



A nomogram for predicting overall survival in patients with follicular thyroid cancer after thyroidectomy: a SEER database analysis

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Background: A good predictive model requires patient participation in prognostic counseling and subsequent clinical follow-up. We aimed to construct and validate a nomogram for predicting overall survival (OS) in patients with follicular thyroid cancer (FTC) after thyroidectomy.

Methods: This was a retrospective observational study. We screened 802 patients with initially diagnosed FTC from the Surveillance Epidemiology and End Results (SEER) database between 2010 and 2015. Then the patients were all divided into the training set and validation set randomly at a ratio of 7:3. Univariate and multivariate Cox proportional hazard models were used to analyze the influence of different variables on OS. The concordance index (C-index) and calibration curves were used to evaluate the precision of the nomogram.

Results: Univariate and multivariate analyses demonstrated that four factors, namely age, grade, race, and M stage (all $P < 0.05$), were independent predictors of OS in FTC patients. Based on these factors, a predictive model was established by using the training cohort and validated by the validation cohort. A good consistency between the actual OS and predicted OS was showed by the calibration curves. Moreover, compared with the traditional tumor-node-metastasis (TNM) staging system, the nomogram had better predictive ability for the survival of patients with FTC. The C-index of the nomogram in the training set and validation set had high consistency in evaluating the survival rate of patients with FTC [training set: C-index = 0.904, 95% confidence interval (CI): 0.883–0.925; validation set: C-index = 0.835, 95% CI: 0.772–0.898; TNM: C-index = 0.775, 95% CI: 0.732–0.818].

Conclusions: Based on several clinical variables, we established the first predictive model of FTC after thyroidectomy by using Cox multivariate analysis which provide a basis for each patient with prognosis and postoperative follow-up.

Keywords: Nomogram; concordance index (C-index); follicular thyroid cancer (FTC); overall survival (OS)

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Introduction

Thyroid cancer (TC) is the most common malignant tumor of the neck, originating from thyroid follicular epithelial cells or parafollicular epithelial cells (1,2). In the past few decades, the incidence of TC has been increasing. The most common pathological type is papillary thyroid cancer (PTC), accounting for about 80% of cases, followed by follicular thyroid cancer (FTC), accounting for 10–15% of TC cases (3,4). Both PTC and FTC are types of differentiated thyroid carcinoma (DTC). They are often analyzed and treated as the type of TC. FTC is usually diagnosed by histopathological findings of vascular and/or capsule filling, but occasionally diagnosis is missed because of inadequate material or absence of a definite invasion (5,6). Due to the relatively low incidence of FTC and insufficient evidence from large samples and multicenter clinical trials, it is still unclear whether FTC and PTC should be treated equally (7).

FTC is a moderately differentiated carcinoma. Although the prognosis of patients after standardized treatment is good, 10% of patients still have recurrence and metastasis (7). Total thyroidectomy or subtotal thyroidectomy is the main treatment for FTC patients with or without distant metastasis (8). At present, the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system is the main criterion to guide the treatment and prognosis of FTC patients (9,10). However, traditional TNM staging is not effective in predicting the prognosis of individual patients (11). In addition, some other factors, including age, race, sex, treatment type, surgery, tumor size, and marital status, may also be important factors related to the prognosis of patients with FTC (12–14). Therefore, the combination of AJCC TNM staging and these variables may be better for predicting outcomes and would be better for clinical guidance.

Nomograms are a common tool to predict the prognosis of patients with cancers by incorporating and validating certain relevant factors (15). Previous studies have demonstrated that nomograms play an increasingly important role in predicting the outcomes of lung cancer, liver cancer, and other cancers (16–19). Moreover, in multiple cancers, nomograms that calculate the numerical probability of clinical events, such as cancer-specific survival (CSS) and overall survival (OS), have predicted more precisely than the traditional TNM staging systems. However, few studies have reported a nomogram model that can predict OS in patients with FTC after thyroidectomy.

