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ORIGINAL RESEARCH

Development and validation of prognostic nomograms for medullary thyroid cancer

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Background: This aim of study was to develop and validate clinical nomograms to predict the survival of patients with medullary thyroid cancer.

Patients and methods: Patient data were collected from the Surveillance, Epidemiology, and End Results database between 2004 and 2013. All included patients were randomly assigned into the training and validation sets. Multivariate analysis using Cox proportional hazards regression was performed, and nomograms were constructed. Model performance was evaluated by discrimination and calibration plots.

Results: A total of 1,657 patients were retrospectively analyzed. The multivariate Cox model identified age, tumor size, extrathyroidal extension, N stage, and M stage as independent covariates associated with overall survival (OS) and cancer-specific survival (CSS). Nomograms predicting OS and CSS were constructed based on these covariates. The nomograms predicting both OS and CSS exhibited superior discrimination power to that of TNM staging system in the training and validation sets. Calibration plots indicated that both the nomograms in OS and CSS exhibited high correlation to actual observed results.

Conclusion: The nomograms established in this study provided an alternative tool for prognostic prediction, which may thereby improve individualized assessment of survival risks and lead to the creation of additional clinical therapies.

Keywords: medullary thyroid cancer, nomogram, overall survival, cancer-specific survival

Introduction

An estimated 53,990 new cases of thyroid cancer will be diagnosed in the United States in 2018.[1] Medullary thyroid cancer (MTC) is a neuroendocrine malignancy of the parafollicular cells of the thyroid.[2] Although MTC only accounts for a minority of all thyroid malignancies, its incidence is increasing, with the greatest increase in patients with localized disease.[3,4] The cornerstone of local treatment of MTC is still surgical resection, with or without adjuvant radiation. Nevertheless, MTC is responsible for a disproportionate percentage of thyroid cancer mortality.[5]

The TNM cancer staging system of American Joint Committee on Cancer (AJCC) is the most common guidelines for the prognosis of MTC.[6] However, this system cannot be used for predicting individual patient outcomes. Moreover, some other factors including age, tumor size, extrathyroidal extension, margin status, vascular invasion, and calcitonin may be important for determining outcomes in individual patients.[7,8] Therefore, it is needed to establish a prognostic indicator system specified for MTC patients.

Nomograms have been accepted as a reliable tool to quantify risk by incorporating and illustrating important factors for the accurate and discriminatory prediction of prognoses.[9–11] They were created by regression analysis and extended beyond the standard TNM anatomical criteria.[12] Nevertheless, no nomogram for individual

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MTC patients on the basis of population-based data is available. Therefore, this study sought to develop nomograms to predict individualized survival of MTC based on the large population data retrieved from the Surveillance, Epidemiology and End Results (SEER) program.

Patients and methods

Patients

MTC patients from 2004 to 2013 were selected from the SEER program of the US National Cancer Institute (NCI). SEER program is established to comprehensively collect clinical information on various cancer types for associated incidence, prevalence, and prognostic studies.[13] We used the SEER*STAT software (version 8.3.5) to extract data from the SEER database. The cohort for this analysis consisted of adult patients (≥18 years) diagnosed with MTC who underwent thyroid surgery. The primary site and ICD for Oncology (ICD-O-3) were used to identify cases of MTC. The following site code and ICD-O-3 codes for histological type were used: C73.9 and 8345–8347, 8510. The criteria for exclusion were listed as follows: 1) patients were diagnosed at autopsy or death certificate; 2) patients with second primary malignancies; 3) patients had incomplete information (demographic data, clinical parameters, staging information, pathological findings, therapeutic procedure records, and full follow-up results). Two thirds of all patients were randomly selected to the training set for developing the nomogram, and the rest of patients served as a validation set for the purposes of validation. No ethical approval nor informed consent was required in this study due to the publicly available data of SEER.

Variables

Several clinical variables were extracted, including age, sex, race, tumor size, extrathyroidal extension, multifocality, surgery, T stage, N stage, and M stage, which were collected in the training set. Tumor size was classified into four parts, including "≤2.0 cm," "2.1–4.0 cm," and ">4 cm" options. Overall survival (OS) was the primary endpoint, defined as the time period from the diagnosis to the death or last follow-up. Cancer-specific survival (CSS) was the second endpoint, defined as the time period from the diagnosis to the death caused by MTC or censoring.

Statistical analyses

Nomogram construction

All the categorical variables were presented with frequencies and proportions, and analyzed by a chi-squared test. Survival curves were depicted using the Kaplan–Meier method and compared using the log-rank test. Only variables that were found to be associated with survival in univariable analysis were included in the multivariable analysis (significance with two-sided $P<0.05$). Variables were selected through the forward stepwise selection method using the Cox proportional hazard regression model. The nomogram was constructed based on the significant prognostic factors.

