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ORIGINAL RESEARCH

Nomograms for estimating survival in patients with papillary thyroid cancer after surgery

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Background: The aim of this study was to develop and validate nomograms to predict the survival in patients with papillary thyroid cancer (PTC).

Patients and methods: Adult patients who were surgically treated for PTC were selected from the Surveillance, Epidemiology and End Results (SEER) program (2004–2013). A multivariate analysis using the Cox proportional hazards regression was performed, and nomograms for predicting 10-year overall survival (OS) and cancer-specific survival (CSS) were constructed. The discrimination and calibration plots were used to measure the accuracy of the nomograms.

Results: The records of 63,219 patients with PTC were retrospectively analyzed. Nine independent factors including age, race, sex, marital status, tumor size, extrathyroidal extension, radioactive iodine, T stage, and M stage were assembled into the OS nomogram. A nomogram predicting CSS was constructed based on eight factors (age, sex, marital status, tumor size, extrathyroidal extension, T stage, N stage, and M stage). With respect to the training set, the nomograms displayed improved discrimination power compared to the TNM staging system (6th edition) in both sets. The calibration curve for the probability of survival showed agreement between the predictive nomograms and the actual observation.

Conclusion: We have successfully developed prognostic nomograms to predict OS and CSS for PTC with excellent discrimination and calibration.

Keywords: papillary thyroid cancer, nomogram, SEER, prognosis

Introduction

Thyroid cancer (TC) is the most common endocrine malignancy, with an estimated 53,990 new cases in the US in 2018.[1] The incidence rate for TC has increased more than 2.5 folds (5.57/100,000–13.98/100,000) in the recent decades.[2] This progressive increase was nearly entirely attributable to an increase in papillary thyroid carcinoma (PTC). Differentiated thyroid carcinoma is the major subtype of TC, and is subdivided into papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). PTC is the most common type of differentiated TC, accounting for approximately 90% of all the cases.[3] Radical surgical intervention remains the primary treatment for TC. Despite a favorable rate of survival for PTC, the risk of recurrence ranges from 5% to 21%.[4,5]

The TNM Cancer Staging System of the American Joint Committee on Cancer (AJCC) is the most widely used system to predict the survival outcomes.[6] In this classification system, patients are stratified according to depth of invasion (T), number of metastatic nodes (N), and the status of distant metastasis (M). This system is effective for patient populations but is not very useful in predicting individual patient

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outcomes.[7] In addition, it does not account for other variables, such as sex, race, marital status, multifocality, surgery, presence of vascular invasion, margin status, and radioactive iodine, which have been identified as independent prognostic factors in TC.[8–10]

Nomograms have been accepted as reliable tools to accurately predict an individual's clinical outcome by utilizing multiple variables. Nomograms provide a visual explanation for the predicted probabilities of an outcome as obtained by statistical predictive models. They were created by regression analysis and have extended beyond the standard TNM anatomical criteria.[11] Nomograms have been widely used in multiple malignancies due to their ability to handle the complexity in a systematic and unbiased manner.[12–15] Well-designed nomograms have been incorporated into the National Comprehensive Cancer Network (NCCN) guidelines.[16,17] Nevertheless, no nomograms are available for individual PTC patients on the basis of population-based data. Therefore, we aimed to develop a prognostic nomogram based on the large population of PTC data retrieved from the Surveillance, Epidemiology and End Results (SEER) database, to predict the individualized survival in patients with PTC.

Patients and methods

Patients

This study is a retrospective cohort analysis using data from the SEER database which was designed and maintained by the National Cancer Institute (NCI). The SEER database collects clinical information on various cancer types for associated incidence, prevalence, and survival from 17 population-based cancer registries covering approximately 28% of the US population.[18] 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 PTC who underwent thyroid surgery between 2004 and 2013. The histological subtypes of PTC were limited using the site code C73.9 and the International Classification of Diseases for Oncology-3: 8050, 8260, 8340–8344. The exclusion criteria were: (1) patients with second primary malignancies, (2) patients diagnosed at autopsy and those lost to follow-up, and (3) patients with incomplete clinical information (marital status, cause of death, survival month, tumor size, staging information, and follow-up months). All patients were randomly assigned to either the training set for nomograms or the validation set for the purposes of validation. Neither ethical approval nor informed consent was required because the data is publicly available, and the database does not hold any identifying patient data.