In the present study, to predict prognosis for patients with FTC who underwent thyroidectomy, we developed and verified a nomogram based on several clinical variables using the Surveillance Epidemiology and End Results (SEER) database, which consists of research data from 20 regions in the United States (20). We present the following article in accordance with the TRIPOD reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gs-22-386/rc>).

Methods

Data source

The clinical data of 802 patients initially diagnosed with FTC was collected from the SEER database between 2010 and 2015. A nomogram to predict the prognosis of FTC patients at 3- and 5-year was established by the statistical analysis of regression model. Then, we measured the Harrell's concordance index (C-index) to quantify the indication ability of the nomogram. Moreover, the survival rate between the actual survival rate and the predicted probability of survival by the nomogram was calibrated by a calibration curve. The inclusion criteria were as follows: (I) the diagnosis of FTC was made by histopathological examination; (II) patients with known survival months, cause of death, complete dates, and follow-up records; (III) sufficient information on variables including age, sex, race, grade, TNM staging, radiotherapy, chemotherapy, lymphadenectomy, tumor size, and marital status, among others. The exclusion criteria were as follows: (I) patients with benign tumors; (II) controversial cases; (III) patients with missing follow-up records or cause of death.

Ethical statement

This study was conducted on the basis of public data from the SEER database. Therefore, we have applied for the waive of the ethics committee agreement due to no personal identifying information being involved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Clinical characteristics

Some information was gained from the SEER dataset: patient demographics, tumor characteristics, therapeutic patterns, and survival results. The patient demographic

analysis was used with age, sex, race, and marital status. Histological type, tumor stage, grade, as well as surgical information, were used in the analysis of tumor characteristics. We categorized the patients into several groups according to age (≤ 30 , 31–40, 41–50, 51–60, 61–70, and >70 years). Sex was classified as female and male. We categorized the marital status as married and unmarried. Race was classified as black, white, and others (including American Indians, Asian, Alaskan natives, Pacific Islanders). Tumor size also was classified as 3 groups (cm): <2.0 , 2.1–4.0, and ≥ 4.0 . The TNM staging system was the AJCC 7th surgical-pathological staging classification. The World Health Organization histological classification and the ICD-0-3 site/histology validation list were used to identify FTC (8330/3). Tumor grade was divided into G1–G4, indicating respectively as undifferentiation, poor differentiation, moderate differentiation and well differentiation. In addition, radiotherapy, chemotherapy, and lymphadenectomy were all divided into treatment group and untreated group.

Statistical analysis

We analyzed the following variables for each patient: age, sex, race, grade, TNM stage, radiotherapy, chemotherapy, tumor size, and marital status. The Chi-square test was used to compare the patient baseline characteristics. Furthermore, the association between survival and different variables in patients with FTC was evaluated by univariate and multivariate Cox proportional hazards regression models with a hazard ratio (HR) and corresponding 95% confidence interval (CI). Modeling a nomogram with R software (version 3.4.5; <https://www.r-project.org/>) and all data were processed by SPSS 24.0 (IBM, USA). All statistical tests were two-sided, and $P < 0.05$ indicated that the difference was statistically significant.

Results

Patient characteristics

A total of 802 FTC patients from the SEER database fulfilled the inclusion criteria and were enrolled in this study. Patients were randomly divided into two groups according to the proportion of 7:3 by R software. A total of 562 patients were included in the training set and 240 patients were included in the validation set. We reported the specific baseline clinicopathological variables in

Table 1. Overall, the proportion of patients of different ages was equal. Most of the patients were female (71.4%) and white (76.9%). Moreover, G1 patients accounted for 77.3%. Additionally, 20.2% of patients were T1 stage, 39.7% of patients were T2 stage, 36.0% of patients were T3 stage, and 4.1% of patients were T4 stage. A total of 96.1% of patients had negative lymph nodes and 94.0% of patients had no distant metastasis. In addition, 66% of patients were treated with radiotherapy and only 0.7% of patients received chemotherapy. A total of 521 patients (65%) were treated with surgery without lymphadenectomy. No significant difference was observed in variables including age, sex, race, grade, T stage, N stage, M stage, radiotherapy, chemotherapy, tumor size, and marital status between the two groups (all $P > 0.05$).

