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Independent risk factors evaluation for overall survival and cancer-specific survival in thyroid cancer patients with bone metastasis

A study for construction and validation of the predictive nomogram

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Abstract

Bone is a frequent site for the occurrence of metastasis of thyroid cancer (TC). TC with bone metastasis (TCBM) is associated with skeletal-related events (SREs), with poor prognosis and low overall survival (OS). Therefore, it is necessary to develop a predictive nomogram for prognostic evaluation. This study aimed to construct an effective nomogram for predicting the OS and cancer-specific survival (CSS) of TC patients with BM. Those TC patients with newly diagnosed BM were retrospectively examined over a period of 6 years from 2010 to 2016 using data from the Surveillance, Epidemiology and End Results (SEER) database. Demographics and clinicopathological data were collected for further analysis. Patients were randomly allocated into training and validation cohorts with a ratio of ~7:3. OS and CSS were retrieved as research endpoints. Univariate and multivariate Cox regression analyses were performed for identifying independent predictors. Overall, 242 patients were enrolled in this study. Age, histologic grade, histological subtype, tumor size, radiotherapy, liver metastatic status, and lung metastatic status were determined as the independent prognostic factors for predicting the OS and CSS in TCBM patients. Based on the results, visual nomograms were separately developed and validated for predicting 1-, 2-, and 3-year OS and CSS in TCBM patients on the ground of above results. The calibration, receiver operating characteristic (ROC) curve and decision curve analysis (DCA) also demonstrated the reliability and accuracy of the clinical prediction model. Our predictive model is expected to be a personalized and easily applicable tool for evaluating the prognosis of TCBM patients, and may contribute toward making an accurate judgment in clinical practice.

Abbreviations: ATC = anaplastic thyroid cancer, AUC = area under the curve, BM = bone metastasis, CI = confidence interval, C-index = Harrell's concordance index, CSS = cancer-specific survival, DCA = decision curve analysis, DM = distant metastasis, FTC = follicular thyroid carcinoma, HR = hazard ratios, MTC = medullary thyroid carcinoma, OS = overall survival, PTC = papillary thyroid cancer, ROC = receiver operating characteristic, SEER = Surveillance, Epidemiology and End Results, SRE = skeletal-related event, TC = thyroid cancer, TCBM = thyroid cancer with bone metastasis, TCDM = thyroid cancer with distant metastasis.

Keywords: cancer-specific survival, nomogram, overall survival, prognosis, SEER, thyroid cancer with bone metastasis

Editor: Balaji Thas Moorthy.

YT, ZH, and CH contributed equally to this work.

Ethics approval and consent to participate: Since the data comes from the SEER database, and due to no identification information was recorded, the study was exempted by the SEER database administrators.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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

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How to cite this article: Tong Y, Huang Z, Hu C, Chi C, Lv M, Li P, Zhao C, Song Y. Independent risk factors evaluation for overall survival and cancer-specific survival in thyroid cancer patients with bone metastasis: A study for construction and validation of the predictive nomogram. Medicine 2020;99:36(e21802).

Received: 10 April 2020 / Received in final form: 4 July 2020 / Accepted: 14 July 2020

http://dx.doi.org/10.1097/MD.0000000000021802

1. Introduction

According to the 2019 Cancer statistic report, thyroid cancer (TC) accounts for ~90% of all endocrine malignancies.[1] TC is usually associated with a favorable *prognosis*, with a 10-year survival rate over of 80%. This is predominantly attributed to the biological characteristics of the tumor and effective medical interventions.[2,3] However, thyroid cancer with distant metastasis (TCDM) has a less favorable prognosis.[4–6] Many risk stratification systems have classified TCDM as a high-risk group.[7–9] Among various metastatic sites, See Anna et al[10] reported that bone is the most common site for distant metastasis in TC (36.8%). A relevant research showed that the 10-year survival rate even dropped to 14% for patients older than 40 years having TCBM.[11] In addition, the quality of life is severely affected for TCBM patients. One study showed that 78% of TCBM patients had at least one skeleton-related event (SRE) during a median follow-up period, and 49% had multiple SREs during a 5-year follow-up period, with significantly increased mortality in patients with bone metastasis (BM).[12] Therefore, the survival prognostic evaluation for TCBM patients is an important topic in the field of thyroid malignancy research.

The UICC/AJCC TNM classification and staging system is generally considered as a credible tool for evaluating the prognosis of malignancies in clinical diagnosis and treatment,[13,14] TC is no exception. However, the TNM staging system does not sufficiently cover cancer the biological characteristics, treatment information of the tumor and specifically predict the OS for TCBM patients. During the past decades, numerous studies focusing on identifying prognosis-related variables of TCBM, including histological type, SREs, serum thyroglobulin (Tg), hypercalcemia, surgical resection of primary thyroid lesions, stereotactic radiotherapy, were conducted.[15–18] However, to the best of our knowledge, there have been no studies focusing on the development of a predictive model for the overall survival (OS) and cancer-specific survival (CSS) in TCBM patients. In other words, the specific contribution of demographics, clinicopathological features and treatment methods in the survival rate of TCBM patients has not elucidated clearly. For this reason, our study aimed at constructing and validating a nomogram to predict the 1-, 2-, and 3-year OS and CSS for TCBM patients.

2. Materials and methods

2.1. Patients

This retrospective study was conducted using the SEER*Stat software version 8.3.5 to identify patients diagnosed as TCBM from the SEER program financed by the National Cancer Institute, and extract their data. The SEER database is the largest nationally representative cancer database consisting of 18 population-based cancer registries with nearly 30% of the US population.[19] There was no requirement for the ratification of the ethics committee clearance and patient agreement and consent as no specific personal information was publicly available. As the information about site-specific metastasis was available from 2010 onwards, we limited our analysis between 2010 and 2016. Patients were excluded if a definite diagnosis was made based on necropsy findings or death certificate and detailed information was unavailable. Patients whose TC was not the first primary malignant tumor were also excluded. A total of 242 cases were found eligible for the study.

2.2. Data elements

The demographic, clinicopathological, and systematic treatment data of all included patients were extracted. A total of 15 variables, including age, race, sex, histological subtype, grade, laterality, tumor size, T stage, N stage, surgery, chemotherapy, radiotherapy, brain metastasis, liver metastasis, and lung metastasis were evaluated. Furthermore, information on other rare metastatic sites was extracted for this study. The histological subtype was classified into four categories with the following IDO-O-3 codes: 8340. 8341.8342.8344.8260—papillary thyroid cancer (PTC), 8330.8331.8335—follicular thyroid carcinoma (FTC); 8020.8021.8030.8032—anaplastic thyroid cancer (ATC); 8510. Medullary thyroid carcinoma (MTC). All cases were staged according to the 7th AJCC TNM classification.