Variables

Several variables, including age, sex, race, marital status, tumor size, extrathyroidal extension, multifocality, surgery, radioactive iodine, T stage, N stage, and M stage were collected in the training set. Tumor size was categorized as "≤1.0 cm", "1.1–2.0 cm", "2.1–4.0 cm", and ">4 cm". The primary end point was the overall survival (OS) and cancer specific survival (CSS). While the OS was defined as the time from diagnosis of PTC to death or censoring, the CSS was defined as the time from diagnosis to death due to PTC or censoring.

Statistical analyses

The baseline patient features were compared using the Chi-square test. Survival curves were depicted using the Kaplan-Meier method and compared using the log-rank test. The construction of nomograms was based on the independent prognostic variables determined by multivariate Cox proportional hazards regression analyses. Variables were selected through the backward stepwise selection method with a threshold of $P<0.050$. The performance of the nomogram was evaluated by discrimination and calibration. Discrimination was assessed using the concordance index (C-index), which is similar to the area under receiver operating characteristic (ROC) curve (AUC), with values ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination).[19] Calibration was performed by comparing the observed versus predicted mean survival rate. Significance was achieved at $P<0.05$ in a two-tailed test. Statistical analyses were conducted using the SPSS version 23 (IBM, Armonk, NY, USA), and the nomogram was constructed using R version 3.5.1 (http://www.r-project.org) via the design and survival packages.

Results

Clinicopathological features

In total, 63,219 eligible PTC patients were selected and randomly assigned into a training set (n=31,610) and a validation set (n=31,609). The flow diagram of data selection is presented in Figure 1. In the whole study cohort, 35,337 (55.9%) patients were older than 45 years. While 49,959 (79.0%) patients were women, 13,260 (21.0%) of them were men. Most tumors

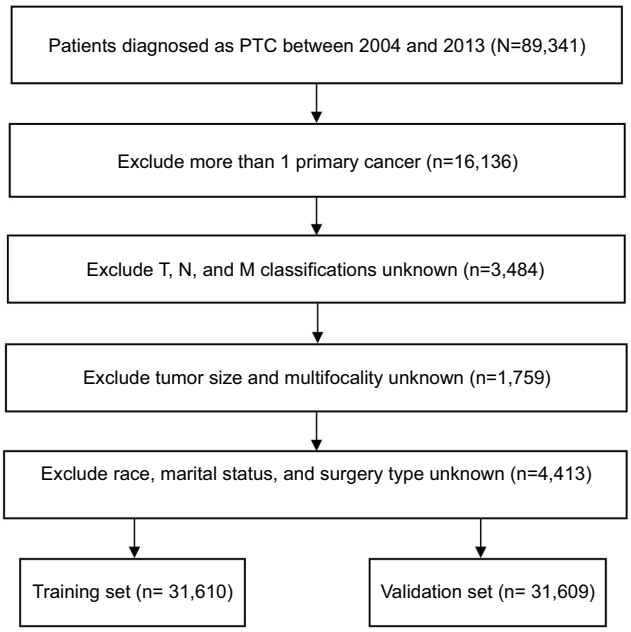

Figure 1 Flow chart of the data selection process.
Abbreviation: PTC, papillary thyroid cancer.