Validation of the nomogram

The performance of the nomogram was measured by discrimination and calibration. Discrimination was evaluated using Harrell's concordance index (C-index). The area under the curve (AUC) from receiver operating characteristic (ROC) analysis was used for assessing the precision of the 5- and 10-year survival predictions.[14] The value of the AUC ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination). Calibration plot was used to visualize the variance between nomogram-predicted prognosis and actual prognosis. All the statistical analyses were performed using R software version 3.5.1 (http://www.r-project.org). Differences were considered statistically significant if the P-value was <0.05.

Results

Patient characteristics

A total of 1,657 patients were collected in this study with 1,105 patients randomly assigned to the training set and 552 to the validation set. Figure 1 lists the data selection process. In the whole study set, 1,197 (72.2%) patients were >45 years of age, 1,004 (60.6%) patients were female, and 653 (39.4%) patients were male. For tumor size, ≤2.0 cm was the most common type (50.0%), followed by 2.1–4.0 cm (30.7%). Multifocal tumors were observed in 515 (31.3%) patients and a gross extrathyroidal extension of cancer in 297 (17.9%) patients. Most patients (45.3%) received total thyroidectomy and were categorized as T1 stage (45.3). Few patients had lymph node invasion (39.2%) and distant metastasis (99.2%) at diagnosis. The median follow-up was 55 months (range: 1–143 months). By the end of follow-up, 188 (11.3%) patients had died, including 100 who died from MTC and 88 who died from other causes. The clinicopathologic characteristics of patients are listed in Table 1.

Establishment of the nomogram

In the univariable analysis, age, sex, tumor size, extrathyroidal extension, multifocality, T stage, N stage, and M stage were significantly associated with OS in the training set ($P<0.05$). These significant factors were included in the

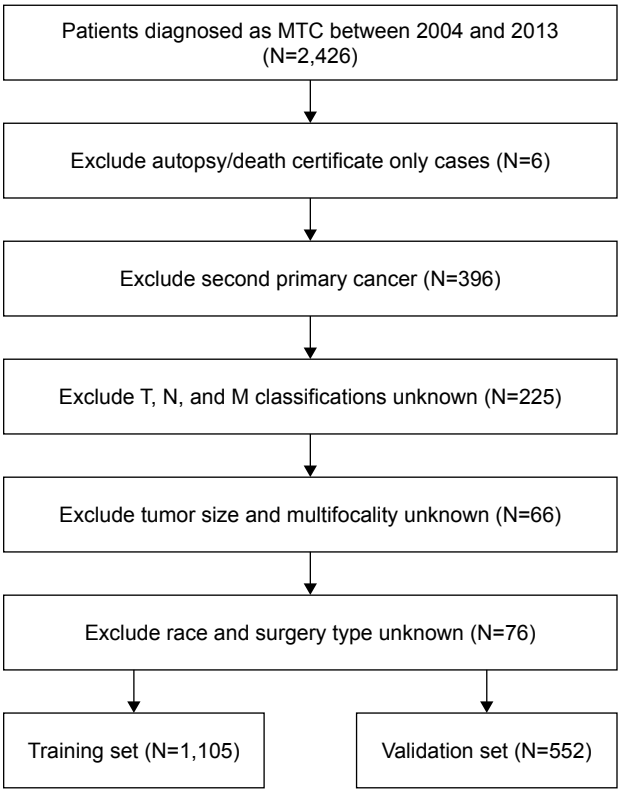

Figure 1 Flow diagram of the included medullary thyroid cancer patients.
Abbreviation: MTC, medullary thyroid cancer.

multivariable analysis. The result indicated that age, tumor size, extrathyroidal extension, N stage, and M stage were identified as independent prognostic factors (Table 2). These variables were then incorporated into the OS nomogram in the training set (Figure 2A). Moreover, those independent variables were also found significantly associated with CSS and therefore used to build a CSS nomogram (Figure 2B).