2.3. Statistical analysis

Of the total 242 eligible TCBM patients, 170 were randomly allocated to the training cohort and the remaining 72 patients were allocated to the validation cohort to construct and validate the nomogram. All the demographic and clinicopathological variables were tested between two cohorts using Chi-squared (χ^2) test. OS and CSS were designated as the two endpoints for this study. OS and CSS are defined as the period of time from the initial definitive diagnosis till death or till the day of the final clinical follow-up with the reason for death being attributed to all causes and TCBM, respectively. The age of the patients and tumor size of patients were compartmentalized using the X-tile program.[20]

The establishment and validation of the nomogram was initiated with an univariate *Cox* regression analysis to study the correlation between each prognostic variable and OS&CSS, individually. Following that, variables with a *P*-value below .05 from the univariate analysis we univariate analysis were subjected to a multivariate Cox regression analysis. The variables with a final *P*-value below .05 were designated as independent prognostic factors. The above steps were performed using the *Cox* proportional hazards *regression model*. Additionally, *Hazard ratios* (HRs) and *95%* confidence intervals (*CIs*) *were also reported* for each prognostic factor. Finally, based on the identified independent prognostic factors nomograms were established separately for the 1-, 2-, and 3-year OS and CSS via the RMS package in R software. The ROC curve was drawn, and the area under the curve (AUC) was used to represent the differentiation of the nomogram. A model was considered well-functioning if the AUC was between 0.5 and 1. On the whole, with an AUC > 0.75, is the model was considered to have excellent performance in measuring separability.[21] Calibration curves and DCA were also used to evaluate the accuracy of the nomogram, and $P < .05$ was considered statistically significant.

3. Results

3.1. Population information

All included TC patients were confirmed to have BM at initial diagnosis, with the bone being the only metastatic site or as a component of multiple organ metastasis. Table 1 shows the demographic and clinicopathological variables of all patients. The optimal cutoff value of age was identified as 58 years for OS and 59 years for CSS. The patients were divided into two groups to facilitate data processing (20–58 years and 59–90 years).

Table 1

Demographic and clinicopathological variables for TCBM patients.

	Total cohort (N = 242)		Training cohort (N = 170)		Validation cohort (N = 72)	
Variables	**n**	**%**	**n**	**%**	**n**	**%**
Age						
20–58	93	38.43	63	37.06	30	41.67
59–90	149	61.57	107	62.94	42	58.33
Race						
White	170	70.25	117	68.82	53	73.61
Black	35	14.46	26	15.29	9	12.5
Other	37	15.28	27	15.88	10	13.89
Sex						
Female	130	53.72	93	54.71	37	51.39
Male	112	46.2	77	45.29	35	48.61
Histological subtype						
Papillary	122	50.41	86	50.58	36	50
Follicular	61	25.21	42	24.71	19	26.39
Anaplastic	31	12.81	24	14.12	7	9.72
Medullary	28	11.57	18	10.59	10	13.89
Grade						
Low (I, II)	57	23.55	42	24.71	15	20.83
High (III, IV)	59	24.38	40	23.53	19	26.39
Unknown	126	52.07	88	51.76	38	52.78
Laterality						
Left—origin of primary	7	2.89	5	2.94	2	2.78
Right—origin of primary	7	2.89	4	2.35	3	4.16
Bilateral	2	0.83	2	1.18	0	0
Not a paired site	226	93.39	159	93.53	67	93.06
T stage						
T1–2	74	30.58	49	28.82	25	34.72
T3–4	168	69.42	121	71.18	47	65.28
N stage						
N0	134	55.37	96	56.47	38	52.78
N1	108	44.63	74	43.53	34	47.22
Radiotherapy						
No/unknown	74	30.58	45	26.47	29	40.28
Yes	168	69.42	125	73.53	43	59.72
Chemotherapy						
No/unknown	200	82.64	142	83.53	58	80.56
Yes	42	17.36	28	16.47	14	19.44
Surgery						
No/unknown	48	19.83	28	16.47	20	27.78
Yes	194	80.17	142	83.53	52	72.22
Brain metastasis						
No	226	93.39	158	92.95	68	94.44
Yes	12	4.96	8	4.7	4	5.56
Unknown	4	1.65	4	2.35	0	0
Liver metastasis						
No	212	87.6	146	85.88	66	91.67
Yes	27	11.16	21	12.35	6	8.33
Unknown	3	1.24	3	1.77	0	0
Lung metastasis						
No	143	59.09	101	59.41	42	58.33
Yes	92	38.02	64	37.65	28	38.89
Unknown	7	2.89	5	2.94	2	2.78
Tumor size						
3–80	209	86.36	144	84.71	65	90.28
81–160	33	13.64	26	15.29	7	9.72

Analysis of the demographic data revealed that 112 patients (46.28%) were male and the remaining 130 (53.72%) were female. As for the race of the enrolled patients, majorities were White (n = 170 [70.25%]). Of the various histological subtype, PTC (n = 122 [50.41%]) was the most common subtype, followed by follicular thyroid cancer (n = 61 [25.21%]), ATC (n = 31 [12.81%]), and medullary carcinoma (n = 28 [11.57%]). The most common T and N stages T3–4, respectively (32.3%) and N0 (55.37%). Some patients, besides having bone involvement, also had accompanying distant metastases to other sites. Of

them, 92 patients (38.02%) had lung metastases, 27 (11.46%) had liver metastases, and 12 (4.96%) had brain metastases. In addition, the data highlighted that surgery was the most widely accepted mode of treatment by the patients (80.17%), while chemotherapy and radiotherapy were given in a few cases (n = 42 [17.36%] and n = 168 [69.42%], respectively).

3.2. Prognostic factors of OS and CSS

Univariate and multivariate Cox analyses were performed to explore independent prognostic factors in the training cohort. The results for OS are shown in Table 2. Statistical evaluation revealed age ($P = .001$), grade ($P = .009$), combined liver metastasis ($P = .001$), histological subtype ($P = .003$) and radio-

Table 2

Univariate and multivariate Cox proportional hazards regression analysis based on all variables for OS.

