Development and Evaluation of Prognostic Nomogram for Patients with Differentiated Thyroid Carcinoma

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Research

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Abstract

Background: Papillary thyroid carcinoma and follicular thyroid carcinoma are both well-differentiated thyroid carcinomas. Here, we aimed to establish and evaluate a nomogram for patients with differentiated thyroid cancer.

Methods: Patient records were available from SEER database. We enrolled 17,659 patients in total and randomly separated them into a modeling cohort (n = 12,363, 70%) and a validation cohort (n = 5,296, 30%). Predictive models were established via univariate and multivariate Cox regression analysis of potential risk factors and used to produce a nomogram. Performance of the nomograms in terms of discrimination ability and calibration was evaluated by determining the concordance index (C-index) and by generating calibration plots, respectively, using the internal (modeling cohort) and external (validation cohort) validity.

Results: Seven independent prognostic factors (age, race, sex, grade, AJCC T stage, AJCC N stage, and AJCC M stage) were identified and used to develop the nomogram for OS prediction of patients with DTC. The C-index for the modeling cohort was 0.829 (95% CI: 0.807-0.851), and the C-index for the validation cohort was 0.833 (95% CI: 0.803-0.862). Calibration plots of the nomogram indicated acceptable agreement between the predicted 3-, 5-year survival rates and the actual observations in the modeling and validation groups.

Conclusions: We have constructed and verified a nomogram containing clinical factors, which showed better prognostic judgment and predictive accuracy for DTC. This will enable clinicians and patients to easily personalize and quantify the probability of DTC during the postoperative period.

Background

Thyroid cancer is the most prevalent endocrine malignancy, and its incidence has increased considerably over the past 20 years [1, 2]. It can be divided into differentiated thyroid carcinoma (DTC) and anaplastic carcinoma (ATC) [3]. Differentiated thyroid cancer is the most common type of thyroid cancer. Among them, papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) have an excellent prognosis with a long-term survival rate of more than 90% [4]. Although it is generally considered to have a good prognosis, its prognosis is related to the presence of certain clinicopathological features.

PTC constitutes 90% of thyroid cancers, and it will become the top five most common malignant tumors in the United States by 2030 [5]. The incidence of thyroid cancer is increasing, but its mortality rate is still very low, which may be related to the development of medical diagnosis technology. The recurrence rate of PTC within 5 years after operation was about 77%, and patients with recurrent PTC will receive additional surgical treatment, and it is likely to be accompanied by surgical laryngeal nerve injury [4]. The mechanism of this high recurrence rate is still unclear [6]. It is speculated that BRAFV600E, RAS, and TERT mutations are related to this phenomenon and need to be further determined.

Among all well-differentiated thyroid cancers, follicular thyroid cancer accounts for approximately 10%-15% [7]. Follicular adenoma is more common than FTC, and the incidence rate reported by postoperative analysis has increased by approximately 5-fold [8]. Compared with the very little spread of lymph nodes in PTC, lymphatic spread in FTC is also possible, so follicular thyroid cancer is generally considered to be more aggressive than PTC because FTC patients usually present with a more serious disease. However, when age and stage are matched, the prognosis of these two cancer types is similar, although FTC-related causes have a slightly higher mortality rate compared to PTC [4, 7].

The nomogram is used as a reliable scale tool to quantify risk. It integrates and illustrates important factors for accurate and discriminatory prediction of prognosis. Numerous staging systems have been available for estimating prognosis in oncology and medicine and the AJCC TNM staging system remains the gold standard for prognostication in oncology [9]. However, the AJCC TNM system has several disadvantages. First, it is developed for a patient population, but has little effect on the prognosis of individual patients. Second, The AJCC TNM system does not include variables that control prognosis, such as genetic differences, tumor mitosis rate, or histology, all of which have a huge impact on tumor prognosis. Overcoming the limitations of TNM staging, the nomogram has become a simpler and more complex tool with advantages of accurate predictability, accessibility, and strong robustness [10, 11]. However, so far, the nomogram has not yet been applied to patients with DTC. Thus, we constructed a comprehensive prognostic nomogram combining the AJCC staging system and examined its performance in patients diagnosed with DTC.