Validation of nomograms

The predictive accuracy of the nomograms was evaluated by C-index. Our nomogram displayed better accuracy in predicting survival in both sets. The internal validation was performed via the training set with the C-index as 0.766 (95% CI, 0.722–0.810) in OS and 0.862 (95% CI, 0.815–0.909) in CSS, respectively (Table 3). The external validation was performed via the validation set with the C-index as 0.800 (95% CI, 0.744–0.856) in OS and 0.893 (95% CI, 0.842–0.944) in CSS, respectively. Calibration curve showed good agreement between prediction and observation in the probability of 5- and 10-year OS and CSS in both training and validation sets (Figures 3 and 4). Furthermore, the comparisons between the nomograms and TNM sixth staging system were performed in the training set. The nomogram discrimination

Table 1 The demographics and pathological characteristics of included patients

Variables	All patients (n=1,657)		Training set (n=1,105)		Validation set (n=552)	
	N	%	N	%	N	%
Age (years)						
<45	460	27.8	317	28.7	143	25.9
≥45	1,197	72.2	788	71.3	409	74.1
Sex						
Female	1,004	60.6	664	60.1	340	61.6
Male	653	39.4	441	39.9	212	38.4
Race						
White	1,405	84.8	936	84.7	469	85.0
Black	145	8.8	97	8.8	48	8.7
Other	107	6.5	72	6.5	35	6.3
Tumor size (cm)						
≤2.0	829	50.0	541	48.9	288	52.1
2.1–4.0	532	32.1	368	33.3	164	29.7
>4.0	296	17.9	196	17.7	100	18.1
Extrathyroidal extension						
Absent	1,360	82.1	898	81.3	462	83.7
Present	297	17.9	207	18.7	90	16.3
Multifocality						
Unifocal	1,142	68.9	749	67.8	393	71.2
Multifocal	515	31.1	356	32.2	159	28.8

(*Continued*)

Table 1 (*Continued*)

Variables	All patients (n=1,657)		Training set (n=1,105)		Validation set (n=552)	
	N	%	N	%	N	%
Surgery						
Lobectomy	147	8.9	88	8.0	59	10.7
Total thyroidectomy	1,510	91.1	1,017	92.0	493	89.3
T stage						
T1	751	45.3	484	43.8	267	48.4
T2	426	25.7	291	26.3	135	24.5
T3	343	20.7	240	21.7	103	18.7
T4	137	8.3	90	8.1	47	8.5
N stage						
N0	1,007	60.8	662	59.9	345	62.5
N1	650	39.2	443	40.1	207	37.5
M stage						
M0	1,570	94.7	1,052	95.2	518	93.8
M1	87	5.3	53	4.8	34	6.2

Table 2 Univariate and multivariate analyses of overall survival in the training set

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
<45	Reference		Reference	
≥45	3.621 (2.073–6.325)	<0.001	4.886 (2.763–8.639)	<0.001
Sex				
Female	Reference		Reference	
Male	1.701 (1.19–2.43)	0.004	0.8191 (0.543–1.237)	0.343
Race				
White	Reference			
Black	0.974 (0.524–1.812)	0.934		
Other	0.279 (0.069–1.132)	0.074		
Tumor size (cm)				
≤2.0	Reference		Reference	
2.1–4.0	1.842 (1.176–2.885)	0.008	1.492 (0.653–3.412)	0.342
>4.0	3.925 (2.517–6.123)	<0.001	3.730 (1.779–7.820)	<0.001
Extrathyroidal extension				
Absent	Reference		Reference	
Present	4.141 (2.896–5.923)	<0.001	3.075 (1.455–6.502)	0.003
Multifocality				
Unifocal	Reference			
Multifocal	1.145 (0.788–1.665)	0.478		
Surgery				
Lobectomy	Reference			
Total thyroidectomy	1.324 (0.646–2.712)	0.444		
T stage				
T1	Reference		Reference	
T2	1.580 (0.926–2.694)	0.093	1.0647 (0.405–2.802)	0.899
T3	2.755 (1.681–4.514)	<0.001	0.3947 (0.1475–1.056)	0.064
T4	6.850 (4.108–11.423)	<0.001	0.6262 (0.2047–1.916)	0.412

(*Continued*)

Table 2 (*Continued*)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
N stage				
N0	Reference		Reference	
N1	3.016 (2.081–4.371)	<0.001	1.769 (1.0919–2.865)	0.020
M stage				
M0	Reference		Reference	
M1	7.713 (4.922–12.09)	<0.001	3.839 (2.256–6.533)	<0.001