(55.6%) were ≤1.0 cm in size. Multifocal tumors were observed in 26,546 (42.0%) patients and a gross extrathyroidal extension of cancer in 10,047 (15.9%) patients. Total thyroidectomy was performed in 83.4% of all the patients, and 49.0% of them received adjuvant radioactive radioiodine. Most patients (62.5%) were categorized as having T1 stage cancer. Additionally, a few patients had lymph node invasion (22.6%) and distant metastasis (99.2%) at diagnosis.

The median follow-up was 68 months (1–143 months). By the end of the follow up, 2015 of the 63,219 (3.2%) patients had died, which included 545 deaths due to PTC and 1,470 due to other causes. The clinicopathologic characteristics of the patients are listed in Table 1.

Construction and validation of nomograms

Data on age at diagnosis, sex, race, marital status, tumor size, extrathyroidal extension, multifocality, surgery, radioactive iodine, T stage, N stage, and M stage were collected and analyzed for patients in both the training and validation sets. Univariate analysis showed that 10 of the above variables were significantly associated with OS in the training set ($P<0.05$). After performing a multivariate analysis, 9 out of the 10 variables (age, sex, race, marital status, tumor size, extrathyroidal extension, radioactive iodine, T stage, and M stage) were found to be significantly associated with OS (Table 2). Therefore, a nomogram of the OS was established with these independent variables in the training set (Figure 2A). As is shown in Table 3, 8 variables (age, sex, marital status, tumor size, extrathyroidal extension, T stage, N stage, and M stage) were confirmed to have a significant impact on patient CSS by both univariate and multivariate analyses in the training set ($P<0.05$). A nomogram for predicting the 10-year CSS was constructed based on the independent variables (Figure 2B).

We next validated the nomograms. Following an internal validation in the training set, the C-indices for the nomograms to predict the OS and CSS were 0.776 (95% CI: 0.770–0.792) and 0.924 (95%CI: 0.907–0.941), respectively. Following an external validation using the validation set, C-indices were found to be 0.770 (95% CI: 0.753–0.787) and 0.925 (95% CI: 0.905–0.945) for the OS and CSS nomograms, respectively. The calibration curve showed good agreement between prediction and observation in the probability of 10-year OS and CSS in both the training and validation sets (Figure 3). Furthermore, comparisons were performed between the nomograms and TNM 6th staging system in the training set. Results comparable to those of the TNM staging system were obtained with nomograms for the OS (C-index=0.776, 95% CI: 0.770–0.792 vs 0.317, 95% CI: 0.301–0.333) and CSS (C-index=0.924, 95% CI: 0.907–0.941 vs 0.152, 95% CI: 0.136–0.168). Moreover, discrimination was also enhanced with the nomogram compared to the TNM staging system when analyzed in the validation set (Table 4).

Comparison of AUC values of the nomogram and TNM 6th staging system

The predictive abilities of the nomograms and the TNM 6th staging system were compared by analyzing the AUC values (Figure 4). The AUC values for the nomogram and the TNM 6th staging system predicting the 10-year OS rates were 0.734 and 0.524, respectively, while those for predicting the 10-year CSS rates were 0.894 and 0.569, respectively. Taken together, the OS and CSS nomograms showed superior discriminative capacity compared to the TNM 6th staging system.

Discussion

Several scoring systems are used for prognostic purposes. Although these systems are easier to use in the clinic, they provide a stratified population risk assessment rather than an individualized patient risk.[6,20–22] Nomograms are useful tools, which have been widely used for predicting survival outcomes in individual patients. They address the complexity of balancing different variables through statistical modelling and risk quantification. Their

