Original Article

Nomogram for predicting the overall survival of the patients with oesophageal signet ring cell carcinoma

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Background: The purpose of this study was to explore the prognostic factors of oesophageal signet ring cell (SRC) carcinoma and to construct a nomogram for predicting the outcome of SRC carcinoma of oesophagus.

Methods: A total of 968 cases of oesophageal SRC carcinoma were extracted from the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2016. Cases were divided into training cohort and validation cohort. Univariate and multivariable Cox analyses was performed to select the predictors of overall survival (OS for the nomogram. The performance of nomogram was validated with Harrell's concordance index (C-index), calibration curves and decision curve analysis (DCA).

Results: The 1- and 5-year OS in the training cohort were 0.446 and 0.146, respectively, and the 1- and 5-year OS in the validation cohort were 0.459 and 0.138. The independent prognostic factors for establishing the nomogram were marital status, invasion of the surrounding tissue, lymph node metastasis, distant metastasis, surgery and chemotherapy. The Harrell's c-index value of the training cohort and validation cohort were 0.723 and 0.708. In the calibration curves, the predicted survival probability and the actual survival probability have a considerable consistency. DCA indicated the favourable potential clinical utility of the nomogram.

Conclusions: A nomogram to predict the OS of patients with oesophageal SRC carcinoma was established. The validation of the nomogram fully demonstrates its great performance.

Keywords: Oesophageal cancer; signet ring cell (SRC); nomogram

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Introduction

Oesophageal cancer is the 9th most common cancer and the 6th most common cause of cancer death globally (1). The main pathological types of oesophageal cancer are adenocarcinoma and squamous cell carcinoma. Squamous cell carcinoma is the predominant pathological type of oesophageal carcinoma worldwide. However, in the USA, Australia and some European countries, the incidence of oesophageal adenocarcinoma now exceeds that of oesophageal squamous cell carcinoma (2,3).

As a special pathological type of adenocarcinoma, signet ring cell (SRC) carcinoma is characterized by the appearance of a large vacuole containing mucin that squeezes the nucleus to the periphery of the cancer cell, making the cell look like a signet ring (4). SRC carcinoma can be diagnosed if more than 50% of tumours contain SRCs, according to the World Health Organization (WHO) criteria (5). SRC carcinoma is a rare pathological type of oesophageal cancer, and only approximately 3.5% to 5% of oesophageal cancers are SRC carcinomas (6-8). The first article to describe SRC carcinoma in the oesophagus was published in 1978 (9). SRCs have been found in colorectal cancer, prostate cancer, bladder cancer, breast cancer, gastric cancer and other adenocarcinomas. Various studies have shown that SRC carcinoma is an aggressive adenocarcinoma, and its presence suggests a poor prognosis (8,10-12). At present, most studies on SRC carcinoma are focused on gastric cancer and colorectal cancer, and there are relatively few studies on SRC carcinoma of the oesophagus.

A nomogram is also known as an alignment diagram. Based on multivariate regression analysis, a nomogram integrates multiple prediction indicators and then uses line segments with scales to draw them on the same plane in a certain proportion to express the predictive value of each variable in the prediction model. A nomogram is a convenient model for predicting clinical events, which is helpful in individualized treatment, clinical decision making and clinical trial design. Most of the current nomograms are for localized or metastatic oesophageal squamous cell carcinoma or adenocarcinoma, and no studies have established a predictive model for oesophageal SRC carcinoma (13-16). Therefore, the purpose of our study was to construct and validate a novel nomogram for predicting the outcomes of oesophageal SRC carcinoma patients using data from the Surveillance, Epidemiology, and End Results (SEER) database.

We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-3084).

