of lymph nodes, distant metastasis, surgery of primary site, radiotherapy, insurance recode, and marital status at diagnosis (*Table 2*). *Table 2* demonstrates that for 1, 3, and 5 years after diagnosis, the CIFs of EAC-specific survival were 60.9%, 37.1%, and 31.3% respectively. Moreover, the CIFs of survival calculated by several characteristics decreased over time. The patients with a high CIF of survival were typically male, had low-grade tumors, were low T, N (no lymph node involvement), and M (no distant metastasis) categories, received surgical treatment-administered radiotherapy, had an insurance record, and were married. The curves are summarized in *Figure 1*. As can be seen, earlier T stage, N0, and M0 predicted decreased CIFs of cancer-specific death. As for CIFs of other causes of death, there was no significant difference.

Nomogram and clinical usage

As *Table 3* shows, incorporated into the prognostic prediction nomogram, the seven variables of tumor grade, tumor extension, involvement of lymph nodes, distant metastasis, surgery of primary site, insurance record, and marital status at diagnosis (all the significance of P<0.001) were found to be statistically associated with cancer-specific mortality. In addition to the above seven factors, age at diagnosis was also statistically significant (P<0.001) in the nomogram model of overall mortality.

The nomograms, which calculated the sum of points corresponding to the patient's characteristics, predicted the probability of 1-, 3- and 5-year cancer-specific mortality via the competing risk model and overall mortality (*Figure 2*). Regarding the clinical application of this nomogram, we can take a patient who has recently been diagnosed EAC as an example. This patient is a married, 50-year-old Chinese man who has health insurance records. CT showed no distant metastasis. After eliminating relevant contraindication, he received primary site surgery. Combined with intraoperative findings, the stage was evaluated as T2M0N1. Biopsy showed poorly differentiated cell type. As for the EAC mortality prediction, G3 corresponds to 63.7 points vertically at the top bar in nomogram; T2 corresponds to 17 points; and N1 corresponds to 22 points. Moreover, factors of M0, receiving surgery, having health insurance records, and being married correspond to 0. The sum of all the points constitutes the total points and is then used to predict the mortalities according to the corresponding percent at the bottom bar. The result shows that he has 102.7 points and 80.2 points in EAC mortality and overall mortality nomogram respectively. The predictive 1-year EAC mortality is slightly lower than 23%, and the 1-year overall mortality rate is a bit lower than 21%. The predictive 3- and 5-year EAC mortalities are both lower than 50%. Through this practical tool, the physician can stratify this patient and make individualized recommendations for his follow-up administration.

The C-indexes of the 1-, 3- and 5-year EAC-specific mortality nomogram in the training cohort were 0.733, 0.728, and 0.728, respectively, while the values in the validation cohort were 0.721, 0.721, and 0.720 respectively. Moreover, the C-indexes of the 1-, 3-, and 5-year overall mortality nomogram in the training cohort were 0.726, 0.720, and 0.719 respectively, while the values in the validation cohort were 0.715, 0.713, and 0.712 respectively. The td-area under the curve (td-AUC) of the 1-, 3-, and 5-year EAC-specific mortality nomogram in the training cohort were 0.801, 0.852, and 0.863 respectively, while the values in the validation cohort were 0.791, 0.854, and 0.856 respectively. As for 1-, 3- and 5-year overall mortality nomogram, the values of td-AUC were 0.793, 0.843, 0.858 in the training cohort respectively, and 0.782, 0.839, 0.849 in the validation cohort respectively. *Figures 3*,*4* show the curves of the td-ROC. Above all, the nomograms have a good model discriminative capacity. The calibration curves are shown in *Figures 5*,*6*. The actual CIFs and the predicted probability of mortalities for 1, 3, and 5 years between training and validation cohorts were in good agreement. Hence, the nomograms were well-calibrated.

To evaluate the clinical utility, the DCA was introduced. The plots of DCA cancer-specific mortality and overall mortality between the training and validation cohorts are shown in *Figure 7*, indicating the positive net benefit of the established models.

Discussion

In the current study, we estimated the probability of death for patients diagnosed with EAC in the SEER database between 2004 and 2013 and calculated the 1-, 3-, and

Table 2 1-, 3- and 5-year cumulative incidences of survival among patients in the training cohort