Table 1 Patient demographics and pathological characteristics

Variables	All patients (n=63,219)		Training set (n=31,610)		Validation set (n=31,609)		*P*-value
	No.	%	No.	%	No.	%	
Age							0.193
<45	27,882	44.1	13,860	43.8	14,022	44.4	
≥45	35,337	55.9	17,750	56.2	17,587	55.6	
Sex							0.583
Female	49,959	79.0	25,008	79.1	24,951	78.9	
Male	13,260	21.0	6,602	20.9	6,658	21.1	
Race							0.952
White	52,195	82.6	26,083	82.5	26,112	82.6	
Black	3,825	6.1	1,917	6.1	1,908	6.0	
Other	7,199	11.4	3,610	11.4	3,589	11.4	
Marital status							0.100
Married	42,469	67.2	21,332	67.5	21,137	66.9	
Unmarried	20,750	32.8	10,278	32.5	10,472	33.1	
Tumor Size							0.658
≤1.0 cm	25,984	41.1	13,012	41.2	12,972	41.0	
1.1–2.0 cm	18,778	29.7	9,437	29.9	9,341	29.6	
2.1–4.0 cm	13,786	21.8	6,835	21.6	6,951	22.0	
>4.0 cm	4,671	7.4	2,326	7.4	2,345	7.4	
Extrathyroidal extension							0.101
Absent	53,172	84.1	26,511	83.9	26,661	84.3	
Present	10,047	15.9	5,099	16.1	4,948	15.7	
Multifocality							0.131
Unifocal	36,673	58.0	18,243	57.7	18,430	58.3	
Multifocal	26,546	42.0	13,367	42.3	13,179	41.7	
Surgery							0.369
Lobectomy	10,522	16.6	5,219	16.5	5,303	16.8	
Total thyroidectomy	52,697	83.4	26,391	83.5	26,306	83.2	
Radioactive iodine							0.997
Yes	30,950	49.0	15,475	49.0	15,475	49.0	
No	32,269	51.0	16,135	51.0	16,134	51.0	
T stage							0.352
T1	39,520	62.5	19,771	62.5	19,749	62.5	
T2	10,257	16.2	5,063	16.0	5,194	16.4	
T3	11,346	17.9	5,702	18.0	5,644	17.9	
T4	2,096	3.3	1,074	3.4	1,022	3.2	
N stage							0.134
N0	48,927	77.4	24,385	77.1	24,542	77.6	
N1	14,292	22.6	7,225	22.9	7,067	22.4	
M stage							0.320
M0	62,727	99.2	31,353	99.2	31,374	99.3	
M1	492	0.8	257	0.8	235	0.7	

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

Variable	Univariate Analysis	Multivariate analysis	
	P-Value	HR (95%CI)	*P*-Value
Age	<0.001		
<45		Reference	
≥45		2.706 (2.339–3.131)	<0.001
Sex	<0.001		
Female		Reference	
Male		1.919 (1.681–2.192)	<0.001
Race	0.005		
White		Reference	
Black		1.471 (1.185–1.825)	0.014
Other		0.849 (0.687–1.048)	0.127
Marital status	<0.001		
Married		Reference	
Unmarried		1.939 (1.709–2.199)	<0.001
Tumor Size	<0.001		
≤1.0 cm		Reference	
1.1–2.0 cm		0.954 (0.799–1.139)	0.603
2.1–4.0 cm		1.445 (1.080–1.934)	0.013
>4.0 cm		2.787 (2.087–3.721)	<0.001
Extrathyroidal extension	<0.001		
Absent		Reference	
Present		2.297 (1.665–3.170)	<0.001
Multifocality	0.685		
Unifocal			
Multifocal			
Surgery	0.521		
Lobectomy			
Total thyroidectomy			
Radioactive iodine	<0.001		
Yes		Reference	
No		1.901 (1.669–2.167)	<0.001
T stage	<0.001		
T1		Reference	
T2		0.706 (0.504–0.988)	0.042
T3		0.563 (0.390–0.814)	0.002
T4		1.418 (0.910–2.207)	0.123
N stage	<0.001		
N0		Reference	
N1		1.104 (0.945–1.289)	0.214
M stage	<0.001		
M0		Reference	
M1		6.374 (5.054–8.038)	<0.001