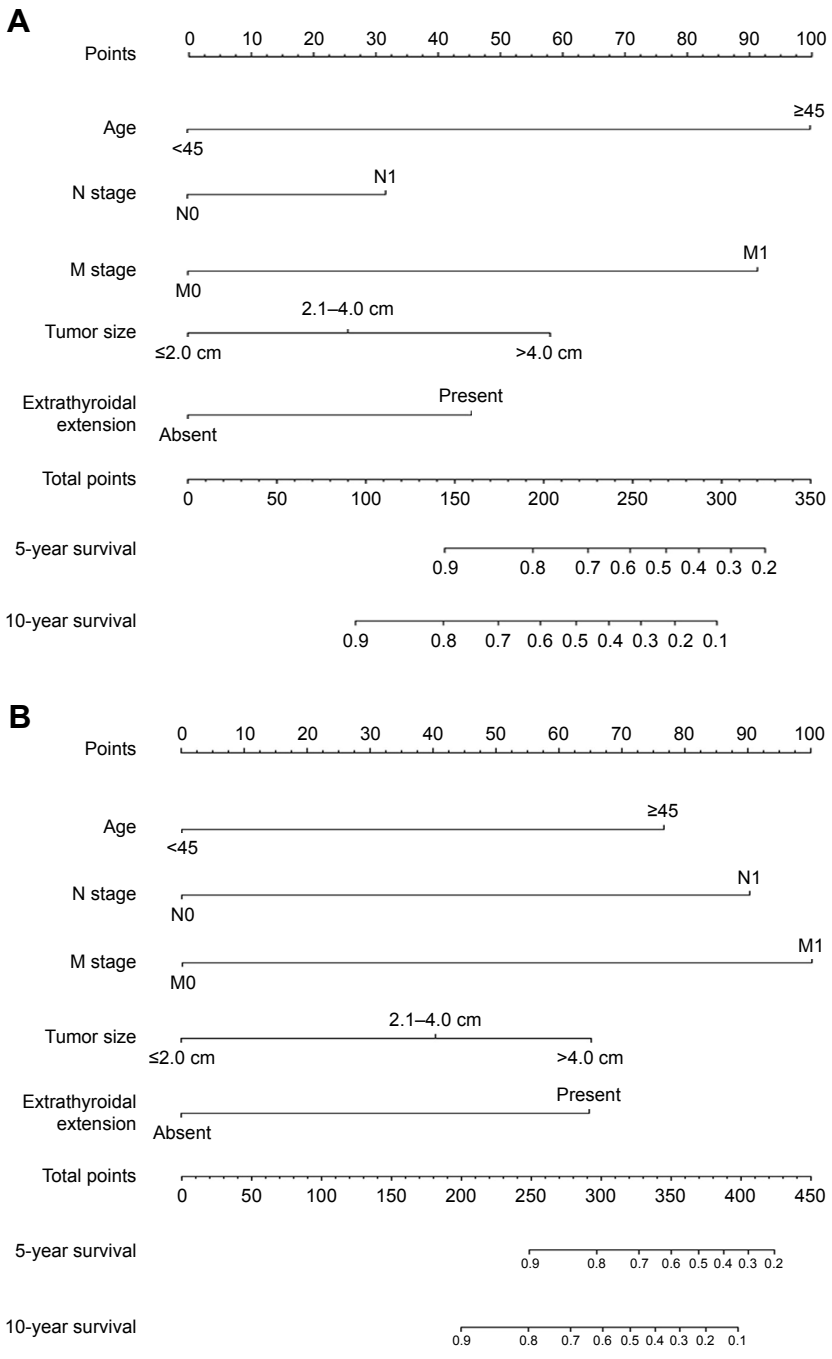

Figure 2 Nomograms for medullary thyroid cancer patients.
Notes: (**A**) Nomograms for 5- and 10-year overall survival (OS); (**B**) nomograms for 5- and 10-year cancer-specific survival (CSS).

Table 3 Univariate and multivariate analyses of cancer-specific survival in the training set

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
<45	Reference		Reference	
≥45	2.223 (1.159–4.266)	0.016	3.527 (1.787–6.963)	<0.001
Sex				
Female	Reference		Reference	
Male	2.224 (1.347–3.673)	0.002	0.675 (0.374–1.217)	0.191
Race				
White	Reference			
Black	1.200 (0.547–2.634)	0.649		
Other	3.832 (0–)	0.995		
Tumor size (cm)				
≤2.0	Reference		Reference	
2.1–4.0	3.060 (1.530–6.12)	0.002	1.530 (0.582–4.022)	0.088
>4.0	6.966 (3.527–13.76)	<0.001	3.099 (1.230–7.808)	0.006
Extrathyroidal extension				
Absent	Reference		Reference	
Present	9.543 (5.65–16.12)	<0.001	3.322 (1.175–9.392)	0.023
Multifocality				
Unifocal	Reference		Reference	
Multifocal	1.721 (1.047–2.83)	0.032	0.743 (0.435–1.270)	0.277
Surgery				
Lobectomy	Reference			
Total thyroidectomy	1.875 (0.588–5.981)	0.288		
T stage				
T1	Reference		Reference	
T2	2.834 (1.030–7.798)	0.043	1.558 (0.387–6.271)	0.532
T3	7.807 (3.165–19.258)	<0.001	0.779 (0.179–3.387)	0.739
T4	25.455 (10.438–62.076)	<0.001	1.320 (0.269–6.462)	0.731
N stage				
N0	Reference		Reference	
N1	10.29 (5.076–20.85)	<0.001	4.734 (2.041–10.979)	<0.001
M stage				
M0	Reference		Reference	
M1	14.43 (8.461–24.63)	<0.001	5.082 (2.699–9.569)	<0.001