Variable	Cumulative incidence of EAC-specific survival			P value
	1-year (%) (95% CI)	3-year (%) (95% CI)	5-year (%) (95% CI)	
All patients	60.9 (60.1–61.7)	37.1 (36.3–38.1)	31.3 (30.3–32.3)	–
Age at diagnosis (years)				
Median (IQR)	64.0 (59.3–68.7)	38.4 (32.9–43.9)	30.9 (25.0–36.8)	–
Gender				0.043
Male	61.3 (60.3–62.3)	37.2 (36.2–38.2)	31.6 (30.4–32.8)	
Female	58.6 (56.2–61.0)	36.2 (33.7–38.7)	30.5 (27.8–33.2)	
Tumor grade				<0.001
1	81.5 (79.0–84.0)	65.2 (61.9–68.5)	61.2 (57.7–64.7)	
2	67.6 (66.2–69.0)	42.2 (40.6–43.8)	35.4 (33.6–37.2)	
3	52.8 (51.6–54.0)	28.5 (27.1–29.9)	23.3 (21.9–24.7)	
4	56.9 (49.6–64.2)	38.4 (30.8–46.0)	31.3 (23.1–39.5)	
Tumor extension				<0.001
Tis	90.3 (86.4–94.2)	83.5 (78.0–89.0)	75.8 (68.9–82.7)	
1	60.9 (59.5–62.3)	42.2 (40.6–43.8)	38.2 (36.6–39.8)	
2	69.4 (67.0–71.8)	42.9 (40.2–45.6)	35.1 (32.2–38.0)	
3	60.0 (58.6–61.4)	29.7 (28.1–31.3)	22.3 (20.7–23.9)	
4	41.1 (37.4–44.8)	15.6 (11.9–19.3)	9.6 (5.5–13.7)	
Involvement of lymph nodes				<0.001
0	63.4 (62.2–64.6)	42.3 (41.1–43.5)	37.1 (35.7–38.5)	
1	55.7 (54.1–57.3)	28.8 (27.0–30.6)	21.8 (19.8–23.8)	
2	69.1 (64.8–73.4)	29.1 (24.2–34.0)	20.6 (15.9–25.3)	
3	55.0 (49.7–60.3)	17.7 (12.8–22.6)	11.9 (7.2–16.6)	
Distant metastasis				<0.001
No	72.9 (71.9–73.9)	48.9 (47.7–50.1)	41.8 (40.4–43.2)	
Yes	31.8 (30.2–33.4)	6.9 (5.9–7.9)	4.5 (3.5–5.5)	
Surgery of primary site				<0.001
Yes	85.3 (84.3–86.3)	63.0 (61.4–64.6)	55.2 (53.4–57.0)	
No	46.7 (45.5–47.9)	20.2 (19.0–21.4)	15.5 (14.3–16.7)	
Radiotherapy				0.193
Yes	63.1 (61.9–64.3)	33.8 (32.4–35.2)	26.7 (25.3–28.1)	
No	58.3 (56.9–59.7)	41.1 (39.7–42.5)	36.9 (35.3–38.5)	
Insurance recode				<0.001
Yes	61.3 (60.5–62.1)	37.4 (36.4–38.4)	31.7 (30.7–32.7)	
No	48.0 (42.9–53.1)	26.7 (21.6–31.8)	22.1 (17.0–27.2)	
Marital status				<0.001
Married	64.0 (63.0–65.0)	39.5 (38.3–40.7)	34.0 (32.8–35.2)	
Unmarried	55.2 (53.6–56.8)	32.4 (30.8–34.0)	26.4 (24.6–28.2)	

CI, confidence interval; EAC, esophageal adenocarcinoma; IQR, interquartile range.