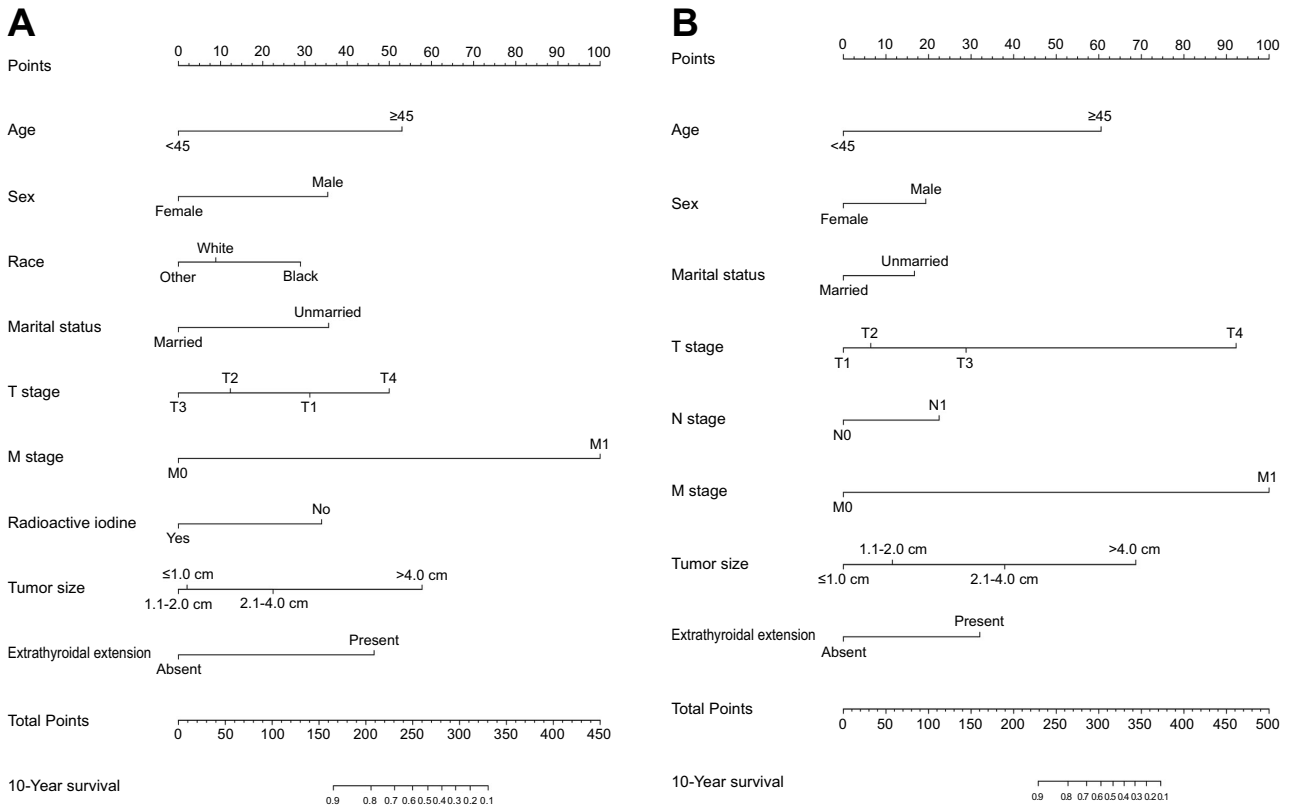

Figure 2 Nomogram for predicting 10-year OS (**A**) and CSS (**B**) of patients with PTC.

systematic approach also avoids the bias of individual physicians or individual abnormal clinical variables. Nomograms have been proven to be superior to the traditional staging scoring systems in a variety of tumors.[15,23,24] In addition, they may be the most valuable when the potential benefits of added therapy are unclear.[25,26] They are also very useful for individualized risk stratification and help doctors in the management of clinical care when no firm guidelines are available.