for OS and CSS prediction was superior to that of the TNM sixth stage system (C-index =0.766, 95% CI, 0.722–0.810 vs 0.679, 95% CI, 0.633–0.725; 0.862, 95% CI, 0.815–0.909 vs 0.778, 95% CI, 0.728–0.828). Moreover, the discrimination was also enhanced with the nomogram compared to TNM staging system when analyzed in the validation set (Table 4).

Comparison of AUC values of the nomogram and TNM sixth staging system

The two ROC models of the 5- and 10-year survival were compared in training set (Figure 5). The AUCs for predicting the 5- and 10-year OS were both 0.726, whereas the AUCs of TNM sixth staging system were 0.616 and 0.592, respectively. Regarding the prediction of 5- and 10-year CSS rates, the AUCs of the nomogram were 0.829 and 0.841, while the AUCs of the TNM sixth staging system were 0.647 and 0.643. Taken together, the nomograms had a superior discriminative capacity for predicting both OS and CSS compared with the TNM sixth staging system.

Discussion

Nomograms are becoming increasingly popular decision aids for predicting cancer risk, predicting prevention, and therapeutic outcomes.[12,15] They have been widely used in

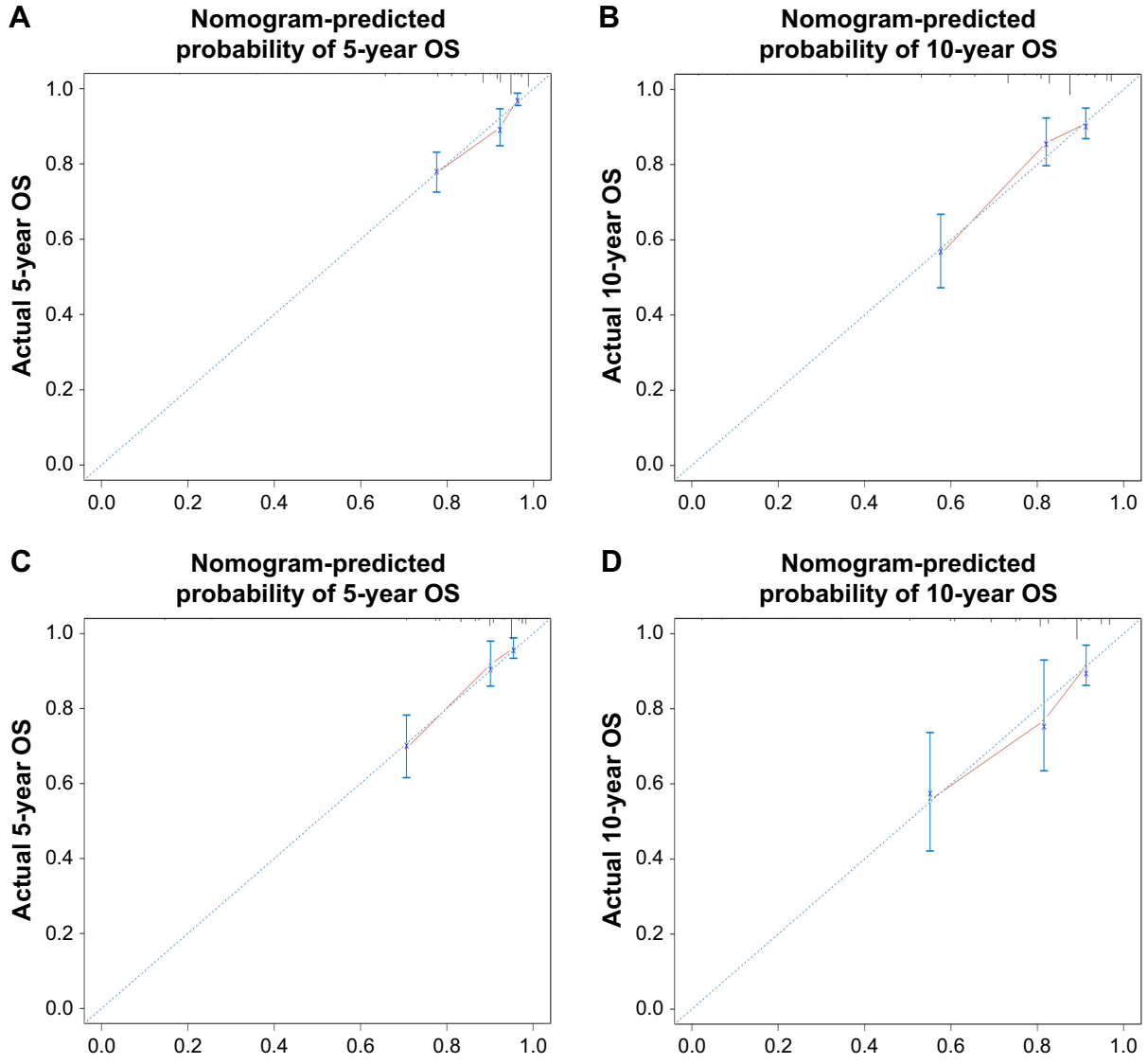

Figure 3 Calibration plots of the nomogram for 5- and 10-year overall survival (OS) prediction of the training set (**A**, **B**) and validation set (**C**, **D**).

multiple malignancies due to their ability to handle complexity in a systematic, unbiased manner.