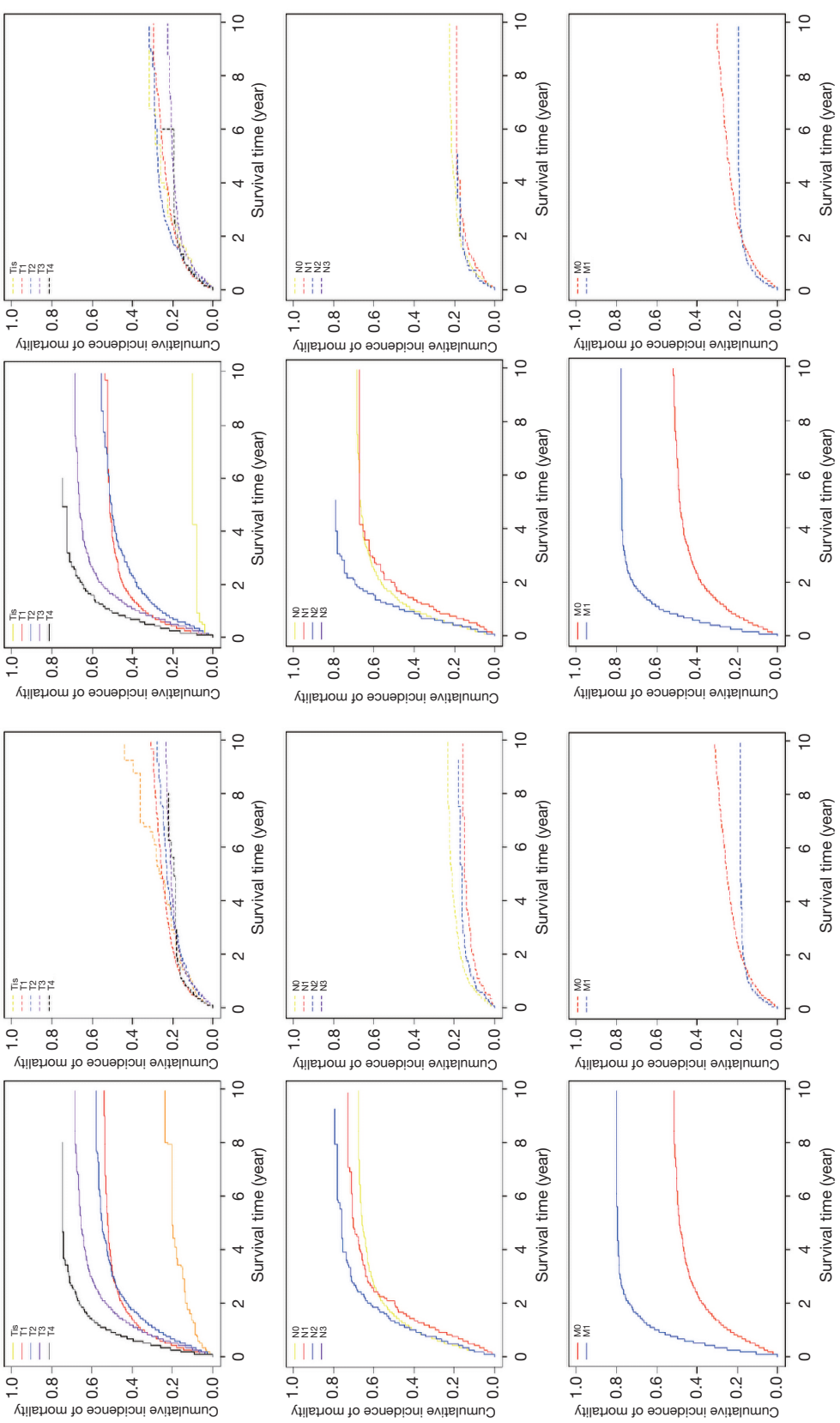

Figure 1 The CIF curves of death according to patient characteristics of T, M, N (solid line indicates cancer-specific death; dotted line indicates other causes of death). (A) The CIF curves of death in the training cohort; (B) the CIF curves of death in the validation cohort. T, extension; N, involvement of lymph nodes; M, distant metastasis; CIF, cumulative incidence function.

Table 3 Univariate and multivariate analyses of death in patients of the training cohort

Variables	Cancer-specific death			Overall death		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	P value	P value	HR (95% CI)	P value
Age at diagnosis, years	0.085	–	–	<0.001	1.018 (1.016–1.020)	<0.001
Gender	0.047	–	0.882	<0.001	–	0.248
Male						
Female						
Race	0.296	–	–	0.317	–	–
Tumor grade	<0.001		<0.001	<0.001		<0.001
1		Reference	–		Reference	–
2		1.384 (1.230–1.558)	<0.001		1.337 (1.218–1.469)	<0.001
3		1.843 (1.640–2.072)	<0.001		1.706 (1.555–1.872)	<0.001
4		1.532 (1.235–1.901)	<0.001		1.430 (1.196–1.711)	<0.001
Tumor extension	<0.001		<0.001	<0.001		<0.001
Tis		Reference	–		Reference	–
1		2.275 (1.659–3.119)	<0.001		1.612 (1.318–1.972)	<0.001
2		2.234 (1.621–3.079)	<0.001		1.497 (1.216–1.842)	<0.001
3		2.628 (1.914–3.609)	<0.001		1.755 (1.431–2.151)	<0.001
4		2.552 (1.841–3.538)	<0.001		1.745 (1.407–2.165)	<0.001
Involvement of lymph nodes	<0.001		<0.001	<0.001		<0.001
0		Reference	–		Reference	–
1		1.081 (1.027–1.138)	0.002		1.065 (1.018–1.113)	0.006
2		1.949 (1.718–2.211)	<0.001		1.730 (1.545–1.938)	<0.001
3		1.825 (1.603–2.077)	<0.001		1.756 (1.563–1.973)	<0.001
Distant metastasis	<0.001			<0.001		
Yes		2.270 (2.155–2.391)	<0.001		2.056 (1.964–2.153)	<0.001
No		Reference	–		Reference	–
Surgery of primary site	<0.001			<0.001		
Yes		0.345 (0.324–0.368)	<0.001		0.372 (0.353–0.392)	<0.001
No		Reference	–		Reference	–
Radiotherapy	0.201	–	–	0.21	–	–
Yes						
No						
Insurance recode	<0.001			0.001		
Yes		0.765 (0.677–0.864)	<0.001		0.753 (0.672–0.843)	<0.001
No		Reference	–		Reference	–
Marital status	<0.001			<0.001		
Married		0.804 (0.767–0.843)	<0.001		0.810 (0.779–0.844)	<0.001
Unmarried		Reference	–		Reference	–

HR, hazard ratio.