	Univariate analysis		Multivariate analysis	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age				
20–58	Reference		Reference	
59–90	2.484 (1.448–4.26)	.001	2.468 (1.415–4.304)	.001
Race				
Black	Reference			
Other	0.598 (0.252–1.422)	.245		
White	1.085 (0.581–2.028)	.798		
Sex				
Female	Reference			
Male	1.43 (0.915–2.234)	.116		
Histological subtype				
Papillary	Reference		Reference	
Follicular	0.714 (0.376–1.355)	.303	0.544 (0.284–1.045)	.068
Anaplastic	17.279 (8.689–34.363)	<.001	3.93 (1.577–9.794)	.003
Medullary	2.397 (1.116–5.147)	.025	0.953 (0.405–2.241)	.912
Grade				
Low (I, II)	Reference		Reference	
High (III, IV)	0.479 (0.324–0.709)	<.001	3.039 (1.312–7.038)	.009
Unknown	3.155 (2.274–4.378)	<.001	0.841 (0.424–1.669)	.621
Laterality				
Bilateral	Reference			
Left—origin of primary	0.516 (0.047–5.702)	.59		
Not a paired site	0.801 (0.111–5.797)	.826		
Right—origin of primary	1.664 (0.172–16.132)	.661		
T stage				
T1–2	Reference			
T3–4	1.96 (1.13–3.4)	.017		
N stage				
N0	Reference			
N1	2.316 (1.467–3.656)	<.001		
Radiotherapy				
No	Reference		Reference	
Yes	0.307 (0.195–0.483)	<.001	0.407 (0.241–0.688)	.001
Surgery				
No/unknown	Reference			
Yes	0.205 (0.125–0.334)	<.001		
Chemotherapy				
No/unknown	Reference			
Yes	4.912 (2.949–8.182)	<.001		
Brain metastasis				
No	Reference			
Yes	1.975 (0.483–8.079)	.344		
Unknown	1.177 (0.429–3.229)	.752		
Liver metastasis				
No	Reference		Reference	
Yes	0.971 (0.134–7.035)	.977	2 (0.268–14.951)	.499
Unknown	4.120 (2.349–7.226)	<.001	4.986 (2.612–9.517)	<.001
Lung metastasis				
No	Reference			
Yes	0.306 (0.04–2.352)	.255		
Unknown	2.746 (1.736–4.342)	<.001		
Tumor size				
3–80	Reference			
81–160	2.718 (1.578–4.682)	<.001		

Table 3

Univariate and multivariate Cox proportional hazards regression analysis based on all variables for CSS.

Characteristics	Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	P	HR (95% CI)	P
Age				
20–59	Reference		Reference	
60–90	2.669 (1.424–5.003)	.002	2.572 (1.319–5.017)	.006
Race				
Black	Reference			
Other	0.631 (0.235–1.697)	.362		
White	1.242 (0.609–2.533)	.552		
Sex				
Female	Reference			
Male	1.474 (0.901–2.411)	.123		
Histological subtype				
Papillary	Reference		Reference	
Follicular	0.757 (0.363–1.577)	.457	0.586 (0.275–1.249)	.167
Anaplastic	20.915 (9.942–43.999)	<.001	4.654 (1.736–12.473)	.002
Medullary	3.121 (1.408–6.917)	.005	1.677 (0.684–4.111)	.258
Grade				
Low (I, II)	Reference		Reference	
High (III, IV)	8.618 (3.997–18.579)	<.001	3.897 (1.426–10.645)	.008
Unknown	1.705 (0.801–3.631)	.166	1.279 (0.546–2.998)	.571
Laterality				
Bilateral	Reference			
Left—origin of primary	0.512 (0.046–5.651)	.584		
Not a paired site	0.645 (0.089–4.685)	.665		
Right—origin of primary	1.602 (0.165–15.566)	.685		
T stage				
T1–2	Reference			
T3–4	2.373 (1.239–4.545)	.009		
N stage				
N0	Reference			
N1	2.581 (1.557–4.276)	<.001		
Radiotherapy				
No	Reference		Reference	
Yes	0.29 (0.176–0.477)	<.001	0.492 (0.274–0.882)	.017
Surgery				
No/unknown	Reference			
Yes	0.198 (0.116–0.337)	<.001		
Chemotherapy				
No/unknown	Reference			
Yes	5.782 (3.367–9.931)	<.001		
Brain metastasis				
No	Reference			
Yes	2.347 (0.571–9.645)	.237		
Unknown	1.027 (0.321–3.282)	.964		
Liver metastasis				
No	Reference		Reference	
Yes	1.202 (0.165–8.751)	.856	3.681 (0.353–38.374)	.276
Unknown	4.599 (2.548–8.304)	<.001	3.267 (3.267–6.427)	.001
Lung metastasis				
No	Reference		Reference	
Yes	0.62 (0.083–4.613)	.641	0.685 (0.066–7.129)	.751
Unknown	3.671 (2.195–6.141)	<.001	2.174 (1.241–3.81)	.007
Tumor size				
3–72	Reference		Reference	
73–160	3.151 (1.895–5.24)	<.001	2.307 (1.269–4.195)	.006

therapy ($P=.001$) to be the independent risk factors. An identical method which was used to conducted for CSS identified age ($P=.006$), grade ($P=.008$), tumor size ($P=.006$), combined liver metastasis ($P=.001$), combined lung metastasis ($P=.007$), histological subtype ($P=.002$), and radiotherapy ($P=.017$) as the independent risk factors, as shown in Table 3.

3.3. Predictive nomogram

Based on the univariate and multivariate cox regression results, the parameters mentioned above were integrated to construct a prognostic nomogram for predicting the 1-, 2-, and 3- year OS and CSS (Fig. 1). Every parameter was assigned a corresponding score on a point-graduated scale. The 1-, 2-, and 3-year OS and