Methods

Patient selection

All of the cases in this study were from the SEER database (the SEER 18 registries database with the additional treatment field, released in April 2019, www.seer.cancer.gov). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The SEER database, which includes approximately 30% of the United States population, is supported by the National Cancer Institute. The SEER*Stat 8.3.6 software was installed to extract the information of patients with oesophageal SRC carcinoma diagnosed between 2004 and 2016. We limited the period to 2004–2016, as detailed information about the TNM stage (AJCC 6th edition) and distant metastasis is only available from 2004. The selection criteria were as follows: (I) the site recorded was the oesophagus; (II) the histology code was 8490/3 SRC carcinoma; and (III) the year of diagnosis was 2004–2016. The exclusion criteria were (I) cases without race information; (II) cases without accurate TNM stage information. Ultimately, 968 cases were enrolled in our study cohort (*Figure 1*).

Outcome

The variables extracted from the SEER database included age, sex, race, marital status, primary site, T stage, N stage, M stage (the TNM staging of some patients undergoing surgery were pathological staging, while the others were clinical staging), grade, surgery, chemotherapy, radiation sequence with surgery, total number of malignant tumours, cause of death, survival time, and vital status. Patient deaths from all causes were regarded as uncensored cases for the overall survival (OS) analysis.

Patients were divided into 2 groups based on age (≤75, >75 years). Marital status was reclassified as married and single/unknown (divorced, separated, single, widowed, unknown). According to the 6th edition of the Union for International Cancer Control-American Joint Committee on Cancer (UICC-AJCC), tumour, node, metastasis (TNM) staging system, and T stage were reclassified into 2 groups (no invasion of the surrounding tissue: T1–T3; invasion of the surrounding tissue: T4). The N stage was converted into

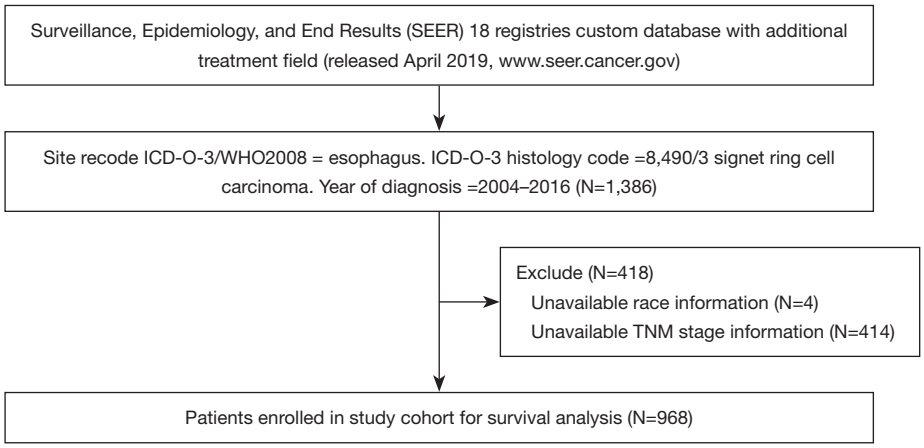

Figure 1 Study diagram of the selection process. ICD-O-3, 3rd edition of the International Classification Disease for Oncology; WHO, World Health Organization.

a variable named lymph node metastasis (yes: N1, no: N0). The M stage was converted into a variable named distant metastasis (yes: M1, no: M0). Surgery was reclassified into 3 groups (no surgery: SEER codes 00; local destruction or excision: SEER codes 10–14, 20–27; surgery: SEER codes 30, 40, 50–55, 80). Radiation sequences with surgery were converted into a variable named radiation therapy (yes, no).

All enrolled cases were divided into a training cohort and a validation cohort at a ratio of 7:3 randomly. The training cohort was used to establish the nomogram, and the validation cohort was used to validate the nomogram.

Statistical analysis

The clinicopathological features between the training and validation cohorts were compared by the using Chi-square (χ^2) test. OS was calculated using the Kaplan-Meier method. The Cox proportional hazard regression model was used for univariate and multivariate analyses. Variables with statistical significance (P<0.1) according to univariate analysis were included in the multivariate analysis. SPSS software (version 25.0 IBM, USA) was used for statistical analysis.