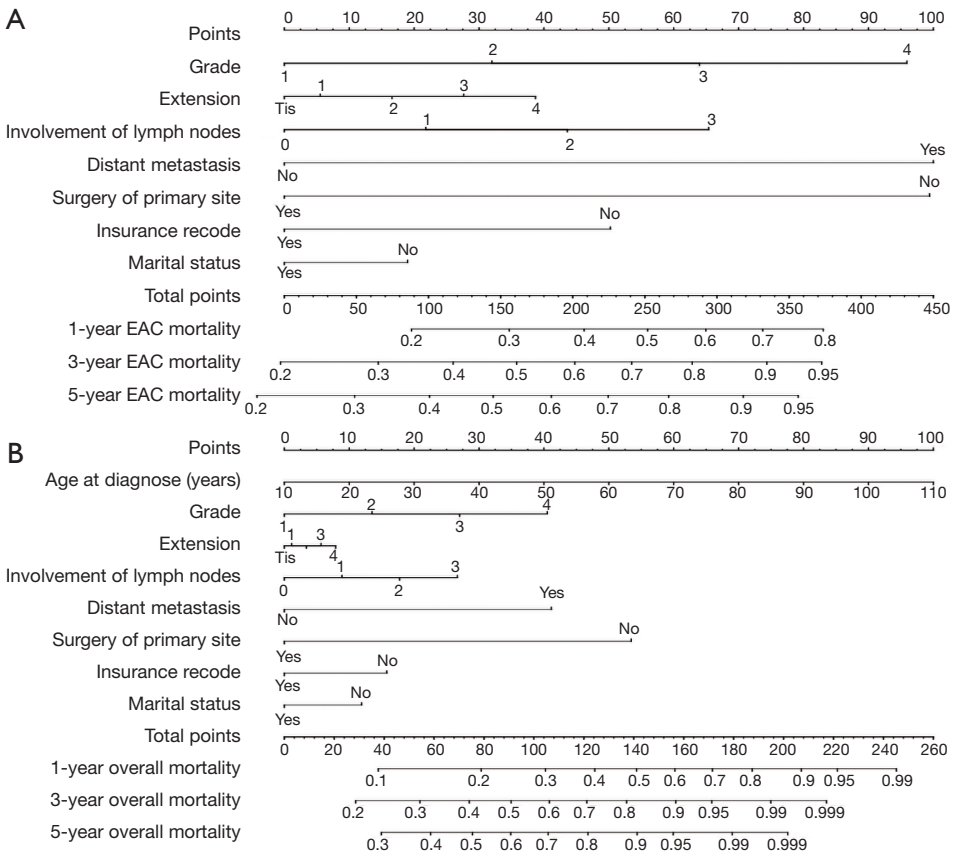

Figure 2 Nomogram for predicting 1-, 3- and 5-year cancer-specific mortality (A) and overall mortality (B) of EAC patients. Instructions for use of the nomogram: first, assign the points of each characteristic of the patient by drawing a vertical line from that variable to the points scale. Then, sum all the points and draw a vertical line from the total points scale to obtain the probability of 1-, 3- and 5-year cancer-specific mortality. EAC, esophageal adenocarcinoma.

5-year CIFs for EAC-specific survival. The brief nomogram based on a competing risks model was built to predict the probability of EAC-specific death and the other nomogram was built to predict the probability of overall death.

We observed that gender made none statistical difference in cancer-specific mortality, which was consistent with a previous study of the relationship between gender and prognosis in esophageal cancer (20,21) but conflicted with several previous studies (22-26), which indicated the higher incidence and poorer prognosis in men. To some extent, the reasons for this could be the vitamin D receptor (22), sex steroid hormones (26), and androgen/estrogen balance (24). In previous studies, age was also indicated to be an independent predictor of survival for patients with EAC (27). Increasing patient age was associated with a statistically increased mortality (28). Similarly, we identified the age at diagnosis as an independent negative prognostic factor for EAC patients when estimating overall mortality.

On the contrary, for EAC-specific mortality, age did not make a statistical difference in our study. It was indicated that the tumor itself has a significant effect on mortality caused by EAC, and age should be taken as a reference instead of an unalterable vital condition to evaluate the prognosis of EAC. After evaluation of the EAC-specific mortality nomogram, more aggressive management might be arranged for more elderly patients who still have a good prognosis prediction.

In summary, introducing EAC-specific mortality via competing for risk analysis when estimating the prognosis of patients with EAC is necessary. We also did not find a significant effect of race on prognosis. By contrast, several studies of mortality disparities by race and ethnicity in EAC showed that adenocarcinoma mainly affected the non-whites or the blacks, and led to a worse prognosis