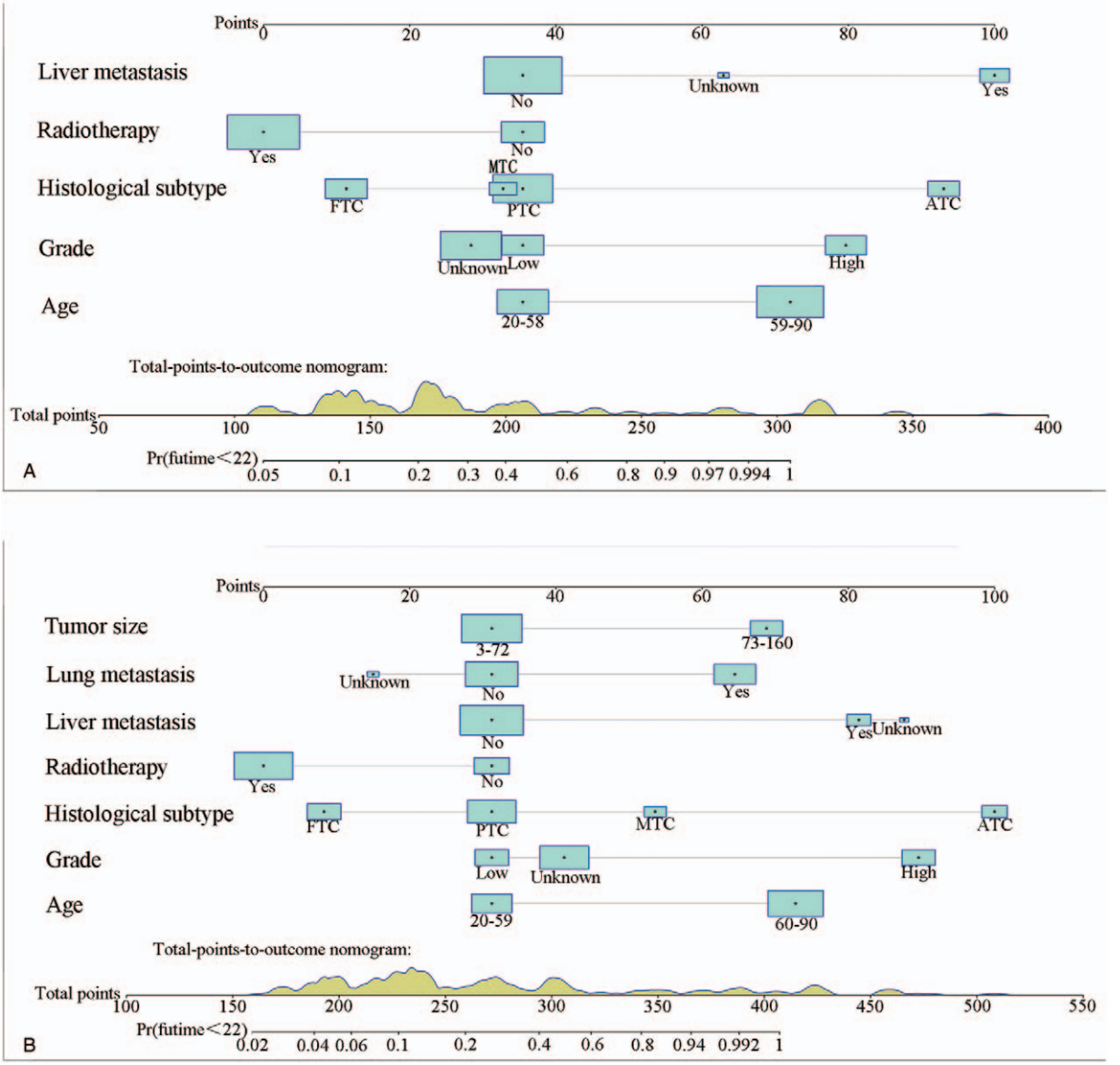

Figure 1. Nomograms predicting 1-, 2-, and 3-year OS (A) and CSS (B).

CSS of TCBM patients could be predicted by adding up these scores for a total. Remarkably, this upgraded nomogram provided a visual impact; the bigger the block area of each indicator, the more number of patients the indicator corresponded to.

3.4. Validation of the nomogram

The nomogram had high C-index, 0.82 (95% CI: 0.767–0.873) for OS and 0.852 (95% CI: 0.801–0.903) for CSS, which indicated that the models had a high accuracy prediction. The calibration curves demonstrated excellent consistency between the predicted result and the actual survival of the TCBM patients (Figs. 2 and 3). ROC analysis showed that the AUC for OS at 1-, 2-, and 3-year in the training cohort was 0.885, 0.875, and 0.868 and 0.810, 0.729, and 0.729 in the validation cohort, respectively (Fig. 4). The AUC for CSS at the same time points stood at 0.913, 0.909, and 0.909 in the training cohort and 0.840, 0.827, and 0.827 in the validation cohort (Fig. 5). Also, the DCA curve indicated that this nomogram had good clinical utility in predicting the OS and CSS in patients with TCBM (Figs. 6 and 7). Kaplan–Meier survival analysis was also performed in the training and the validation cohorts (Fig. 8), which showed that patients with high-risk scores had shorter OS and CSS than those with low-risk scores.

3.5. Comparison of the prediction accuracy between nomogram and single independent prognostic factor

AS shown in Figures 4 and 5, the AUC of every independent prognostic factor for OS and CSS was significantly lower than that of the nomogram, implying that the prediction accuracy of the nomogram for the 1-, 2-, and 3-years OS and CSS was better.

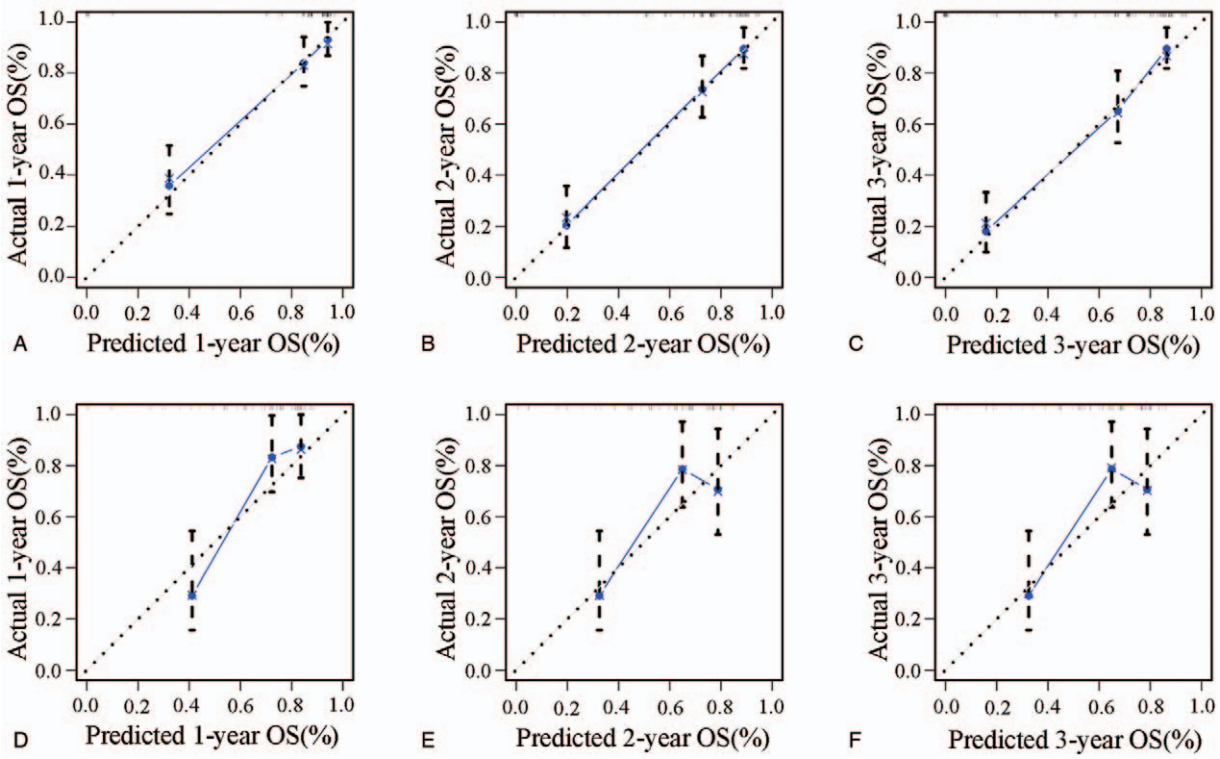

Figure 2. Calibration curves. Calibration curves of the nomogram for the 1- (A), 2- (B), and 3-year (C) OS prediction of the training cohort, calibration curves of the nomogram for the 1- (D), 2- (E), and 3-year (F) OS prediction of the validation cohort.