To the best of our knowledge, this is the first study that describes the development and validation of nomograms to predict 10-year OS and CSS in patients with PTC. A total of 63,219 patients from the SEER dataset were analyzed in this study. Our nomograms displayed favorable discrimination and calibration. Furthermore, the ROC curve showed that the nomograms had better predictive ability than the 6th AJCC staging system. Our nomogram models are easy-to-use clinical tools which can help with patient counselling and personalized treatment.

Our nomograms identified several independent factors that could influence the prognosis in PTC patients. The results showed that most patients older than 45 years of age had the worst OS and CSS. Studies have shown that age is a major determinant of thyroid CSS.[27] Older age has been identified as an independent risk factor, suggesting that older patients have lower survival rates.[28–30] Multiple studies have found that patients with TC who are older than 45 years of age usually have a poor prognosis.[8,31] With advancing age, there is a higher risk of a histological phenotype.[32] The previous edition of the AJCC staging system used 45-years as the cut-off value for age, while the recent eight edition uses 55 years. However, regardless of the cut-off value, age is identified as an important prognostic factor.

The difference in the incidence of TC in the two sexes has also been well documented.[33] The incidence of TC is higher in women compared to men, though the clinical outcomes are worse in men.[34] Our results were consistent with those of previous studies. In addition to the above factors, marital status, tumor size, extrathyroidal extension, T stage, N stage, and M stage were also identified as significant predictors of prognosis. However, we found that multifocality, surgery, and radioactive iodine were not risk factors of the 10-year CSS.

Our study has several limitations. First, the nomograms were constructed from retrospective data. Therefore, the potential risk of selection bias cannot be ruled out. Second, due to the rare specific mortality

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

Variable	Univariate analysis	Multivariate analysis	
	P-value	HR (95%CI)	*P*-value
Age	<0.001		
<45		Reference	
≥45		3.702 (2.667–5.139)	<0.001
Sex	<0.001		
Female		Reference	
Male		1.542 (1.2058–1.972)	<0.001
Race	0.018		
White		Reference	
Black		1.291 (0.790–2.109)	0.309
Other		1.213 (0.881–1.668)	0.236
Marital status	0.008		
Married		Reference	
Unmarried		1.423 (1.116–1.816)	0.004
Tumor Size	<0.001		
≤1.0 cm		Reference	
1.1–2.0 cm		1.272 (0.773–2.094)	0.343
2.1–4.0 cm		2.240 (1.295–3.874)	0.004
>4.0 cm		4.351 (2.521–7.507)	<0.001
Extrathyroidal extension	<0.001		
Absent		Reference	
Present		2.017 (1.209–3.365)	0.007
Multifocality	0.506		
Unifocal			
Multifocal			
Surgery	0.191		
Lobectomy			
Total thyroidectomy			
Radioactive iodine	0.925		
Yes			
No			
T stage	<0.001		
T1		Reference	
T2		1.143 (0.582–2.246)	0.698
T3		1.808 (0.935–3.497)	0.079
T4		7.009 (3.312–14.834)	<0.001
N stage	<0.001		
N0		Reference	
N1		1.643 (1.253–2.153)	<0.001
M stage	<0.001		
M0		Reference	
M1		8.462 (6.334–11.307)	<0.001