By using R software (version 4.0.0 R Foundation, Austria), we constructed a nomogram using the variables selected from the training cohort. Harrell's c-index was used to evaluate the predictive accuracy of the nomogram. Calibration curves were generated to visualize the discrimination between predicted and actual OS. The nomogram, Harrell's c-index and calibration curve were produced using the "rms" package of R software. The decision curve analysis (DCA), a novel diagram for evaluating the prediction model, was used to estimate the clinical utility of the nomogram (17,18).

Results

Baseline characteristics

A total of 968 eligible cases were enrolled in this study cohort and were randomly divided into the training cohort (677 cases) and validation cohort (291 cases) at a ratio of 7:3. The characteristics of the oesophageal SRC carcinoma patients in the training cohort and validation cohort are shown in *Table 1*. In all of the enrolled cases, most of the patients were younger than 75 years old, accounting for approximately 76.9% of the total patients. Approximately 86.9% of the patients were male. White and married people represented the majority of the patients.

Since SRC carcinoma is a type of adenocarcinoma, most (85.2%) of the tumours were located in the lower third of the oesophagus. As SRC carcinoma is a highly malignant tumour, most tumours were found to have a high grade (III+IV). At the same time, there were more cases with lymph node metastasis than without, and approximately 15.5% of the patients had invasion of the surrounding tissue, while 30.1% of the patients had distant metastases.

In terms of treatment, 34.8% of patients received surgical treatment, 27.5% received radiotherapy, and 71.3% received chemotherapy. Approximately 22.3% of the patients were diagnosed with two or more malignant tumours. The Chi-square (χ^2) test was performed to

Table 1 Characteristics of oesophageal SRC carcinoma patients in the training cohort and validation cohort

Variable	Total, N (%)	Training cohort, N (%)	Validation cohort, N (%)	P value
Total	968 (100)	677 (70.0)	291 (30.0)	
Age				0.912
≤75	744 (76.9)	521 (77.0)	223 (76.6)	
>75	224 (23.1)	156 (23.0)	68 (23.4)	
Sex				0.317
Female	127 (13.1)	84 (12.4)	43 (14.8)	
Male	841 (86.9)	593 (87.6)	248 (85.2)	
Marital status				0.769
Married	612 (63.2)	426 (62.9)	186 (63.9)	
Single or unknown	356 (36.8)	251 (37.1)	105 (36.1)	
Race				0.137
White	914 (94.4)	633 (93.5)	281 (96.6)	
Black	27 (2.8)	23 (3.4)	4 (1.4)	
Others	27 (2.8)	21 (3.1)	6 (2.1)	
Site				0.860
Cervical	1 (0.1)	1 (0.1)	0 (0)	
Thoracic	12 (1.2)	8 (1.2)	4 (1.4)	
Abdominal	5 (0.5)	4 (0.6)	1 (0.3)	
Upper third	5 (0.5)	4 (0.6)	1 (0.3)	
Middle third	47 (4.9)	29 (4.3)	18 (6.2)	
Lower third	825 (85.2)	577 (85.2)	248 (85.2)	
Overlapping	38 (3.9)	29 (4.3)	9 (3.1)	
Oesophagus, NOS	35 (3.6)	25 (3.7)	10 (3.4)	
Grade				0.547
I	3 (0.3)	3 (0.4)	0 (0)	
II	35 (3.6)	25 (3.7)	10 (3.4)	
III	755 (78.0)	531 (78.4)	224 (77.0)	
IV	22 (2.3)	17 (2.5)	5 (1.7)	
Unknown	153 (15.8)	101 (14.9)	52 (17.9)	
Invasion of the surrounding tissue				0.238
Yes	150 (15.5)	111 (16.4)	39 (13.4)	
No	818 (84.5)	566 (83.6)	252 (86.6)	
Lymph node metastasis				0.390
Yes	562 (58.1)	387 (57.2)	175 (60.1)	
No	406 (41.9)	290 (42.8)	116 (39.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total, N (%)	Training cohort, N (%)	Validation cohort, N (%)	P value
Distant metastasis				0.322
Yes	291 (30.1)	210 (31.0)	81 (27.8)	
No	677 (69.9)	467 (69.0)	210 (72.2)	
Surgery				0.223
No surgery	607 (62.7)	429 (63.4)	178 (61.2)	
Local destruction or excision	24 (2.5)	13 (1.9)	11 (3.8)	
Surgery	337 (34.8)	235 (34.7)	102 (35.1)	
Radiation therapy				0.634
Yes	266 (27.5)	183 (27.0)	83 (28.5)	
No	702 (72.5)	494 (73.0)	208 (71.5)	
Chemotherapy				0.580
Yes	690 (71.3)	479 (70.8)	211 (72.5)	
No or unknown	278 (28.7)	198 (29.2)	80 (27.5)	
Number of malignant tumours				0.243
=1	752 (77.7)	519 (76.7)	233 (80.1)	
≥2	216 (22.3)	158 (23.3)	58 (19.9)	