Methods

Patient selection from SEER

Patients with a diagnosis of papillary or follicular thyroid carcinoma from 1975 to 2016 were retrieved from the SEER using permission number 14641-Nov2019 without informed patient consent. This study did not require the ethics approval for all data present here were selected from the SEER. We used ICD to verify papillary or follicular thyroid carcinoma and histological codes are 8050, 8260, 8330, 8331, 8332, 8335, 8340, 8341, 8342, 8343, and 8344. The inclusion criteria were as follows: (I) complete survival time and follow-up period; (II) with surgery performed; (III) with complete clinical factors, including age, race, sex, grade, AJCC TNM stage (7th); (IV) with complete tumor-node-metastasis (TNM) stage.

There were 17,659 patients identified as the original DTC set from 2010 to 2015. Then, all patients were randomly classified into a modeling cohort ($n = 12,363$, 70%) to develop a prognostic nomogram and a validation cohort ($n = 5,296$, 30%) to evaluate the developed nomogram.

Clinical Variables of Study Population

Clinicopathological features included age, race, sex, grade, AJCC TNM stage (7th), survival related information. X-Tile software was utilized to group the age category by the optimal cut-off value [12]

Statistical Analysis

Survival analysis was performed by the Kaplan-Meier analysis and log-rank test and comparisons of categorical variables was conducted by the χ^2 test. Univariate and multivariate Cox regression were conducted to evaluate and further confirm the significant variables for the generation of the nomogram. For model validation, C-index was developed to assess the nomogram between performance and predicted results. The Calibration plots were generated to evaluate the consistency between the predicted 3-, 5-year survival rates and the actual observations in the modeling and validation groups. All statistical analyses were performed by Excel software (Microsoft Corporation, California) and R software, version 4.0.2 (R Foundation, Vienna, Austria). $P < 0.05$ was considered statistically significant.

Results

Patient selection from SEER

This study included surgical patients with DTC derived from the SEER from 2010 to 2015. A total of 17,659 were involved in our study, of which 12,363 were randomly divided to the modeling cohort while 5,296 cases were placed into the validation cohort in a ratio of 7: 3 (Fig. 1). Of the enrolled patients, 13,317 were female (75.4%), and 14,223 (80.5%) were White. Based on the optimal cutoff value in age (age ≤ 54 , 55–68, and age ≥ 69), 4767 (27.0%) were between 55–68 years old. Besides, the majority of the grade is I (81.4%) while 57.5% were in the T1 stage, 75.4% were in the N0 stage and 98.5% were in the M0 stage. For the modeling and validation cohort, the median follow-up period was 43.3 (range, 0–83 months) months and 43.0 (range, 0–83 months) months, respectively. The clinicopathological features of patients enrolled in the study are summarized in Table 1.

Table 1
Clinic-pathologic characteristics of patients in the modeling and validation cohorts

Variables	All patients, n (%)	Modeling Cohort, n (%)	Validation Cohort, n (%)	P
Total	17,659 (100.0)	12,363 (70.0)	5,296 (30.0)	
Age				0.25
≤ 54	10,935 (61.9)	7,608 (61.5)	3,327 (62.8)	
55–68	4,767 (27.0)	3,378 (27.3)	1,389 (26.2)	
≥ 69	1,957 (11.1)	1,377 (11.1)	580 (11.0)	
Race				0.71
White	14,223 (80.5)	9,941 (80.4)	4,282 (80.9)	
Black	1,352 (7.7)	947 (7.7)	405 (7.6)	
Other*	2,084 (11.8)	1,475 (11.9)	609 (11.5)	
Sex				0.22
Male	4,342 (24.6)	3,008 (24.3)	1,334 (25.2)	
Female	13,317 (75.4)	9,355 (75.7)	3,962 (74.8)	
Grade				0.56
I	14,375 (81.4)	10,069 (81.4)	4,306 (81.3)	
II	2,604 (14.7)	1,812 (14.7)	792 (14.9)	
III	539 (3.1)	376 (3.0)	163 (3.1)	
IV	141 (0.8)	106 (0.9)	35 (0.7)	
AJCC T stage(7th)				0.87
T1	10,147 (57.5)	7,111 (57.5)	3,036 (57.3)	
T2	3,028 (17.1)	2,128 (17.2)	900 (17.0)	
T3	3,810 (21.6)	2,648 (21.4)	1,162 (21.9)	
T4	674 (3.8)	476 (3.9)	198 (3.7)	
AJCC N stage(7th)				0.20
N0	13,319 (75.4)	9,358 (75.7)	3,961 (74.8)	
N1	4,340 (24.6)	3,005 (24.3)	1,335 (25.2)	