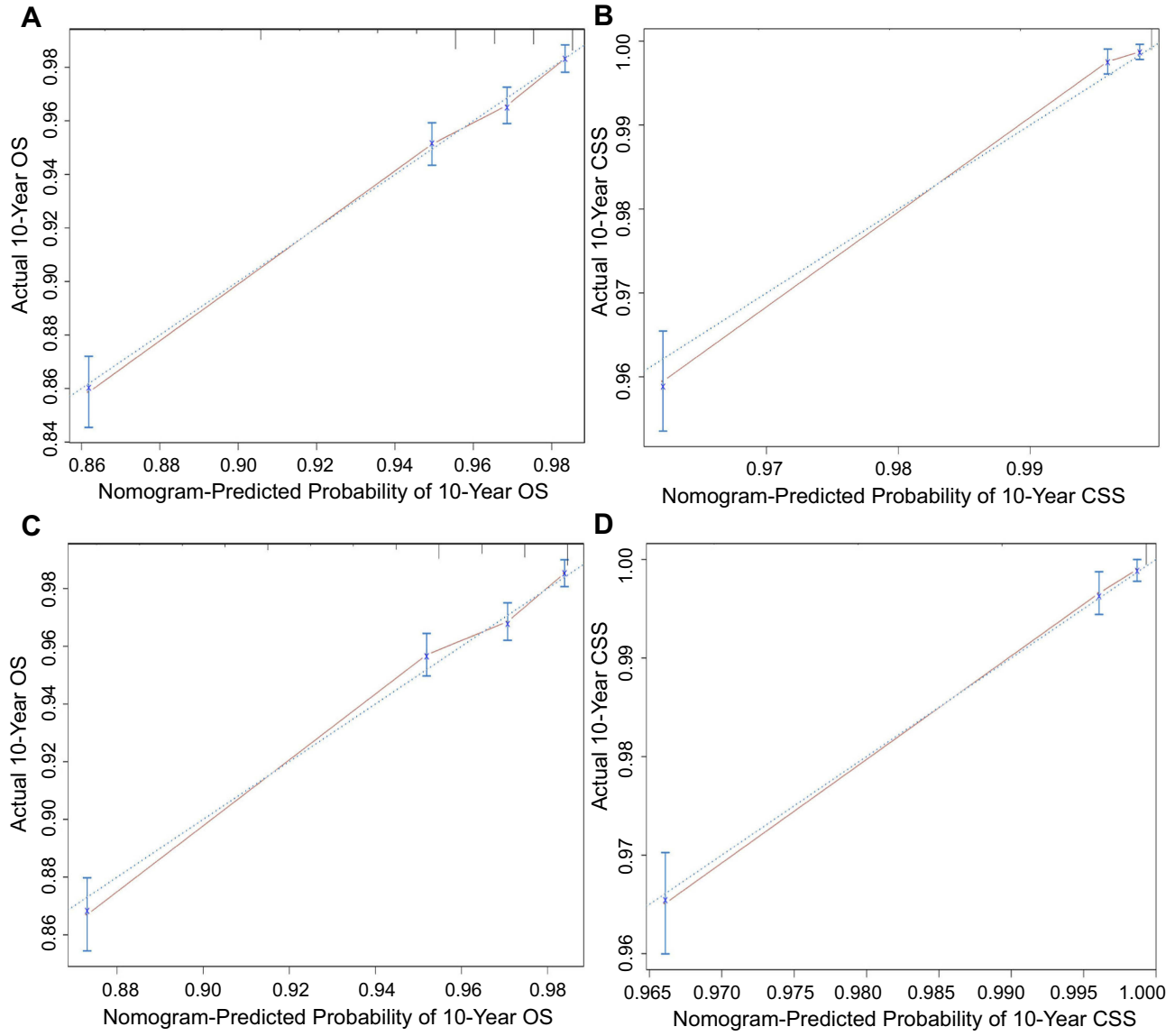

Figure 3 Calibration plots of the training and validation sets for the OS and CSS associated nomograms.
Notes: (**A, B**) The calibration plots of the training set in 10-year OS and CSS; (**C, D**) the calibration plots of the validation set in 10-year OS and CSS. The x-axis represents the nomogram-predicted survival rate, whereas the y-axis represents the actual survival rate.
Abbreviations: OS, overall survival; CSS, cancer-specific survival.