compare categorical variables between groups, but there was no variable with a P value less than 0.05.

The survival curves of the training cohort and the validation cohort generated using the Kaplan-Meier method are shown in *Figure 2*. The 1- and 5-year OS in the training cohort were 0.446 and 0.146, respectively, and the 1- and 5-year OS in the validation cohort were 0.459 and 0.138.

Prognostic factors for oesophageal SRC patients

A Cox proportional hazards regression model was applied for univariate and multivariate analyses of OS. As shown in *Table 2*, according to the univariate analysis, a total of 8 variables (age, marital status, invasion of the surrounding tissue, lymph node metastasis, distant metastasis, surgery, radiation therapy, and chemotherapy) were considered to be statistically significant (P<0.1) and could be included in the multivariate analysis. Before performing the multivariate analysis, a multicollinearity diagnosis was conducted for these 8 variables. The variance inflation factor (VIF) values for age, marital status, invasion of the surrounding tissue, lymph node metastasis, distant metastasis, surgery, radiation therapy, and chemotherapy were 1.135, 1.036, 1.071, 1.080, 1.174, 2.520, 2.569, and 1.270, respectively. We found that the VIF value for radiation therapy was the largest, indicating the existence of a multicollinearity problem.

After removing the variable radiation therapy, multicollinearity diagnosis was performed again, and it was found that none of the variables indicated a significant problem with multicollinearity, with all the VIF values less than 2 (age, 1.135; marital status, 1.033; invasion of the surrounding tissue, 1.071; lymph node metastasis, 1.080; distant metastasis, 1.171, surgery, 1.203; and chemotherapy, 1.080). These 7 variables were thus included in the multivariate Cox regression analysis.

As shown in *Table 3*, the P value of age was 0.901, which was considered to have no statistical significance. Finally, the independent prognostic factors for establishing the nomogram were chosen, and the nomogram was based on marital status, invasion of the surrounding tissue, lymph node metastasis, distant metastasis, surgery and chemotherapy.