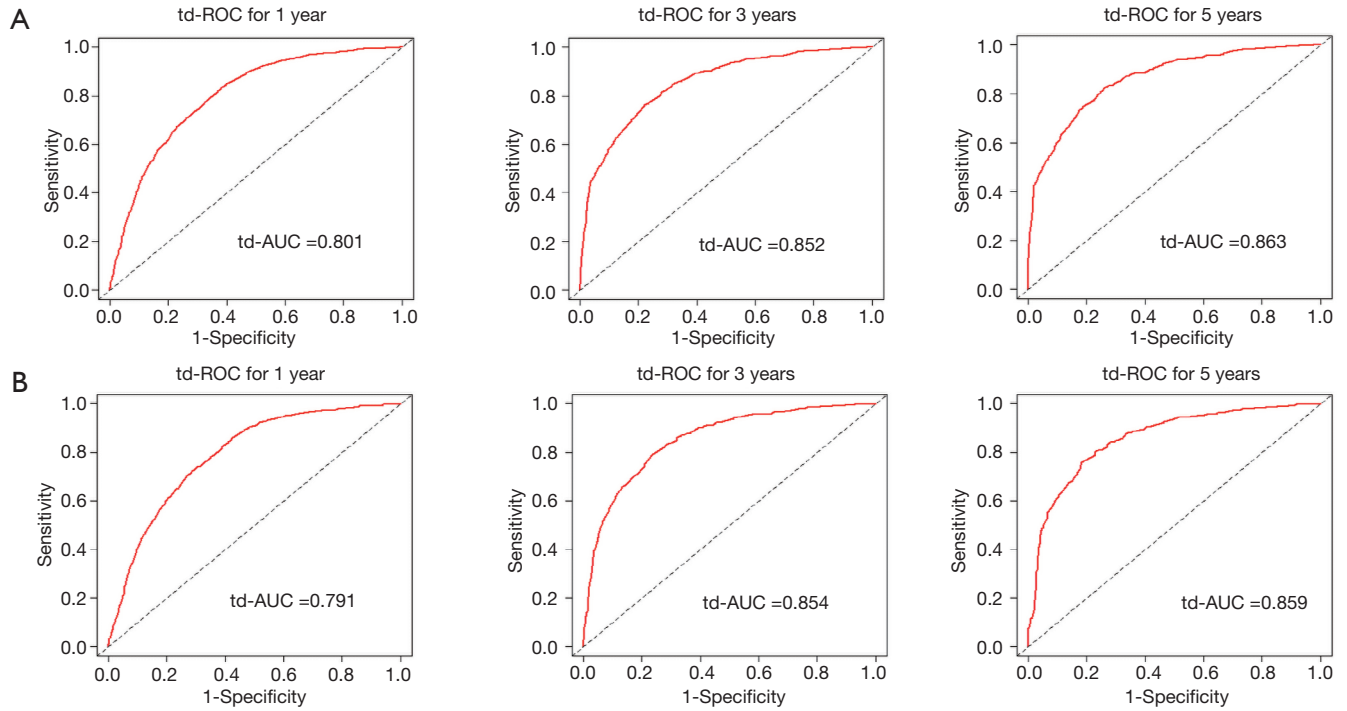

Figure 3 Time-dependent receiver operating characteristic (td-ROC) curves for the 1-, 3- and 5-year cancer-specific mortality nomogram of EAC patients. (A) td-ROC curves of the training cohort; (B) td-ROC curves of the validation cohort. AUC, area under the curve; EAC, esophageal adenocarcinoma.

