



# Development and validation of a prognostic nomogram for Hürthle cell thyroid carcinoma: a SEER-based study

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**Background:** Hürthle cell carcinoma is a rare subtype of thyroid cancer, and its clinical behavior and biological characteristics remain unclear. This study aimed to establish nomogram models for the prognostic evaluation of Hürthle cell thyroid carcinoma (HCTC) in terms of both cancer-specific survival (CSS) and overall survival (OS).

**Methods:** Data for a total of 3,264 patients with HCTC (2004 to 2018) were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Univariate and multivariate Cox regression analysis was performed to identify significant predictors of prognosis and develop a prognostic nomogram. The performance of the model was assessed based on the area under the receiver operating characteristic curve (AUC), concordance index (c-index), and calibration curves.

**Results:** Multivariate Cox regression analysis showed that age, sex, summary stage, tumor size, N stage, M stage, and treatment with thyroidectomy were independent predictors of OS. Moreover, age, summary stage, tumor size, N stage, M stage, AJCC stage, and treatment with thyroidectomy were significantly correlated with CSS. The c-index of the OS and CSS nomograms developed based on these factors was 0.822 (95% CI: 0.803–0.841) and 0.893 (95% CI: 0.866–0.920), respectively. The AUC was 0.888, 0.841, and 0.834 for 1-, 3-, and 5-year OS and 0.970, 0.949, and 0.933 for 1-, 3-, and 5-year CSS, respectively. The calibration curves showed good agreement between observed and predicted values. Moreover, decision curve analysis revealed that the nomogram had a better clinical utility than individual clinicopathological markers.

**Conclusions:** A prognostic nomogram that allows the individualized assessment of OS and CSS in HCTC was developed. This nomogram could be used to guide treatment decisions in patients with HCTC.

**Keywords:** Hürthle cell carcinoma; nomogram; overall survival (OS); cancer-specific survival (CSS); Surveillance, Epidemiology, and End Results database (SEER database)

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## Introduction

Thyroid cancer is the most common endocrine malignancy. This tumor originates from the thyroid follicular epithelium or parafollicular epithelial cells. The latest statistics show

that the incidence of thyroid cancer has rapidly increased worldwide in the past few decades, moreover, this malignancy has also shown an obvious sex preponderance (1-5). Hürthle cell thyroid carcinoma (HCTC), a special

type of thyroid tumor, accounts for approximately 3–4% of all thyroid cancer cases. Owing to its unique biological behavior and genetic characteristics (6), HCTC has been classified separately from follicular thyroid cancer (FTC) in the latest version of the World Health Organization (WHO) Classification of Tumors (7).

Compared with other differentiated thyroid cancers, HCTC typically shows more aggressive behavior, including higher rates of lymph node and distant metastases (8,9). The clinical presentation of HCTC is similar to that of FTC, and most patients present with a single painless thyroid nodule, hoarseness, and dysphagia. The preoperative diagnosis of HCTC through radiology or fine needle aspiration (FNA) is challenging. Currently, the histological evaluation of surgical specimens is the best approach for HCTC diagnosis (10). As for other differentiated thyroid cancers, surgical resection is the mainstay for HCTC treatment. Typically, diagnostic lobectomy is the first choice, and decisions on further surgical resection are taken based on the histological diagnosis (11). The efficacy of radioactive iodine (RAI) therapy for HCTC is currently unclear. Jillard *et al.* (12) suggested that RAI improves survival in HCTC patients. However, other studies have shown that the uptake of radioactive iodine by HCTC tumors is poor, and HCTC is not sensitive enough to show a good response to radiotherapy and chemotherapy (13,14). Therefore, a consensus on the optimal management of patients with HCTC is currently lacking. At present, the prognostic factors for HCTC remain to be fully elucidated (15,16). The early identification of high-risk HCTC patients is crucial for improving prognosis. Hence, it is necessary to obtain accurate information on survival-related factors and to develop a prognostic model.

The Surveillance, Epidemiology, and End Results (SEER) database is the authoritative cancer statistics database in the United States and has a large sample size. Research based on the SEER database has a high clinical reference value. In the present study, data from the SEER database were used to identify predictors of overall survival (OS) and cancer-specific survival (CSS) in patients with HCTC using univariate and multivariate Cox regression analyses. The study aimed to establish nomogram models for the prognostic evaluation of HCTC in order to improve the clinical management of HCTC patients.

We present the following article in accordance with the TRIPOD reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gs-21-781/rc>).