Development and validation of the nomogram

Based on the six variables described above (marital

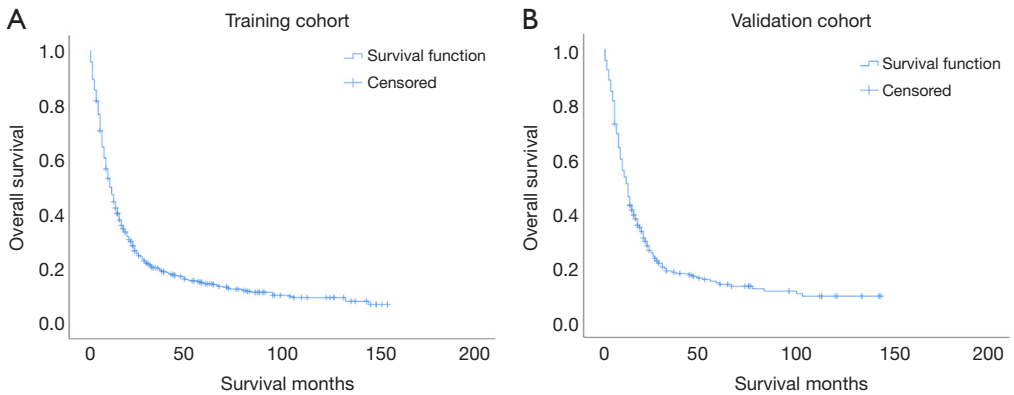

Figure 2 Kaplan-Meier survival curves of the overall survival (OS) for oesophageal signet ring carcinoma patients. (A) Training cohort; (B) validation cohort.

Table 2 Univariate cox analysis of overall survival in the training cohort

Variable	HR	95% CI	P value
Age			0.040
≤75	Reference		
>75	1.222	1.009–1.480	0.040
Sex			0.675
Female	Reference		
Male	0.948	0.738–1.217	0.675
Marital status			<0.001
Single or unknown	Reference		
Married	0.733	0.620–0.868	<0.001
Race			0.445
White	Reference		
Black	1.299	0.855–1.972	0.220
Others	1.094	0.692–1.729	0.701
Site			0.672
Cervical	Reference		
Thoracic	0.327	0.039–2.723	0.301
Abdominal	0.356	0.037–3.429	0.371
Upper third	0.171	0.015–1.897	0.150
Middle third	0.499	0.067–3.695	0.496
Lower third	0.482	0.068–3.437	0.467
Overlapping	0.589	0.080–4.348	0.604
Oesophagus, NOS	0.485	0.065–3.620	0.480

Table 2 (*continued*)

Table 2 (*continued*)

Variable	HR	95% CI	P value
Grade			0.886
I	Reference		
II	1.576	0.369–6.723	0.539
III	1.725	0.430–6.920	0.442
IV	1.48	0.336–6.513	0.604
Unknown	1.777	0.437–7.225	0.422
Invasion of the surrounding tissue			<0.001
No	Reference		
Yes	1.898	1.534–2.347	<0.001
Lymph node metastasis			<0.001
No	Reference		
Yes	1.341	1.134–1.586	<0.001
Distant metastasis			<0.001
No	Reference		
Yes	2.509	2.100–2.998	<0.001
Surgery			<0.001
No surgery	Reference		
Local destruction or excision	0.501	0.274–0.913	0.024
Surgery	0.364	0.302–0.439	<0.001
Radiation therapy			<0.001
No	Reference		
Yes	0.507	0.418–0.616	<0.001
Chemotherapy			<0.001
No or unknown	Reference		
Yes	0.628	0.525–0.751	<0.001
Number of malignant tumours			0.116
=1	Reference		
≥2	0.856	0.706–1.039	0.116

HR, hazard ratio; CI, confidence interval.

status, invasion of the surrounding tissue, lymph node metastasis, distant metastasis, surgery and chemotherapy), a nomogram was constructed to predict the 1-year, 3-year and 5-year OS of patients with oesophageal SRC carcinoma, as shown in *Figure 3*. In the nomogram, surgery had the greatest influence on prognosis, while marital status had the least influence. By adding the scores of each item to obtain the total score, the corresponding survival probability was obtained from the nomogram. The Harrell's c-index value of the training cohort and validation cohort were 0.723 and 0.708, respectively. As shown in *Figure 4*, by drawing the calibration curves (200 bootstrap resamples), it can be seen that the predicted survival probability and the actual survival probability have

Table 3 Multivariate cox analysis of overall survival in the training cohort

Variable	HR	95% CI	P value
Age			0.901
≤75	Reference		
>75	0.987	0.805–1.211	0.901
Marital status			0.090
Single or unknown	Reference		
Married	0.862	0.726–1.024	0.090
Invasion of the surrounding tissue			<0.001
No	Reference		
Yes	1.431	1.147–1.784	<0.001
Lymph node metastasis			<0.001
No	Reference		
Yes	1.446	1.214–1.723	<0.001
Distant metastasis			<0.001
No	Reference		
Yes	1.882	1.553–2.281	<0.001
Surgery			<0.001
No surgery	Reference		
Local destruction or excision	0.516	0.279–0.953	0.034
Surgery	0.419	0.342–0.514	<0.001
Chemotherapy			<0.001
No or unknown	Reference		
Yes	0.487	0.402–0.591	<0.001

HR, hazard ratio; CI, confidence interval.