Prognostic factor analysis of survival based on clinical variables

In the training set, the results of univariate analysis revealed that age ($P < 0.001$), other race ($P = 0.002$), G3 ($P < 0.001$), G4 ($P < 0.001$), T4 stage ($P < 0.001$), N1 stage ($P = 0.001$), and M1 stage ($P < 0.001$) were associated with survival in FTC patients. However, sex, radiotherapy, chemotherapy, lymphadenectomy, tumor size, and marital status were not related to survival (all $P > 0.05$). The univariate analysis results are listed in *Table 2*.

In the multivariate analysis (*Table 3*), age (HR = 1.057; 95% CI: 1.030–1.085; $P < 0.001$), other race (HR = 4.189; 95% CI: 1.781–9.854; $P = 0.001$), G3 (HR = 3.734; 95% CI: 1.571–8.874; $P = 0.003$), G4 (HR = 7.980; 95% CI: 1.579–40.327; $P = 0.012$), and M1 stage (HR = 2.582; 95% CI: 1.182–5.642; $P = 0.017$) were associated with poorer OS rates for patients with FTC.

Construction and validation of the nomogram

A nomogram was established based on clinical variables including age, grade, race, and M stage in the multivariate analysis. The 3- and 5-year OS prediction was estimated by a weighted total score calculated from each variable (*Figure 1A*). Additionally, the TNM staging system was further developed to predict 3- and 5-year OS (*Figure 1B*). The performance of the two predictive models was internally validated by discrimination and calibration methods. The calibration plots of the nomogram based on age, grade, race, and M stage revealed a good correlation

Table 1 Baseline clinicopathological characteristics of all patients and those in the training and validation cohorts

Variables	All patients (n=802)	Training set (n=562)	Validation set (n=240)	P value
Age (years), n (%)				0.597
≤30	110 (13.7)	84 (14.9)	26 (10.8)	
31–40	120 (15.0)	84 (14.9)	36 (15.0)	
41–50	151 (18.8)	105 (18.7)	46 (19.2)	
51–60	160 (20.0)	111 (19.8)	49 (20.4)	
61–70	138 (17.2)	98 (17.4)	40 (16.7)	
>70	123 (15.3)	80 (14.2)	43 (17.9)	
Sex, n (%)				0.553
Female	573 (71.4)	405 (72.1)	168 (70.0)	
Male	229 (28.6)	157 (27.9)	72 (30.0)	
Race, n (%)				0.225
White	617 (76.9)	430 (76.5)	187 (77.9)	
Black	115 (14.3)	77 (13.7)	38 (15.8)	
Other	70 (8.7)	55 (9.8)	15 (6.3)	
Grade, n (%)				0.239
G1	620 (77.3)	443 (78.8)	177 (73.8)	
G2	113 (14.1)	70 (12.5)	43 (17.9)	
G3	61 (7.6)	43 (7.7)	18 (7.5)	
G4	8 (1.0)	6 (1.1)	2 (0.8)	
T stage, n (%)				0.954
T1	162 (20.2)	112 (19.9)	50 (20.8)	
T2	318 (39.7)	221 (39.3)	97 (40.4)	
T3	289 (36.0)	205 (36.5)	84 (35.0)	
T4	33 (4.1)	24 (4.3)	9 (3.8)	
N stage, n (%)				0.61
N0	771 (96.1)	539 (95.9)	232 (96.7)	
N1	31 (3.9)	23 (4.1)	8 (3.3)	
M stage, n (%)				0.156
M0	754 (94.0)	524 (93.2)	230 (95.8)	
M1	48 (6.0)	38 (6.8)	10 (4.2)	
Radiotherapy, n (%)				0.548
No	273 (34.0)	195 (34.7)	78 (32.5)	
Yes	529 (66.0)	367 (65.3)	162 (67.5)	