Table 4 C-indexes for the nomograms and other stage systems in patients with PTC

Survival		Training set		Validation set	
		HR	95%CI	HR	95%CI
OS	Nomogram	0.776	0.770–0.792	0.770	0.7530.787
	TNM 6th stage	0.317	0.301–0.333	0.330	0.313–0.347
CSS	Nomogram	0.924	0.907–0.941	0.925	0.905–0.945
	TNM 6th stage	0.152	0.136–0.168	0.152	0.135–0.169

Abbreviations: HR, hazard ratio; CI, confidence interval; CSS, cancer-specific survival; OS, overall survival; PTC, papillary thyroid cancer.

in PTC, the evaluation of the risk of recurrence may be more meaningful than death. However, the SEER database did not have data on recurrence, and therefore it could not be evaluated. Third, in spite of the patients being chosen randomly, there was still a significant difference between the numbers of male

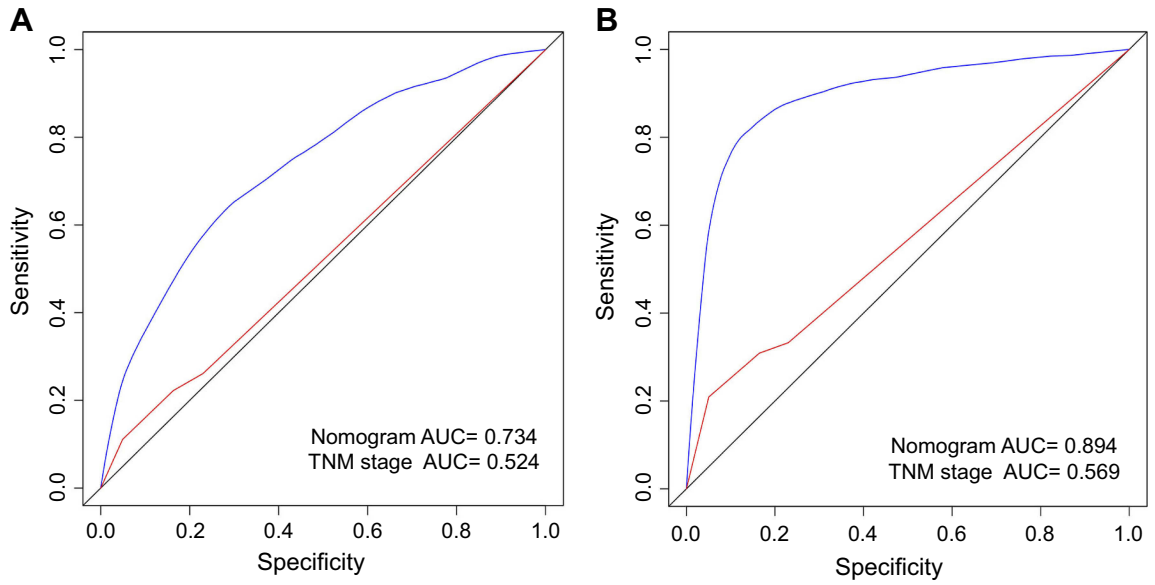

Figure 4 Comparison of the AUCs of the nomogram and TNM staging system in training set.
Notes: Area under the curves of the two models to predict 10-years OS (**A**) and CSS (**B**) in the training set. The blue lines represent nomogram-predicted overall survival rates, whereas the red lines represent TNM stage-predicted overall survival rates.
Abbreviations: AUC, area under ROC curve; CSS, cancer-specific survival; OS, overall survival; ROC, receiver operating characteristic.

and female patients, which could have resulted in gender bias. Finally, some other critical prognostic factors, such as margin status, calcitonin, extent of surgery, radioiodine dosage, thyrotropin suppression, *BRAF* point mutation, and *TERT* promotor point mutation, were unavailable in the SEER database.

In conclusion, we were successful in establishing and validating nomograms to predict the 10-year OS and CSS in individual patients with PTC based on a large study cohort. Our nomograms could be convenient, individualized predictive tools for prognosis, which can help surgeons perform personalized survival evaluation and mortality risk identification in PTC patients.

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Author contributions

GL and SRS participated in study design and data collection. GL and QL analyzed and interpreted the data. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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