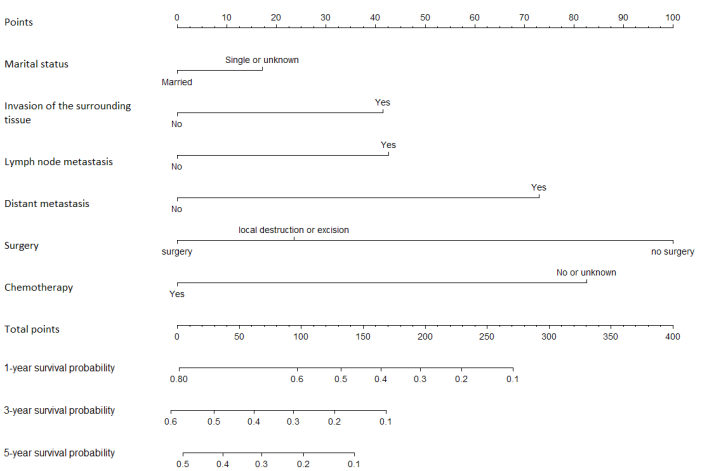

Figure 3 Nomogram for predicting 1-, 3- and 5-year overall survival of patients with oesophageal signet ring cell carcinoma.

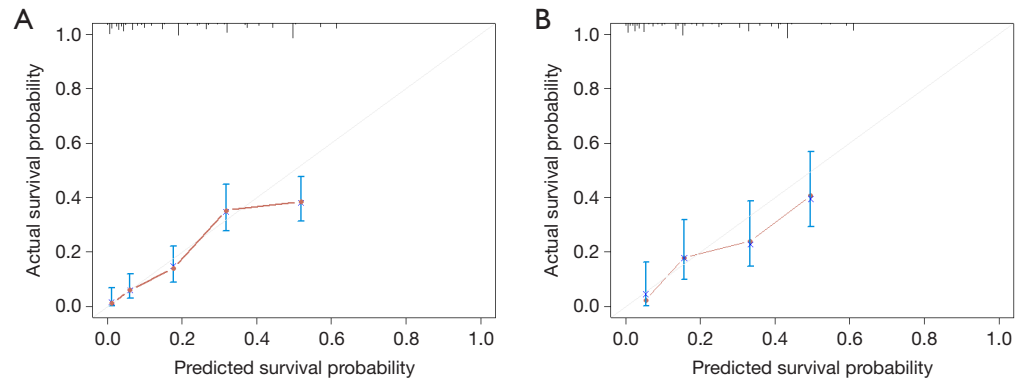

Figure 4 Calibration curves for predicting 3-year overall survival in the training cohort (A) and validation cohort (B).