[16–18] Although some studies have reported risk factors associated with survival in patients with MTC,[7,19] single prognostic factor shows limited utility in prediction of individual survival probability. Few studies have created a prognostic model for this disease. A retrospective study of 249 patients at Memorial Sloan-Kettering Cancer Center by Ho et al conducted a nomogram for predicting cancer-specific mortality in MTC. However, neither large-scale samples nor external validation was applied in this study.

This study established OS and CSS prognostic nomograms for MTC patients based on a large, multicenter data set. We identified five clinicopathological characteristics that could predict both OS and CS for patients with MTC. Our nomograms displayed favorable discrimination and calibration. Furthermore, they exhibited excellent predictive ability of the 5- and 10-year OS and CSS compared with the classic TNM staging system. Our nomogram models were easily used clinical tools which would facilitate the popularization of patient counseling and personalized treatment.

The nomograms highlighted the clinical significance of age, tumor size, extrathyroidal extension, N stage, and M stage in MTC patients. The result showed that most patients were >45 years of age, who suffered worst survival, poor OS and CSS. Multiple studies have found that age is a major determinant of thyroid CSS.[20] Older age has been identified as an independent risk factor, suggesting that older patients had lower survival rates.[21–23] Patients older than 45 years are generally considered to have poor prognosis of differentiated thyroid cancer (DTC) patients.[24,25] With advancing age, a higher-risk histological phenotype is more likely.[26]