Table 1 (continued)

Table 1 (continued)

Variables	All patients (n=802)	Training set (n=562)	Validation set (n=240)	P value
Chemotherapy, n (%)				0.675
No	796 (99.3)	557 (99.1)	239 (99.6)	
Yes	6 (0.7)	5 (0.9)	1 (0.4)	
Lymphadenectomy, n (%)				0.034
No	521 (65.0)	352 (62.6)	169 (70.4)	
Yes	281 (35.0)	210 (37.4)	71 (29.6)	
Tumor size (cm), n (%)				0.701
<2.0	147 (18.3)	99 (17.6)	48 (20.0)	
2.0–4.0	329 (41.0)	231 (41.1)	98 (40.8)	
≥4.0	326 (40.6)	232 (41.3)	94 (39.2)	
Marital status, n (%)				0.920
Married	459 (57.2)	321 (57.1)	138 (57.5)	
Unmarried	343 (42.8)	241 (42.9)	102 (42.5)	

between observed OS and nomogram prediction 3-, 5-year survival (Figure 2A,2B). Moreover, the calibration plots of the TNM staging system also revealed a good correlation between observed OS and nomogram prediction 3-, 5-year survival (Figure 2C,2D). Notably, the nomogram based on age, grade, race, and M stage showed better accuracy, with a C-index of 0.904 (95% CI: 0.883–0.925), compared with the traditional TNM staging system, which had a C-index of 0.775 (95% CI: 0.732–0.818) (Table 4).

Next, we further validated the nomogram model in the validation set. The calibration plots of the nomogram based on age, grade, race, and M stage in the validation set also revealed a good correlation between observed OS and nomogram prediction 3-, 5-year survival (Figure 3A,3B). The calibration plots of the traditional TNM staging system showed a good correlation between observed OS and nomogram prediction 3-, 5-year survival (Figure 3C,3D). In the validation set, the nomogram based on age, grade, race, and M stage also revealed relatively better accuracy, with a C-index of 0.835 (95% CI: 0.772–0.898), compared with the TNM staging system, which had a C-index of 0.758 (95% CI: 0.685–0.832) (Table 4).

Discussion

The nomogram model constructed in this study

incorporated several independent factors that may affect the prognosis of patients with FTC after thyroidectomy, including age, grade, race, and M stage. Compared with the traditional TNM staging system, the nomogram had better performance in terms of differentiation and calibration. The nomogram also had better accuracy in predicting the OS of patients with FTC after thyroidectomy.

In this study, age was a significant independent factor for survival in patients with FTC. Several studies have shown that the prognosis of elderly patients with TC is relatively poor (20–22). In addition, the relationship between older age and poor survival prognosis has been reported in many types of cancer (23–25). Highly DTC is the only malignant tumor that has been included in TNM staging by the AJCC (26). In a variety of staging systems, regardless of the cutoff, age is still identified as an important factor affecting the prognosis of patients with TC, which is consistent with our results.

Ethnic and racial disparities in health care exist and have been reported to be associated with worse prognosis in many diseases (27,28). A previous review has reported that black and white patients have a higher proportion of follicular cancer (14). The study by Asban *et al.* demonstrated significant gender and racial disparities in survival after TC surgery (13). In our study, we found that race other than white and black was a risk factor affecting

Table 2 Univariate analyses of each factor's ability to predict OS for patients with FTC after thyroidectomy

Variables	HR (95% CI)	P value
Age (years)	1.073 (1.048–1.098)	<0.001
Sex		
Female	Reference	
Male	0.987 (0.488–1.999)	0.972
Race		
White	Reference	
Black	1.234 (0.469–3.346)	0.671
Other	3.301 (1.527–7.139)	0.002
Grade		
G1	Reference	
G2	1.234 (0.417–3.649)	0.704
G3	9.062 (4.326–18.986)	<0.001
G4	17.471 (5.110–59.729)	<0.001
T stage		
T1	Reference	
T2	0.342 (0.096–1.212)	0.096
T3	1.473 (0.571–3.797)	0.423
T4	12.341 (4.618–32.982)	<0.001
N stage		
N0	Reference	
N1	4.597 (1.899–11.128)	0.001
M stage		
M0	Reference	
M1	8.391 (4.198–16.775)	<0.001
Radiotherapy		
No	Reference	
Yes	0.783 (0.406–1.510)	0.465
Chemotherapy		
No	Reference	
Yes	2.117 (0.284–15.769)	0.464
Lymphadenectomy		
No	Reference	
Yes	1.552 (0.815–2.958)	0.181