*, American Indian & AK Native & Asian & Pacific Islander; Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated or anaplastic.

Variables	All patients, n (%)	Modeling Cohort, n (%)	Validation Cohort, n (%)	P
AJCC M stage(7th)				0.28
M0	17,399 (98.5)	12,173 (98.5)	5,226 (98.7)	
M1	260 (1.5)	190 (1.5)	70 (1.3)	
*, American Indian & AK Native & Asian & Pacific Islander; Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated or anaplastic.				

Independent prognostic factors in the modeling cohort

Clinic-pathologic characteristics, including age, race, sex, grade, AJCC TNM stage, survival time, and vital status, were obtained from the training set. Age, race, sex, grade, AJCC T stage, AJCC N stage, and AJCC M stage were significantly identified in the modeling cohort ($P < 0.05$, Table 2). Multivariate analysis showed the following important risk factors for survival: age 55–68 (HR = 3.197, $P < 0.001$ vs age ≤ 54), age ≥ 69 (HR = 8.522, $P < 0.001$ vs age ≤ 54), male (HR = 1.269, $P = 0.012$ vs female), grade III (HR = 3.120, $P < 0.001$ vs grade), grade IV (HR = 6.593, $P < 0.001$ vs grade I), AJCC stage T4 (HR = 2.387, $P < 0.001$ vs AJCC stage T1), AJCC stage N1 (HR = 1.337, $P = 0.006$ vs AJCC stage N0), and AJCC stage M1 (HR = 3.475, $P < 0.001$ vs AJCC stage M0). Multivariate analysis revealed that these 7 variables are significantly related to OS, showing as independent predictive factors of survival ($P < 0.05$; Table 2).

Table 2
Univariate and multivariate analysis of OS in the modeling (n = 12,363)

Variables	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	P value
Age	<0.001		
≤54		Reference	
55–68		3.197 (2.507–4.076)	<0.001
≥69		8.522 (6.689–10.858)	<0.001
Race	0.008		
Black		Reference	
White		0.491 (0.370–0.651)	<0.001
Other		0.558 (0.384–0.811)	0.002
Sex	<0.001		
Female		Reference	
Male		1.269 (1.054–1.528)	0.012
Grade	<0.001		
I		Reference	
II		1.142 (0.886–1.472)	0.305
III		3.120 (2.338–4.163)	<0.001
IV		6.593 (4.510–9.637)	<0.001
AJCC T stage(7th)	<0.001		
T1		Reference	
T2		1.038 (0.773–1.394)	0.804
T3		1.162 (0.910–1.484)	0.229
T4		2.387 (1.717–3.318)	<0.001
AJCC N stage(7th)	<0.001		
N0		Reference	
N1		1.337 (1.085–1.649)	0.006
AJCC M stage(7th)	<0.001		
HR: hazard ratio; CI: confidence interval.			

Variables	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	P value
M0		Reference	
M1		3.475 (2.629–4.595)	<0.001
HR: hazard ratio; CI: confidence interval.			

Construction of a prognostic nomogram

Based on the 7 Clinicopathological features, we developed a prognostic nomogram to predict the 3- and 5-year OS (Fig. 2). The nomogram shows that age is most closely related to prognosis, followed by the grade, AJCC M stage, AJCC T stage, race, AJCC N stage, and sex. We can simply and intuitively calculate the survival probability of a single patient through the cumulative score of each selected variable (Table 3).