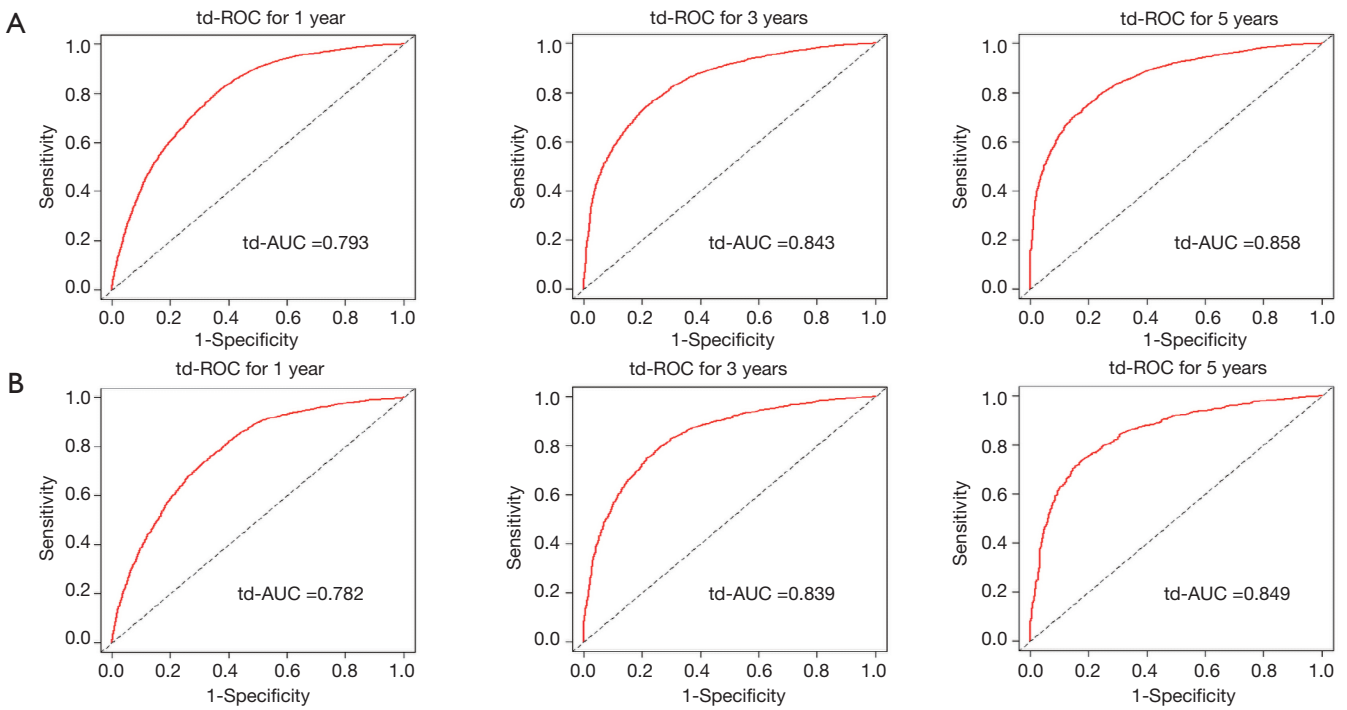

Figure 4 Time-dependent receiver operating characteristic (td-ROC) curves for the 1-, 3- and 5-year overall mortality nomogram of EAC patients. (A) td-ROC curves of the training cohort; (B) td-ROC curves of the validation cohort. AUC, area under the curve; EAC, esophageal adenocarcinoma.

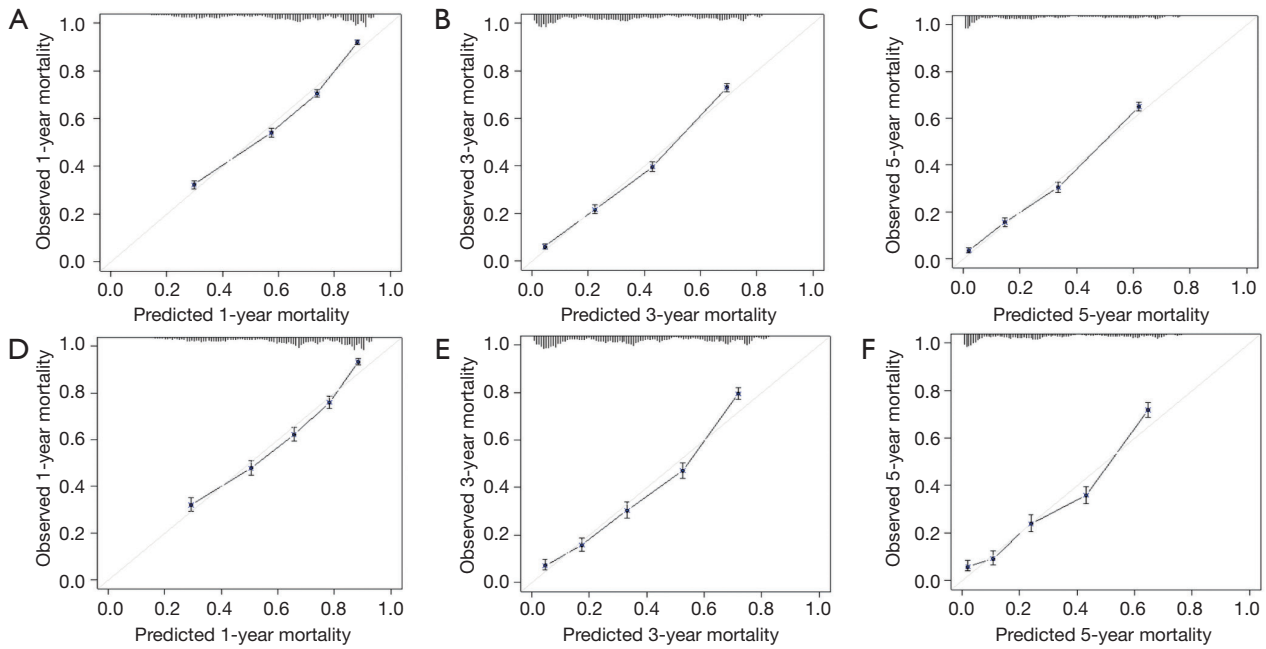

Figure 5 External calibration plots. The x-axis designates the mean predicted probability of EAC-specific mortality based on the model, and the y-axis indicates the observed cumulative incidence for EAC-specific death. (A,B,C) The calibration plots of 1-, 3- and 5-year model in the training cohort; (D,E,F) the calibration plots of 1-, 3- and 5-year model in the validation cohort. The solid line represents equality between the predicted and observed values. EAC, esophageal adenocarcinoma.