Table 2 (continued)

Table 2 (continued)

Variables	HR (95% CI)	P value
Tumor size (cm)		
<2.0	Reference	
2.0–4.0	0.569 (0.212–1.530)	0.264
≥4.0	1.368 (0.581–3.219)	0.473
Marital status		
Married	Reference	
Unmarried	1.879 (0.980–3.602)	0.058

OS, overall survival; FTC, follicular thyroid cancer; HR, hazard ratio; CI, confidence interval.

Table 3 Multivariate analyses of each factor's ability to predict OS for patients with FTC after thyroidectomy

Variables	HR (95% CI)	P value
Age (years)	1.057 (1.030–1.085)	<0.001
Race		
White	Reference	
Black	1.906 (0.677–5.365)	0.222
Other	4.189 (1.781–9.854)	0.001
Grade		
G1	Reference	
G2	0.759 (0.218–2.645)	0.666
G3	3.734 (1.571–8.874)	0.003
G4	7.980 (1.579–40.327)	0.012
T stage		
T1	Reference	
T2	0.440 (0.123–1.579)	0.208
T3	0.861 (0.307–2.417)	0.776
T4	2.474 (0.690–8.869)	0.164
N stage		
N0	Reference	
N1	1.832 (0.610–5.504)	0.28
M stage		
M0	Reference	
M1	2.582 (1.182–5.642)	0.017

OS, overall survival; FTC, follicular thyroid cancer; HR, hazard ratio; CI, confidence interval.