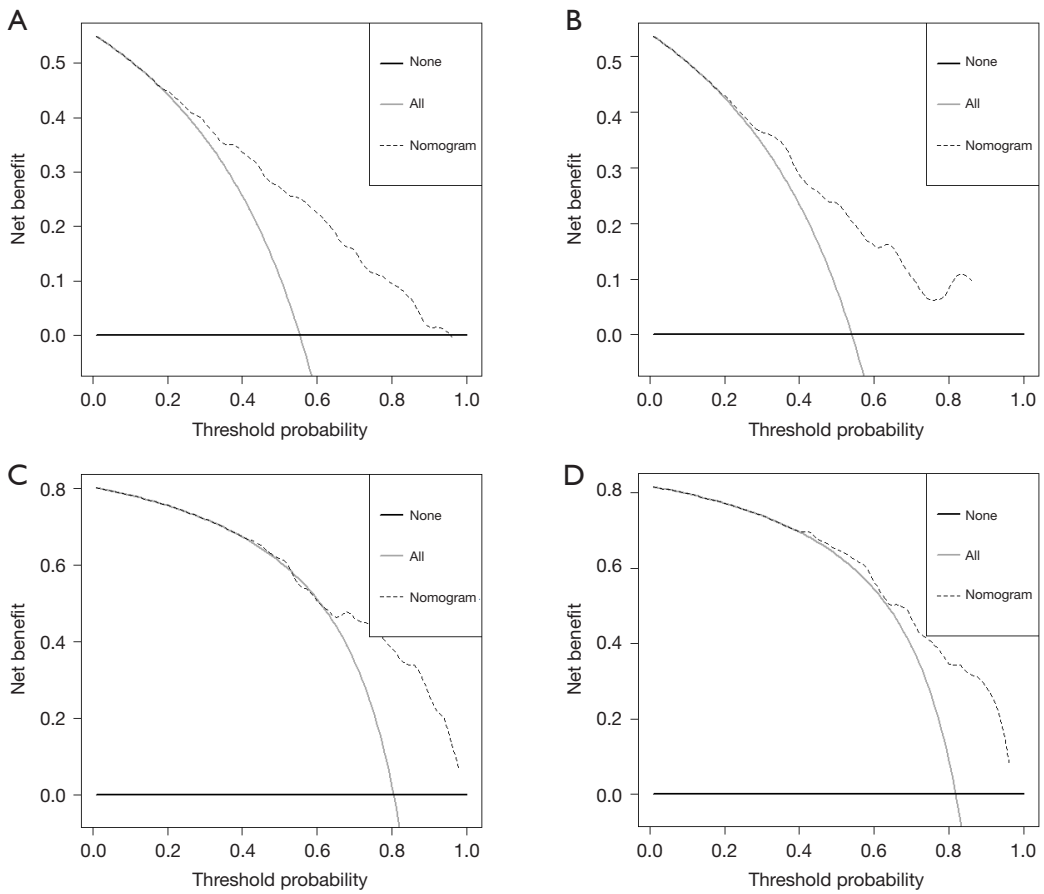

Figure 5 Decision curve analysis of the nomogram for predicting overall survival at 1-year point in the trainning cohort (A) and validation cohort (B) and overall survival at 3-year point in the trainning cohort (C) and validation cohort (D).

a considerable consistency.

Finally, as shown in *Figure 5*, we performed DCA to evaluate the clinical utility of the predictive model. The x-axis represents the threshold probabilities, and the y-axis measures the net benefit calculated by adding the true positives and subtracting the false positives. The horizontal

line assumes that death occurred in no patients, whereas the gray line assumes that all patients will have death at a specific threshold probability. The dashed line represents the net benefit of using the nomogram. As we can see in the DCA, in the range 0–1.0 of threshold probabilities nomogram showed better net benefit than the other two extreme cases. The DCA showed strong positive net benefits in the nomogram among wide ranges of the threshold probabilities, indicating the favourable potential clinical utility of the nomogram.

Discussion

Oesophageal SRC carcinoma is a rare pathological type of oesophageal adenocarcinoma. According to previous studies, SRC carcinoma of the oesophagus is a malignant tumour with a poor prognosis (7-9). There are few studies on the prognostic factors of SRC carcinoma of the oesophagus, and no prognostic model of oesophageal SRC carcinoma has been developed, which makes it difficult to predict the outcomes of patients with oesophageal SRC. In this paper, the first predictive model for oesophageal SRC carcinoma was constructed using the SEER database, and subsequent validation of the model established its great performance in predicting the outcome of oesophageal SRC carcinoma.