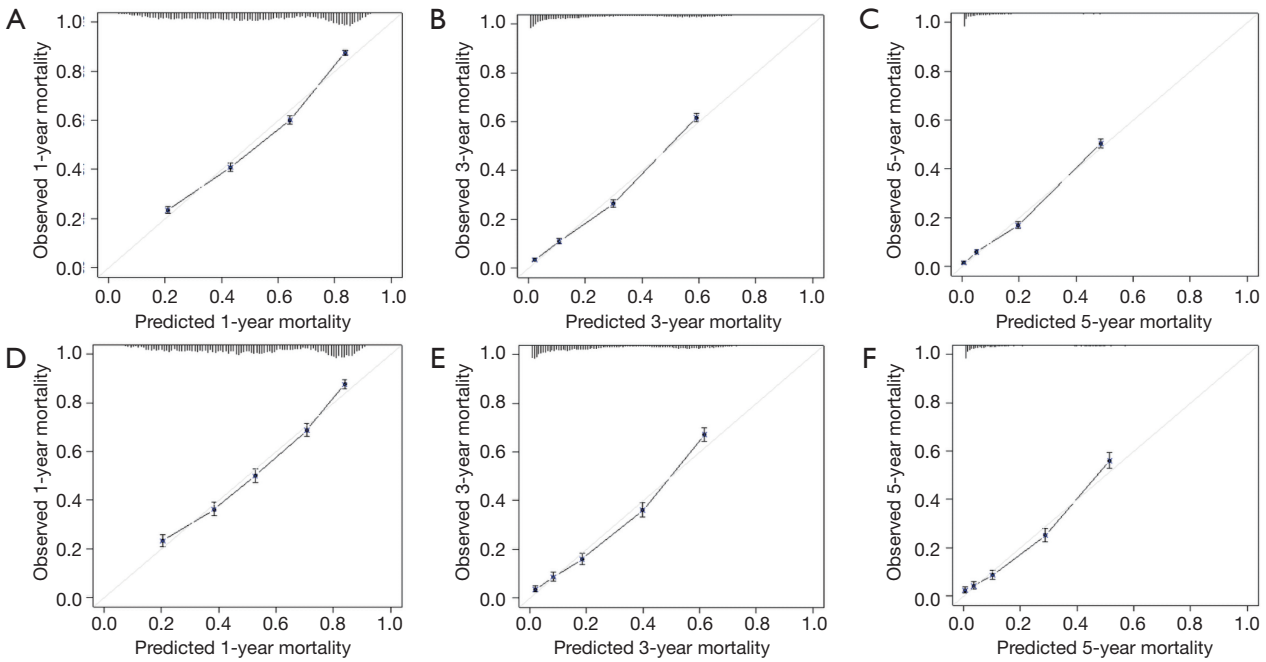

Figure 6 External calibration plots. The x-axis designates the mean predicted probability of overall mortality based on the model, and the y-axis indicates the observed cumulative incidence for overall mortality. (A,B,C) The calibration plots of 1-, 3- and 5-year model in the training cohort; (D,E,F) the calibration plots of 1-, 3- and 5-year model in the validation cohort. The solid line represents equality between the predicted and observed values.

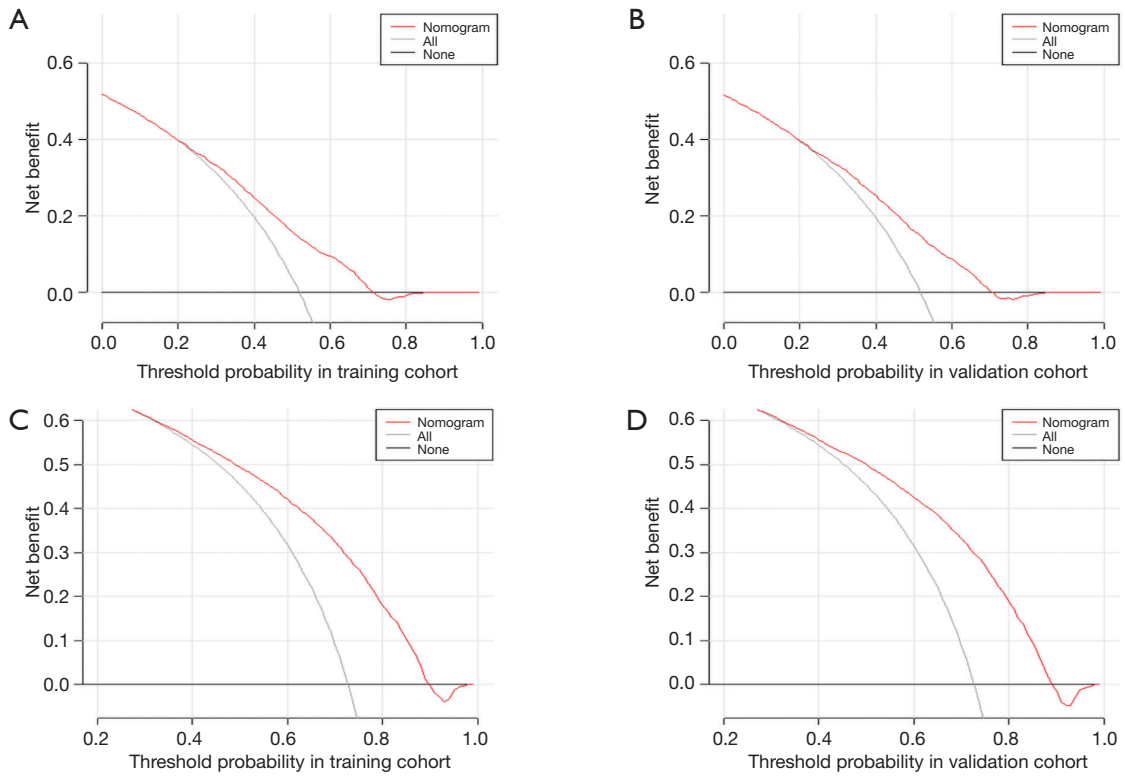

Figure 7 Decision curves for nomogram to predict cancer-specific mortality of EAC in the training cohort (A) and in the validation cohort (B), and decision curves for nomogram to predict overall mortality of EAC in the training cohort (C) and in the validation cohort (D). EAC, esophageal adenocarcinoma.