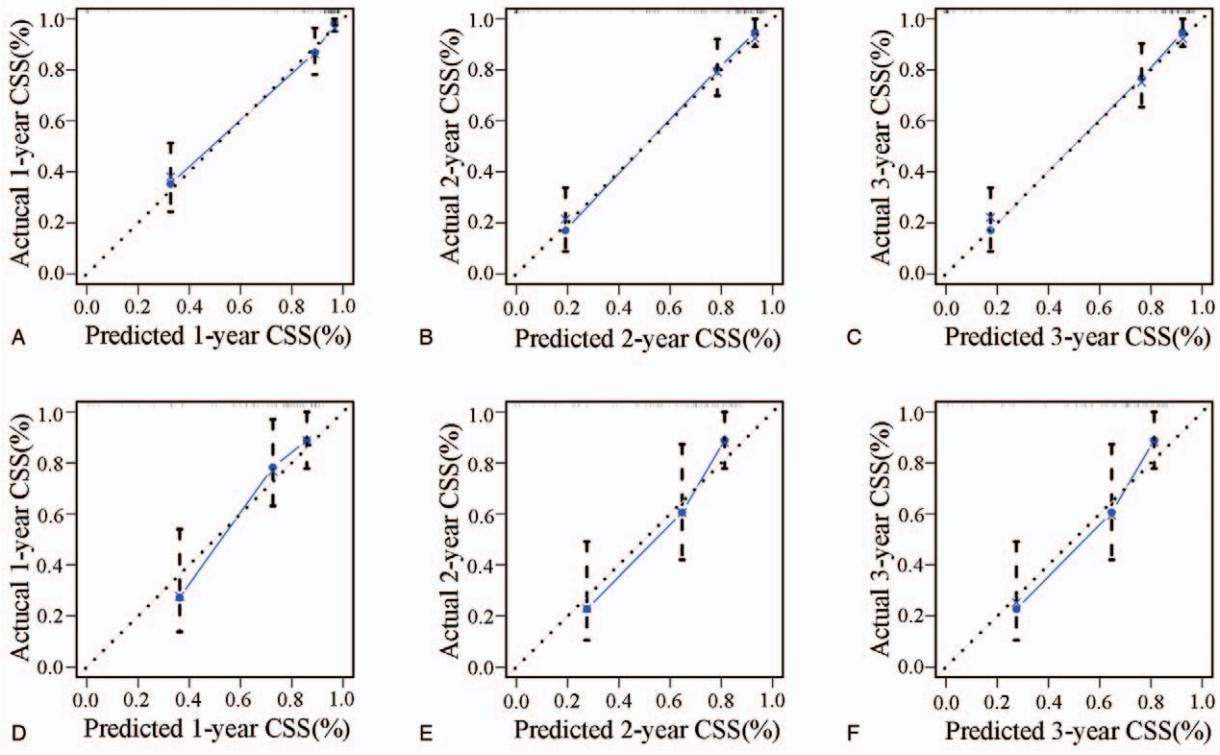

Figure 3. Calibration curves. The calibration curves of the nomogram for the 1- (A), 2- (B), and 3-year (C) CSS prediction of the training cohort, calibration curves of the nomogram for the 1- (D), 2- (E), and 3-year (F) CSS prediction of the validation cohort.

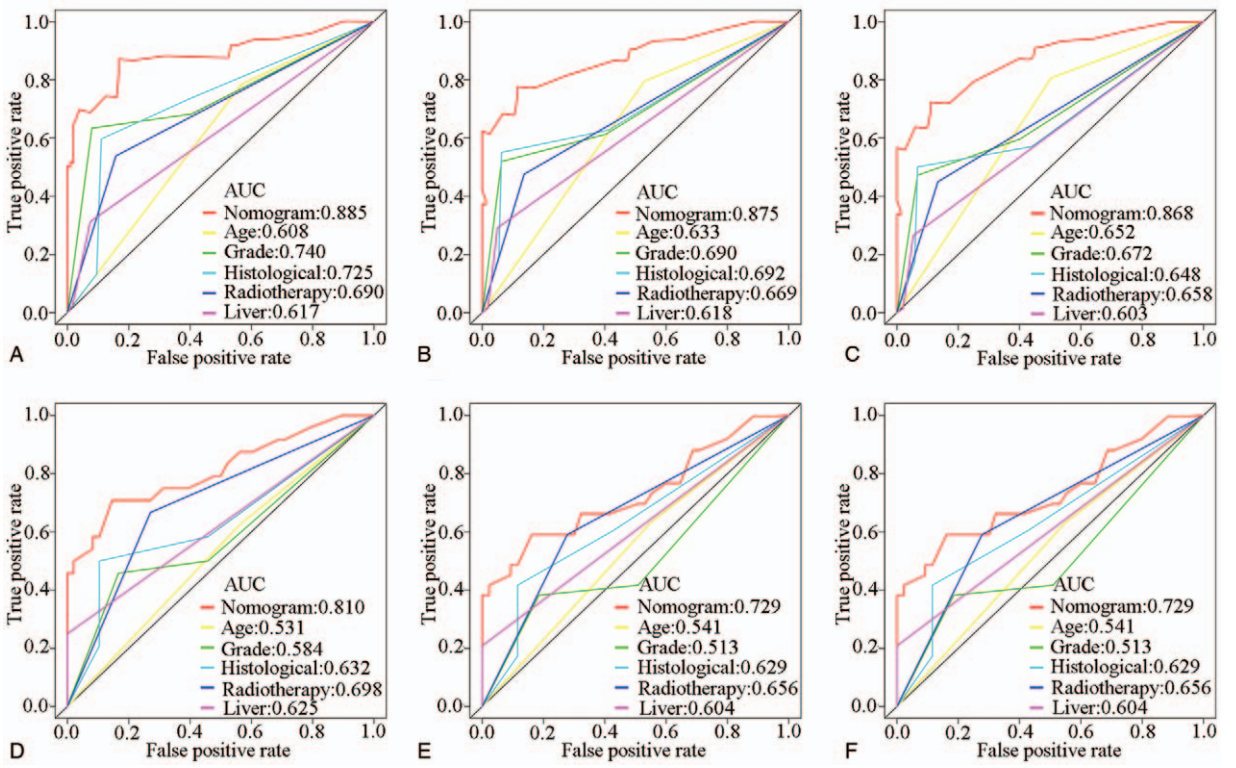

Figure 4. ROC curves. ROC curves for predicting 1- (A), 2- (B), and 3-year (B) OS in the training cohort; ROC curves for predicting 1- (D), 2- (E), and 3-year (F) OS in the validation cohort.