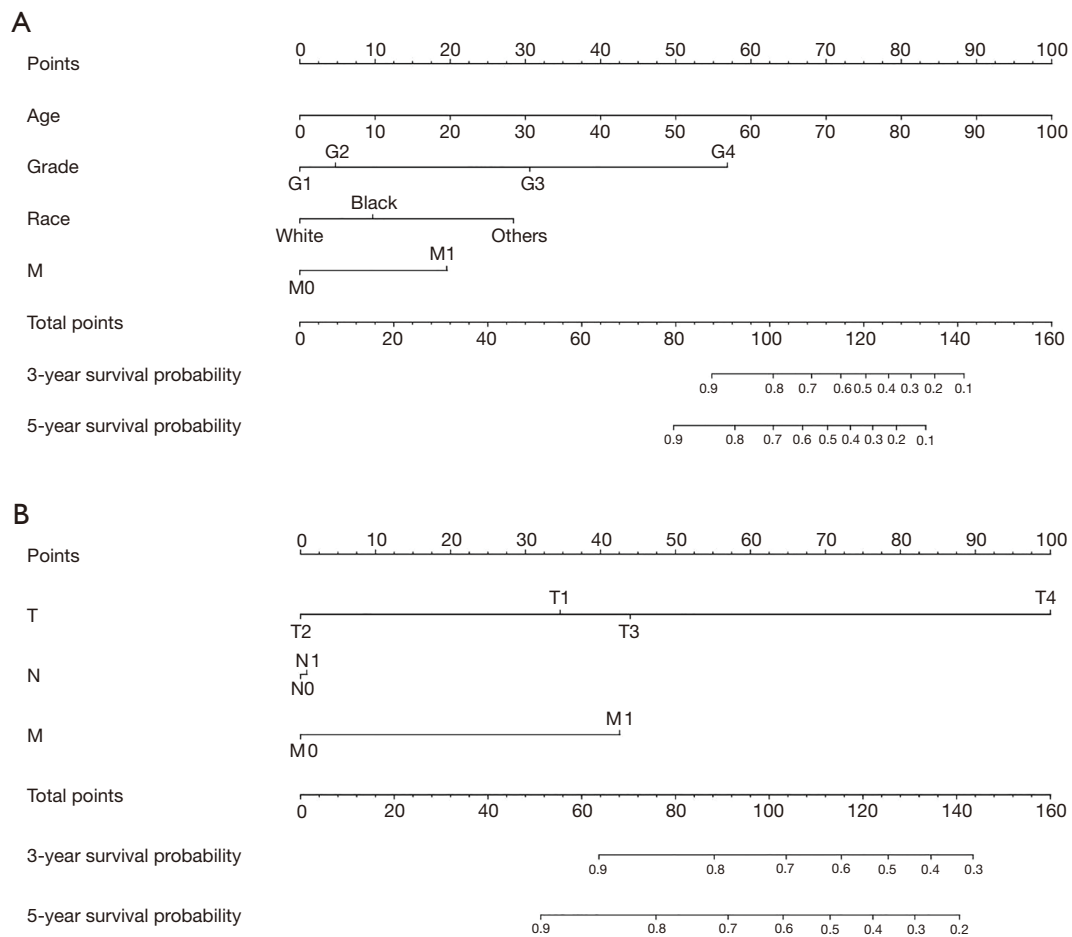


Figure 1 Nomograms for predicting OS. (A) A nomogram based on age, grade, race, and M stage for predicting the 3- and 5-year OS of FTC patients after thyroidectomy. (B) A nomogram based on TNM stage for predicting the 3- and 5-year OS of FTC patients after thyroidectomy. OS, overall survival; FTC, follicular thyroid cancer; TNM, tumor-node-metastasis.

the survival of FTC patients, which was consistent with the results of previous study (5).

Moreover, our results revealed that grade 3, grade 4, and M1 stage were independent risk factors for the prognosis of patients with FTC. In patients with FTC, distant metastasis is the strongest predictor of low OS. A previous study has reported that distant metastasis after surgery is an important factor affecting the death of patients with FTC (29). In addition, it has been demonstrated that distant metastasis at the initial diagnosis is an important factor affecting the poor survival of FTC patients, which is consistent with our results (30). Therefore, in clinical practice, clinicians should take active and effective treatment measures for patients with distant metastasis.

In the current study, we constructed a nomogram based on the above clinical variables that affected the survival of patients with FTC. Compared with the traditional TNM staging system, the C-index of the nomogram performed well in predicting the 3- and 5-year survival rates of FTC patients. According to the nomogram and risk score, clinicians can calculate an individual score for a patient and then predict the 3- and 5-year survival probability for FTC patients after thyroidectomy. To use the nomogram, we could draw a vertical line to mark the point row to allocate point values for each variable. Next, the total point is obtained by weighting the corresponding points. Finally, the total points correspond to the value of 3- and 5-year OS probability. More importantly, the nomogram is an easy-