(29-31). This phenomenon might be caused by the higher proportion of the white population having a better income and hence better opportunity for medical treatment.

Furthermore, radiotherapy did not have a significant effect on cancer-specific mortality, which contrasted with other studies that used the SEER cohort (32,33). While these studies indicated that the impact of radiotherapy was reflected among various subgroup analyses, our study investigated the entire population of EAC rather than subgroup analyses. Since most of the population provided with radiotherapy were patients with most late-stage tumors whose condition were too poor to undergo surgery, the benefit of radiotherapy seemed to be limited for the prognosis of EAC patients in this study.

To our knowledge, this is the first study attempting to develop a nomogram for integrating a competing risk model for predicting cancer-specific mortality in EAC. Since EAC was associated with many complications, there was a maximum number of possibilities leading to biased results. Thus, a competing risk analysis was necessary for our study. The nomogram of our study appeared to capture effective discrimination ability and a satisfying clinical net benefit. All the variables listed could be easily obtained from routine clinical work. Therefore, based on combining clinical features and clinical information, this predictive tool can be easily and graphically used by clinicians to make a quick prognosis judgment for patients by drawing a few lines in seconds without any difficulty in calculation.

Additionally, our nomograms can help patients understand the possibility of prognosis graphically. Another virtue of this study is the large cohort size and long-term follow-up provided by the SEER database to refine the model. Also, we set a validation cohort to attain external validation, and the subsequent results were positive.

Our study has several limitations. Firstly, some clinicopathologic factors commonly cited (such as surgical margins, genetic mutation, presence of Barrett's esophagus, neoadjuvant therapies, the extent of surgery, BMI, and type of surgery) affecting prognosis are not documented in the

SEER database and neither are data on cancer recurrence and chemotherapy. Secondly, the AJCC 8th edition has been widely used since being published in 2017, but tumors were still classified according to the AJCC 7th staging manual in this study since the SEER database had not converted the TNM data according to AJCC 8th standard. In addition to this, G4 (undifferentiated cancer) in AJCC 7th was canceled in AJCC 8th. However, the number of G4 cases in the training cohort and validation cohort account for 1.2% of the total, and the application of the nomogram among EAC patients diagnosed by AJCC 8th could cause no more than a 5.5% change of the predicted mortality.

Additionally, the total stage was not included to avoid multicollinearity influences and limitations of the clinical application of the model when considering the addition of clinical staging (cTNM staging) and pathological staging after neoadjuvant therapy (ypTNM staging) in the AJCC 8th staging system. Undoubtedly, further improvement of this model should be conducted in future clinical research according to the AJCC 8th edition. Thirdly, since our data came from the SEER database produced in America, the model needs to be validated in multi-ethnic and multi-regional investigations.

Conclusions

We calculated the CIFs of cancer-specific death and other causes of death for patients with EAC using the SEER database. The brief nomograms based on the competing and overall risk analyses were built with variables that could be obtained with little difficulty. We believe that these nomograms could be easily used by clinicians to predict prognosis and help determine a personalized treatment for EAC patients.

Acknowledgments

None.

Footnote

Conflicts of Interest: 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.

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Supplementary

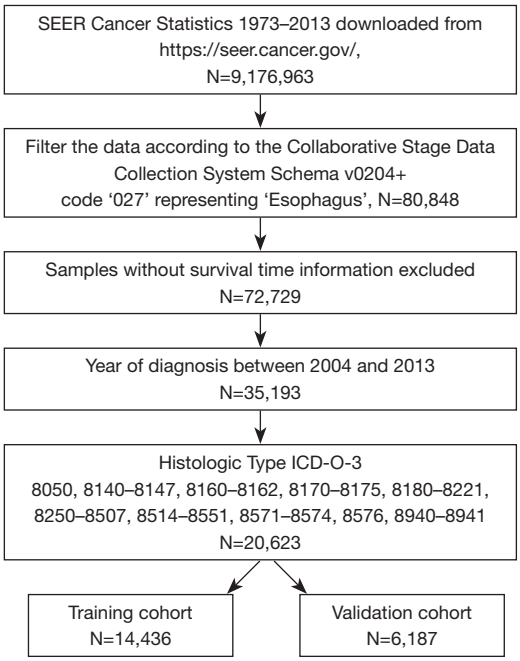

Figure S1 The flow diagram of the selection process for the study. SEER, surveillance, epidemiology, and end results.