Table 3
Detailed scores for all variables in
nomogram

Variables	Nomogram Score
Age	
≤54	0
55–68	54
≥69	100
Race	
Black	33
White	0
Other	6
Sex	
Female	0
Male	11
Grade	
I	0
II	6
III	53
IV	88
AJCC T stage(7th)	
T1	0
T2	2
T3	7
T4	41
AJCC N stage(7th)	
N0	0
N1	14
AJCC M stage(7th)	
M0	0

Variables	Nomogram Score
M1	58

Validation of a prognostic nomogram

The OS nomogram was validated both internally (model cohort) and externally (validation cohort). For the model validation, the C-index of the OS nomogram was 0.829 (95% CI: 0.807–0.851), and the C-index of the external validation was 0.833 (95% CI: 0.803–0.862). Calibration plots of the nomogram close to the dotted line showed the good consistency between the predicted 3-, 5-year survival rates and the actual observations in the modeling and validation groups (Fig. 3).

Discussion

The incidence rate of thyroid cancer has been rising rapidly all over the world in recent decades [3]. Overall, the prognosis of DTC patients is excellent. However, there are also a small number of patients who experience a more aggressive disease, which is often associated with certain poor prognostic factors. Regardless of the treatment provided, only 5% of DTC patients may die. Approximately 15% of patients may benefit from more aggressive tumor resection, supplemented with radioactive iodine therapy, and external beam radiation therapy [13]. Therefore, early identification of these patients is essential to guide treatment decisions.

A nomogram is a graphical tool that is designed to approximate complicated calculations quickly and without a computer or calculator. And it has been applied to most types of cancer [14–18]. We performed the data analysis from 17,659 patients with DTC from the SEER to establish a comprehensive prognostic nomogram and examined its prognostic value with the identified clinical factors in patients with DTC.

Our study has several limitations. We conducted patient selection from the SEER, which makes this a retrospective research with unavoidable inherent biases. There is a selection bias in selecting and excluding patients. Besides, many factors were not included, such as BRAF600E, RAS, and TRER mutation. Because we enrolled only DTC patients, our results cannot be applied to other thyroid cancer types, such as medullary, or anaplastic thyroid carcinoma. Furthermore, we excluded the patients who did not undergo the operation in the present study.

We recommend that clinicians use the nomogram presented in our study when making treatment decisions. This study has several strengths. First, our nomogram was developed based on a large group of DTC patients, which was a population-based cancer database. The population-based design, adequate sample size, and long-term follow-up enhanced the strength of our study. Furthermore, to the best of our knowledge, this is the first study to present a multi-factor survival model of DTC with a nomogram. Second, our nomogram displayed a good discrimination ability verified by both internal and external

validations, showing good performance. Third, our nomogram model contains risk factors easily found from medical records with the advantages of clinical applicability and ease of use.

Conclusions

In conclusion, we generated and validated a high nomogram for the prediction of survival for individual patients with DTC using 7 clinicopathological features based on a large, population-based cohort. This is conducive to individualized treatment and medical decision-making.

Abbreviations

CL: Confidence interval; C-index: Harrell's concordance index; HR: Hazard ratio; DTC: Differentiated thyroid carcinoma; FTC: Papillary thyroid carcinoma; PTC: Follicular thyroid carcinoma; OS: Overall survival; SEER: Surveillance, Epidemiology, and End Results. ICD: International Classification of Diseases.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed for this study can be found in the SEER (<https://seer.cancer.gov/>).

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Not applicable.

Author' Contributions

ZZ conceived and designed the study. GM performed the data collection, bioinformatics analysis, and wrote the initial manuscript. SL analyzed the data and generated the figures and tables. ZZ conceptualized and develop an outline for the manuscript and revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Flowchart of the DTC patients with modeling and validation cohorts.

Figure 2

Nomogram predicting 3-year, 5-year survival.

Figure 3

(A) 3- and (B) 5-year nomogram calibration plots of modeling cohort OS. (C) 3- and (D) 5-year nomogram calibration plots of validation cohort OS