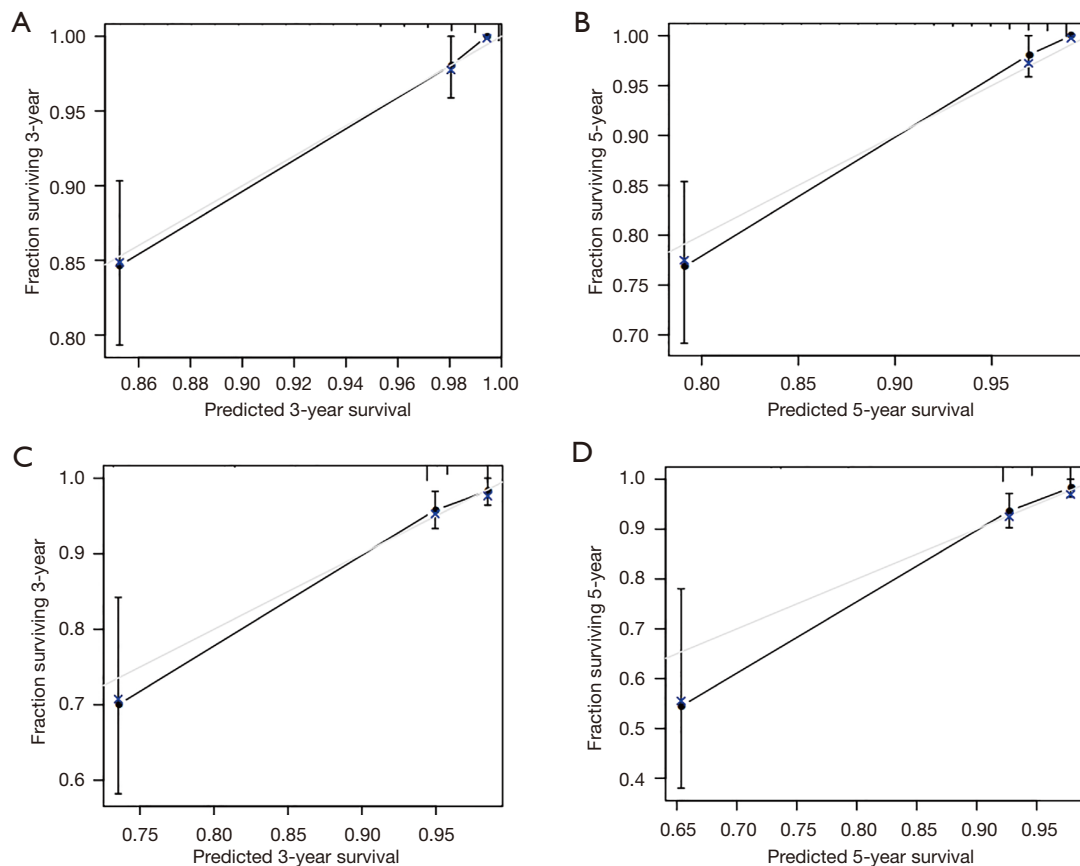


Figure 2 Nomogram model calibration curves. (A,B) Calibration curves of the nomogram based on age, grade, race, and M stage predicting the 3- and 5-year OS rates of FTC patients after thyroidectomy. (C,D) Calibration curves of the nomogram based on TNM stage predicting the 3- and 5-year OS rates of FTC patients after thyroidectomy. OS, overall survival; FTC, follicular thyroid cancer; TNM, tumor-node-metastasis.

Table 4 The C-index of the nomogram

C-index compare	C-index (95% CI)	P value
Training set		
Nomogram model	0.904 (0.883–0.925)	<0.001
TNM staging system	0.775 (0.732–0.818)	<0.001
Validation set		
Nomogram model	0.835 (0.772–0.898)	<0.001
TNM staging system	0.758 (0.685–0.832)	<0.001

C-index, concordance index; TNM, tumor-node-metastasis; CI, confidence interval.

to-use (age, race, grade, and M stage) and inexpensive tool to assist clinicians to predict survival in patients with FTC after surgery in clinical practice.

However, there were some limitations that should be noted in this study. Firstly, this was a retrospective study, which may lead to missing data. Secondly, the overall mortality rate of patients with FTC was lower, so the assessment of the risk of recurrence was more meaningful than the risk of death. However, due to the limitation of the SEER database, the data related to postoperative recurrence could not be collected. Finally, due to the data originating