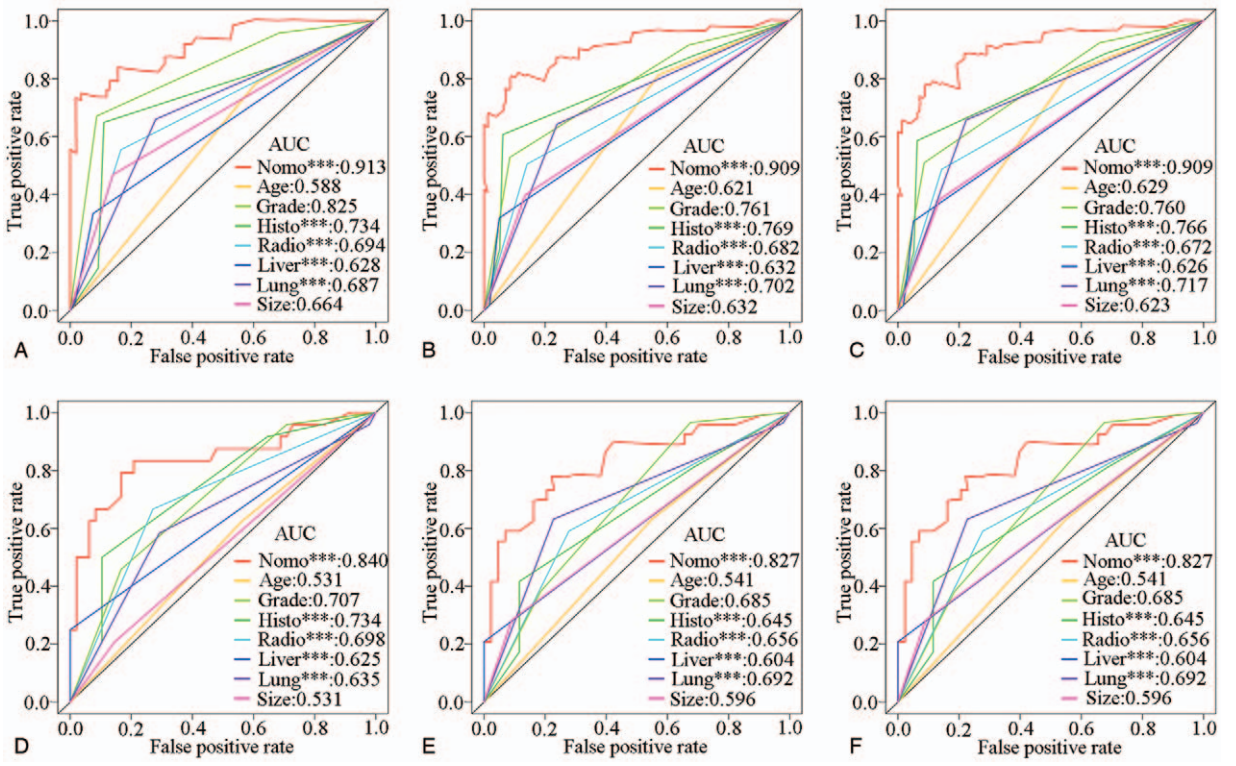

Figure 5. ROC curves. ROC curves for predicting 1- (A), 2- (B), and 3-year (B) CSS in the training cohort; ROC curves for predicting 1- (D), 2- (E), and 3-year (F) CSS in the validation cohort.

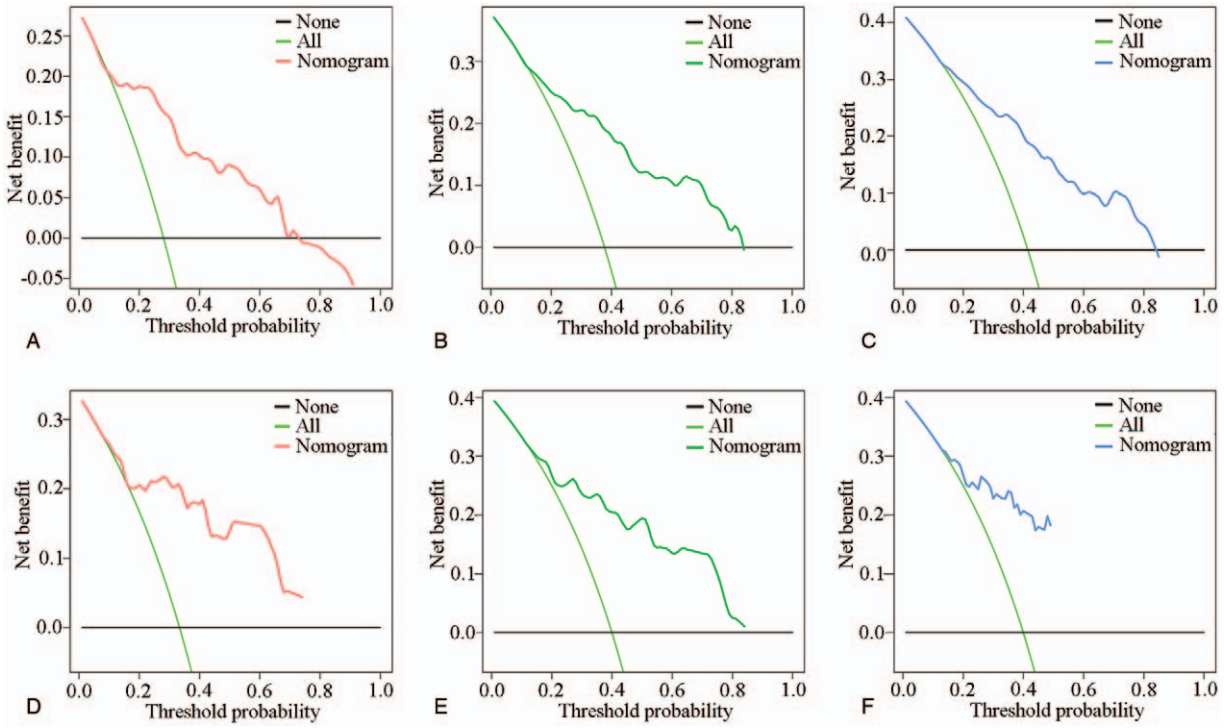

Figure 6. Decision curve analysis (DCA). DCA of the nomogram for predicting the 1- (A), 2- (B), and 3-year (C) OS in the training cohort, and the 1- (D), 2- (E), and 3-year (F) OS in the validation cohort.