Nomograms, as clinical prediction models, have been widely used to predict the outcomes of cancer patients. Several predictive models are currently available for oesophageal cancer (13,14,16,19,20), but none of them focus on SRC carcinoma of the oesophagus. Current studies on the prognosis of SRC of the oesophagus suggest that female sex, unmarried, invasion of adjacent organs, a high tumour grade, metastasis of regional lymph nodes or distant organs and no chemotherapy were independent prognostic factors (21,22). However, the sample sizes of these studies were small and some prognostic factors associated with oesophageal SRC were found, but no predictive models were further constructed and validated.

In this study, nearly 1,000 cases with oesophageal SRC carcinoma from the SEER database were enrolled, and they were randomized into training and validation cohorts to validate the predictive model. Univariate and multivariate analyses of the existing variables in the SEER database were performed. Finally, six variables, including marital status, invasion of the surrounding tissue, lymph node metastasis, distant metastasis, surgery and chemotherapy, were selected as independent prognostic factors for construction of the nomogram.

According to the predictive model constructed in this study, surgery and chemotherapy had the greatest impact on prognosis, which also supports the concept that surgery and chemotherapy are currently the most important treatment methods for oesophageal SRC. This conclusion is consistent with previous studies on oesophageal cancer (23-26). For radiotherapy, this variable was removed in this study due to the collinearity problem. We think the collinearity problem may be related to the fact that most patients receiving radiotherapy are patients in an advanced stage with no chance of surgery. There is a significant correlation between whether a patient receives radiotherapy and the TNM stage of the patient, so the effect of radiotherapy on prognosis will be interfered with by the TNM stage of the patient. In addition, as SRC of the oesophagus is a type of adenocarcinoma and the sensitivity of oesophageal adenocarcinoma to radiotherapy is significantly lower than that of oesophageal squamous cell carcinoma (27), radiotherapy was not included in the final prediction model.

According to our study, invasion of the surrounding tissue, lymph node metastasis, and distant metastasis can all adversely affect the prognosis of patients. The presence of surrounding tissue invasion and lymph node or distant organ metastasis all indicate an advanced TNM stage, so these patients have a worse prognosis, which is consistent with the majority of existing research results. However, there are still some controversial studies on oesophageal adenocarcinoma. Agoston and colleagues found that the T stage and N stage had no effect on the prognosis of oesophageal adenocarcinoma (28). Further studies are expected to clarify the relationship between these factors and the prognosis of SRC of the oesophagus.

In this study, marital status was also found to be a prognostic factor. As seen in the nomogram, single patients had a worse prognosis. The effect of marital status on the prognosis of patients with malignant tumours has been mentioned in many previous retrospective studies. Studies of colorectal cancer, breast cancer and prostate cancer have shown that married patients exhibit better survival than unmarried patients (29,30). The reason for this difference may be that marital status affects a patients' mood and quality of life (31,32). More prospective studies are expected to confirm the relationship between marital status and prognosis in patients with oesophageal SRC.

There are still some limitations in this study. First, this study is a retrospective study, and selection bias is inevitable. Second, since the data in this study were obtained from the SEER database, some information that may impact the

prognosis were not included, including the proportion of SRCs in tumour cells, comorbidities, the chemotherapy regimen, etc. Moreover, chemotherapy and radiation therapy data are categorized as either "yes—patient had chemotherapy or radiation therapy" or "no/unknown—no evidence of chemotherapy or radiation therapy was found in the medical records examined, the biases associated with these unmeasured reasons affect analyses Third, due to the low incidence of SRC carcinoma of the oesophagus, sufficient external data were not available for validation in this study. In the future, it is expected that more prospective multicentre large studies will be conducted on oesophageal SRC carcinoma to improve our diagnosis and treatment of SRC carcinoma of the oesophagus.

Conclusions

We built a nomogram to predict the OS of patients with oesophageal SRC carcinoma. The subsequent validation of the predictive model fully demonstrates its great performance. This model can be used to predict the outcomes of patients with oesophageal SRC carcinoma and provide guidance for their individualized treatment.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-3084). 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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