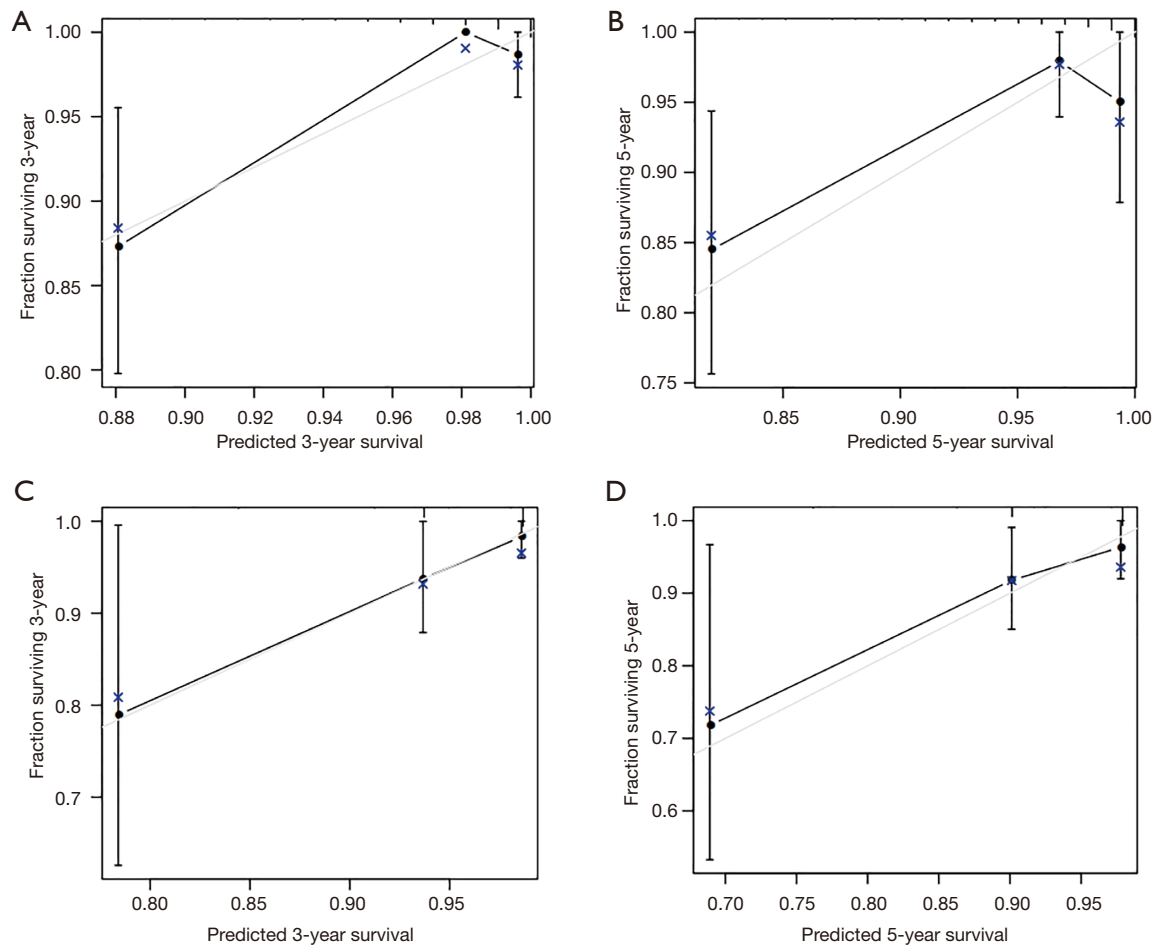


Figure 3 Verification of nomogram model calibration curves in the validation set. (A,B) Calibration curves of the nomogram based on age, grade, race, and M stage predicting the 3- and 5-year OS rates of FTC patients after thyroidectomy. (C,D) Calibration curves of the nomogram based on TNM stage predicting the 3- and 5-year OS rates of FTC patients after thyroidectomy. OS, overall survival; FTC, follicular thyroid cancer; TNM, tumor-node-metastasis.

from the SEER database, the included patients were mainly Westerners, and whether it would be applicable to Asian patients still needs to be verified by future research.

In summary, we have developed an intuitive and accurate tool to predict the prognosis of patients with FTC and their 3- and 5-year survival. This nomogram could provide corresponding treatment assistance for FTC patients and assist clinicians to make treatment decisions.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://gs.amegroups.com/article/view/10.21037/gS-22-386/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gS-22-386/coif>). 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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