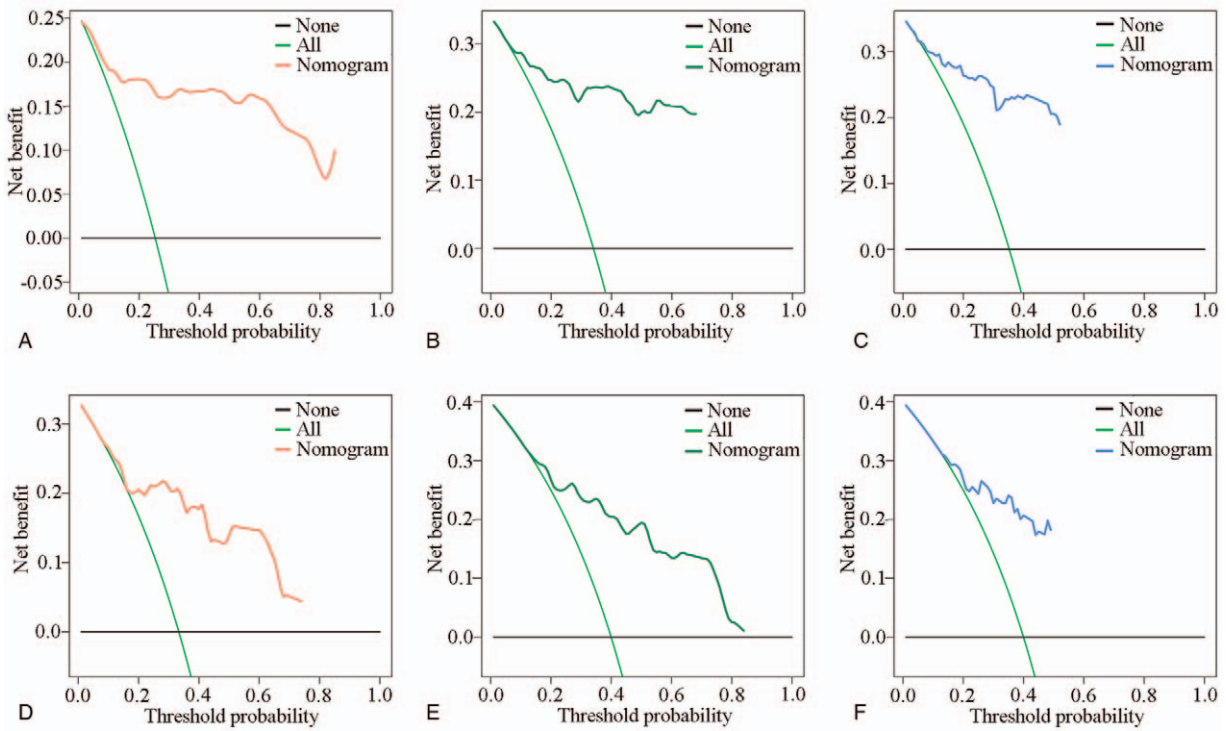

Figure 7. Decision curve analysis (DCA). DCA of the nomogram for predicting the 1- (A), 2- (B), and 3-year (C) CSS in the training cohort, and the 1- (D), 2- (E), and 3-year (F) CSS in the validation cohort.

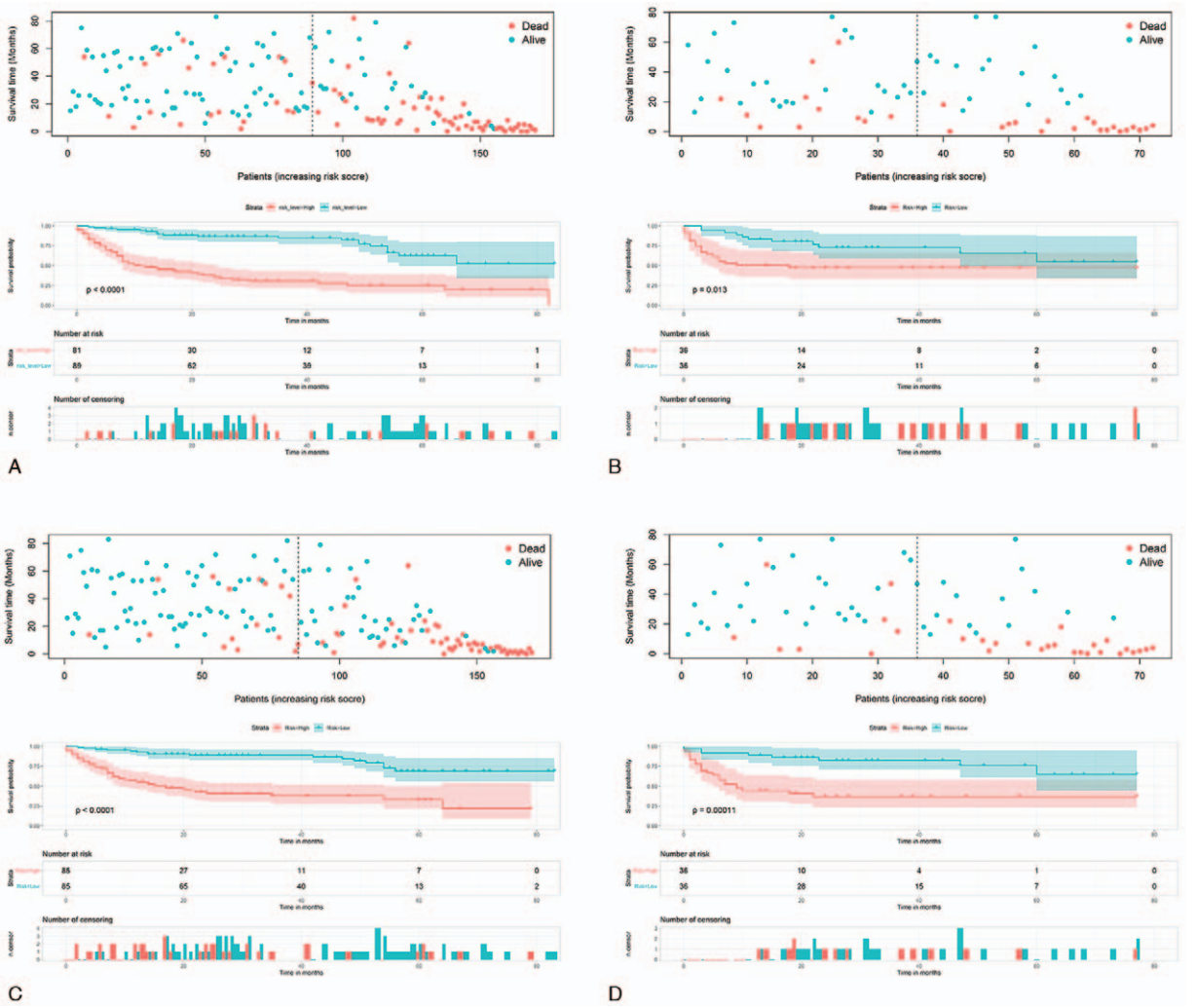

Figure 8. Kaplan–Meier survival analysis. Patients with a higher risk score demonstrated a worse prognosis than those with a low risk score in the training cohort for OS of TCBM patients (A), for CSS of TCBM patients (C), and validation cohort for OS of TCBM patients (B), for CSS of TCBM patients (D).

4. Discussion

Given the treatability and excellent survival rate in patients of TC, an opinion that it is a relatively "good cancer" has pervaded the medical community.[22] However, TCBM still carries an inferior prognosis with the 10-year survival rate varying from 13% to 21%.[23,24] A large-scale study evaluating the long-term prognosis evaluation of 444 TC patients with DM suggested that the 10-year OS of patients with BM was significantly lower than that of patients with lung metastasis (25% vs 63%).[4] Similar results were reported in other studies.[23,25] Therefore, it appears that accurate prediction of survival rates for TCBM patients of utmost significance for effective clinical management and medical decision-making.