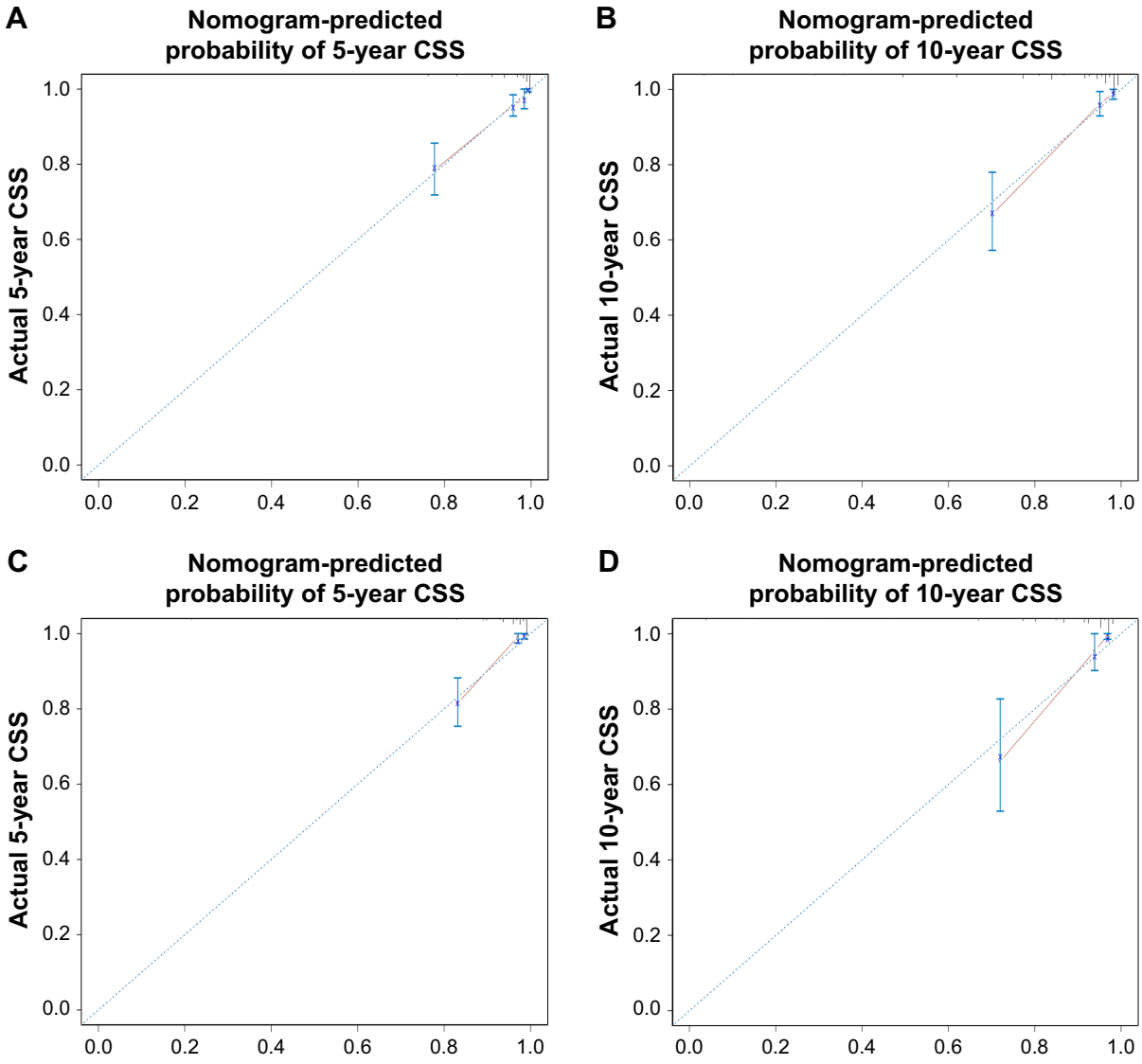

Figure 4 Calibration plots of the nomogram for 5- and 10-year cancer-specific survival (CSS) prediction of the training set (**A**, **B**) and validation set (**C**, **D**).

Previous edition of the AJCC staging system used 45 years of age as a cutoff value for DTC patients. Recently, the eighth edition has moved the cut point to age 55 years. However, regardless of the cutoff value, age is identified as an important prognostic factor for DTC and MTC patients. Tumor size was an independent prognostic variable in the nomogram in this study. In fact, only the tumor >4.0 cm exhibited significant higher prognostic risk than tumor ≤2 cm, whereas the rest stratification remained insignificant. It was possible that the tumor size could be one of the insightful variables for the prognostic risk prediction. T stage represents the extent of the primary tumor, including tumor size and the extrathyroidal extension. Our result indicated that tumors >4 cm and extrathyroidal extension have an impact in OS, while T3 and T4 do not. This may be due to tumors >4 cm and extrathyroidal extension including the total number of T3 and T4 stage patients. However, the current study evaluated T3 and T4, separately. Lymph node metastasis is a crucial prognostic factor in patients with malignancies. The number of metastatic lymph nodes has been incorporated into the

Table 4 Comparison of C-indexes between the nomogram and TNM stages in patients with MTC

Survival	Training set		Validation set	
	HR	95% CI	HR	95% CI
OS				
Nomogram	0.766	0.722–0.810	0.800	0.744–0.856
TNM sixth stage	0.679	0.633–0.725	0.716	0.660–0.772
CSS				
Nomogram	0.862	0.815–0.909	0.893	0.842–0.944
TNM sixth stage	0.778	0.728–0.828	0.815	0.764–0.866

Abbreviations: OS, overall survival; CSS, cancer-specific survival; MTC, medullary thyroid cancer.