The use of nomograms has become increasingly popular and important in personalized cancer prediction, helping clinicians optimize the therapeutic options for patients in accordance with the specific individual variables. Predictive nomograms for the survival prediction of some malignancies have been reported.[26–29] The merit of nomogram lies in simplifying complex statistical predictive models involving a large number of factors to a single brief numerical estimation model, predicting the probability of a clinical outcome. In our model, each independent risk factor included in this model was given a weighted point to evaluate the effect of this factor on prognosis. It has a distinctive advantage of being a tailor-made survival prediction model as compared to the conventional TNM staging system.[30] Nomograms have been previously developed for the survival prediction in patients with TC.[31,32]

Some studies focusing on the evaluation of prognostic factors in TCBM patients have also been reported.[15,17] However, there is an overall lack of a nomogram predicting the OS and CSS for TCBM patients. In the present study, for this reason, we identified the independent risk factors for OS and CSS for TCBM patients, and further established a nomogram for respectively predicting the 1-, 2-, and 3-year OS and CSS in those patients. The developed nomograms performed excellently in prediction of survival rate as supported by C-index, calibration curves, ROC curves, and DCA. This predictive model highlights the relative contribution of the various independent variables associated with clinical outcome so that it may be conveniently and directly used to predict the survival rate in TCBM patients, informing the

patients of individuals benefits of specific treatments, hence optimizing clinical decision-making. Furthermore, some other advantages of this study are as follows: first, it is a longitudinal population-based study with the relatively large sample size that included all types of TC. The results of this study, hence, have a good representative value in providing clinical guidance. Secondly, we believe that this nomogram is of clinical interest and practical utility because the identified independent prognostic predictors are easily accessible and may be use in the daily treatment planning. In addition, another improvement of this nomogram is that the discrimination of nomogram was confirmed to be better than any of those predicted by the independent risk factors separately, which once again showed the significance of a comprehensive predictive model. In our study, age, grade, histological subtype, liver metastasis, and radiotherapy were found to be the independent risk factors for OS of TCBM patients. The independent risk factors of CSS included those above along with were not only the above variables, but also included tumor size and lung metastasis. Interestingly, although previous reports have considered the race of patients as a closely related factor for predicting long-term outcome of TC,[33] it was not identified as an independent prognostic factor in our prognosis analysis. This confirmed the necessity of determining more precisely applicable population characteristics in the prognostic evaluation of these patients. There are some disputes on the correlation between age and prognosis of TCBM. Several lines of evidence suggested that the TCBM patients with older age were associated with worse prognosis.[15,34] However, some scholars[35] hold the opposite viewpoint that age did not significantly affect the prognosis. In our series, age was identified as an independent risk factor for determining the OS and CSS. We also determined the optimum cutoff value of age for both OS and CSS (58 and 59 years, respectively) by using the X-tile program. In our study, patients with age $\geq$ 59 years were found to have inferior OS and CSS. The complexity associated with various other diseases, low physical fitness as well as low tolerance toward cancer treatment methods were identified as the main reasons of an advanced age patients facing increased risk. Similar to other malignancies, the grade was also an independent predictor for TCBM.[36,37] The result of our study suggested that the risk of death in TCBM patients with high-level grade (III, IV) was significantly higher than that in patients with low-level grade (I, II). High grade tumors also showed more extensive tumor invasion and the more complications impairing the treatment efficacy. According to Wu Karl et al,[17] the survival of TCBM patients was significantly longer in patients with papillary and follicular histology than in whose with anaplastic and medullary cancers. Our predictive model also supported this conclusion. Anaplastic histology occupied the most significant weight point of all histological subtypes. Also, TCBM patients having a tumor size $\geq$73 mm indicated poor prognosis. We analyzed that larger tumor size corresponded to greater infiltration range and higher level grade, increasing the overall complexity and risk of surgical resection.

In the clinical practice, more metastasis represents an unfavorable prognosis.[38] Kondraciuk Jessica D et al,[35] in a significant study, pointed out that 3-year OS of TCBM patients reporting other metastatic sites was 13% less than that of those with only BM. However, the previous studies did not specify which combined metastatic sites associated with a lower survival rate. Our study identified liver metastasis as an independent risk factor, speculating that hepatic failure caused by liver involvement might be a possible cause of death for some patients with TCBM.[39,40] It is noteworthy that treatment strategy relies on clinicians personal judgment and experience gained from training and practice in the absence of accurate survival predictive model. As is common knowledge, the effectiveness of conventional external beam radiotherapy in BM is widely accepted.[41,42] Radiotherapy played a vital role in predicting the prognosis of TCBM patients in our model. There are several lines of evidence suggesting that stereotactic radiotherapy following conventional radiation for TCBM demonstrates high local control rates of ~80% to 90%.[18,43] Furthermore. It is widely accepted that radioactive iodine (RAI) therapy was an ideal specific treatment for patients with TC.[9] Related research confirmed that the application of high-dose RAI could considerably benefit the patients by improving the prognosis in patients with metastatic DTC.[44,45] The previous studies were consistent with our results, all of which highlighted the immense significance of radiotherapy in predicting the prognosis of TCBM patients.

Regretfully, no nomogram can assess the impact of a predictor in prognosis with 100% accuracy. Our predictive model also has some limitations. First, since the design of the present study was a clinical retrospective study, selection bias was unavoidable. Second, patients included in our study were diagnosed between 2010 and 2016, leading to a relatively insufficient time frame. This was because the SEER database had recorded the metastatic sites from 2010 onward. We think that a more extended time frame with a larger sample size might help to further enhance the credibility and persuasiveness of the model prediction. Third, the nomogram only provides a relative reference for clinicians due to limitation in the collected variables and data. For example, the severity of other organ metastases is not recorded in the SEER database. It is imperative to remember that the final treatment strategy relies mostly on clinicians' personal judgment and experience in the absence of an accurate survival prediction model. Ideally, more complex clinical factors that doctors face in their daily is an integral element of decision making and prognostic evaluation. Nevertheless, these models do have the potential to revolutionize the practice of personalized medicine.

5. Conclusion

In conclusion, our model shows that TCBM patients with age $\geq$ 59 years, advanced grade, primary tumor size $\geq$ 73 mm, lung metastasis and liver metastasis have a poor prognosis. This study have successfully constructed and validated a visual nomogram for predicting the 1-, 2-, and 3-year OS and CSS of TCBM patients, and could be used as an assistant prediction tool in clinical practice. The same needs to be validated in larger cohorts.

Acknowledgments

We are thankful for the contribution of the SEER database and the 18 registries supplying cancer research information, and thank all colleagues involved in the study for their contributions.

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