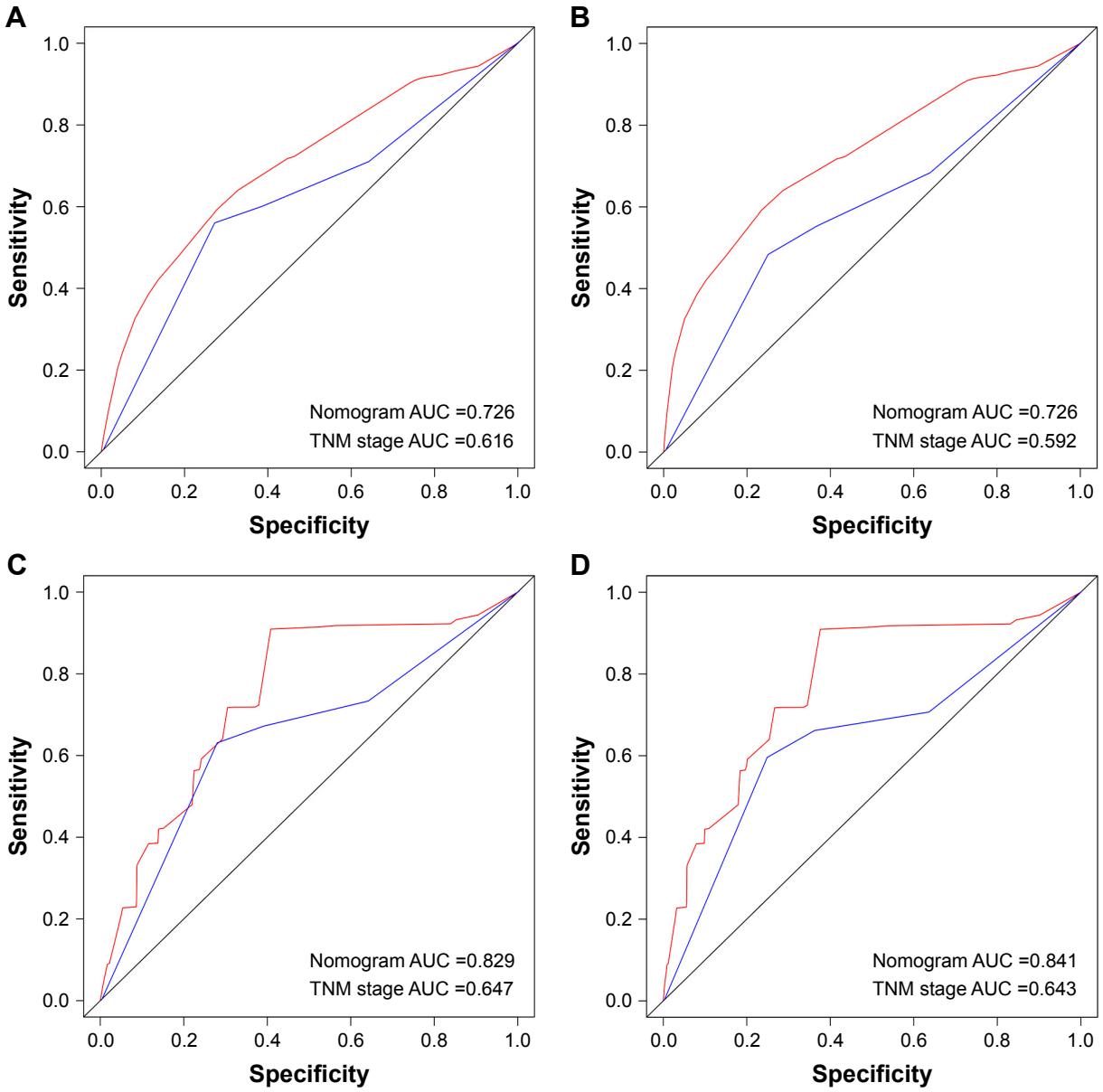

Figure 5 Comparison of the AUCs of the nomogram and TNM staging system in training set.
Notes: AUCs of the two models to predict 5- and 10-years OS (**A**, **B**) and CSS (**C**, **D**) in the training set. The red lines represent nomogram-predicted OS rates, whereas the blue lines represent TNM stage-predicted OS rates.
Abbreviations: AUC, area under the curve; CSS, cancer-specific survival; OS, overall survival.

N-staging of several types of cancer. Several reports indicated that the positive lymph node number was significantly associated with both OS and CSS in patients with DTC.[27–29] Similar to the results of this study, lymph node metastases showed a significance with prognosis in our nomograms. Distant metastasis was also a significant prognostic factor in the reported nomograms.[30,31] However, sex, race, multifocality, surgery, and T stage were not prognostic factors.

Nomograms address the complexity of balancing different variables through statistical modeling and risk quantification. Their systematic approach also avoids the bias of individual physicians or individual abnormal clinical variables. In addition, nomograms may be the most valuable when the potential benefits of added therapy are unclear.[32,33] They are very useful for individualized risk stratification and help doctors identify the management where no firm guidelines may exist.

We recognize several limitations in our study. First, the nomograms were constructed from the collection of retrospective data. Therefore, this may lead to the risk of potential selection bias. Second, due to the rare specific mortality of MTC, the evaluation of recurrence risk is believed to be more meaningful than death. However, SEER database did not record the data with respect

to recurrence. Therefore, the evaluation of recurrence risk cannot be performed. Finally, some other critical prognostic variables were unavailable in the SEER database. For example, RET mutation status and calcitonin doubling times are recognized variables that predict outcome.

Conclusion

We successfully established and validated prognostic nomograms to predict 5- and 10-year OS and CSS of MTC patients based on a large study cohort. The nomograms may provide an alternative tool for prognostic prediction, which may be used to accurately provide information to both physicians and patients, allowing for tailored treatments of MTC.

Disclosure

The authors report no conflicts of interest in this work.

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