## Methods

### Data selection

Data on patients with HCTC (Site recode ICD-O-3/WHO 2008 coded as Thyroid and AYA site recode 2020 Revision coded as Hürthle cell carcinoma) treated between 2004 and 2018 were obtained from the SEER database: Incidence - SEER Research Data, 18 Registries, Nov 2020 Sub (2000-2018). We focused on factors such as sex, year of diagnosis, race, laterality, diagnostic confirmation, Histological type, combined summary stage, surgery status, tumor size, cause of death, cancer-specific death, survival duration, vital status (study cutoff used), AJCC stage group, AJCC T stage, AJCC N stage, AJCC M stage, age at diagnosis, Grade (through 2017), metastasis at bone, metastasis at brain, metastasis at liver, and metastasis at lung. Only patients with histologically confirmed HCTC were included. Patients for whom detailed basic information such as race, combined summary stage, tumor size, surgery status, and AJCC stage were not known (n=443) were excluded from the analysis cohort (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

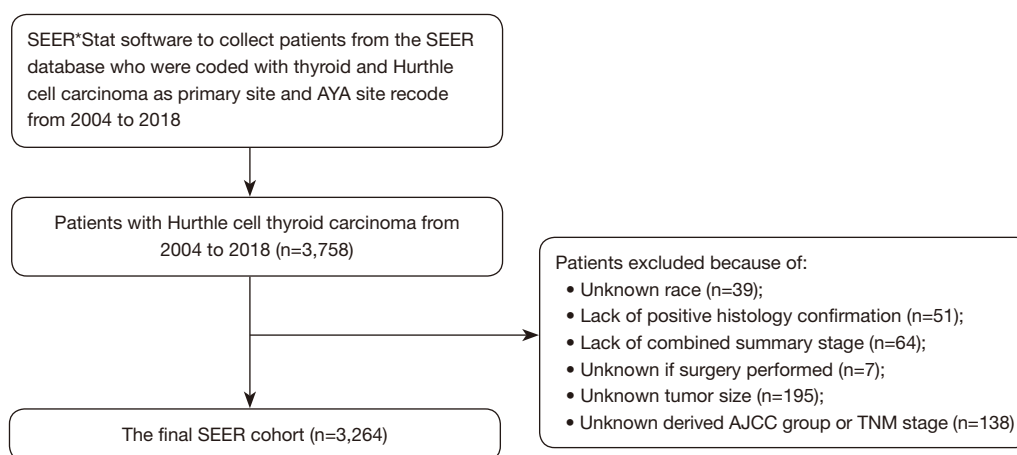
### Statistics analysis

Statistical analysis was performed using the R software (version 3.4.2) and SPSS 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as counts and percentages, whereas continuous variables were expressed as means and ranges. Univariate and multivariate Cox analysis was performed to identify significant predictors and develop a prognostic nomogram. The performance of the models was assessed based on the area under the receiver operating characteristic curve (AUC), concordance index (c-index), and calibration curves. A calibration plot (with bootstrapping) was used to examine the association between actual and predicted survival probabilities. The clinical usefulness of the nomogram was evaluated using decision curve analysis (DCA). All tests were two-sided, and  $P < 0.05$  was considered statistically significant.

## Results

### Demographic and clinical characteristics

Data on a total of 3,264 patients with HCTC (2004 to 2018) were extracted from the SEER database. Female patients



**Figure 1** Flowchart of data selection.

accounted for a majority of the study cohort (68.3%; male patients, 31.7%). The median age of the study cohort was 58 years. Most patients were 55 years old and above (58.6%), whereas patients below the age of 55 accounted for 41.4% of the cohort. Moreover, most patients were White (84.8% of all patients). Localized metastasis was the most common (2,749 patients, 84.2%), followed by regional (11.7%) and distant metastases (4.0%). Further, the median tumor size was 31.5 mm. With respect to tumor stage, 138 patients (4.2%) showed T4 stage disease, 184 (5.6%) showed N1 stage disease, and 90 (2.8%) showed M1 stage disease. Moreover, there were 220 patients (6.7%) with AJCC stage IV disease. Of these patients, 3,223 (98.7%) had undergone thyroidectomy, while 41 (1.3%) did not undergo surgery. The detailed clinical characteristics are shown in *Table 1*.

### Construction of nomogram

The univariate and multivariate Cox regression analyses were employed to identify the predictive factors of OS and CSS in HCTC patients. As shown in *Table 2*, the age at diagnosis, sex, race, summary stage, tumor size, T stage, N stage, M stage, AJCC stage, and treatment with thyroidectomy were all included in the analysis. The univariate Cox analysis indicated that age, sex, summary stage, tumor size, T stage, N stage, M stage, AJCC stage, and treatment with thyroidectomy were all predictive factors for both OS and CSS. However, multivariate Cox analysis showed that age, sex, summary stage, tumor size, N stage, M stage, and treatment with thyroidectomy were independent predictors of OS. In contrast, summary stage, tumor size, N stage, M stage, AJCC stage, and treatment

thyroidectomy were independent predictive factors for CSS. Therefore, Cox analysis findings indicated that HCTC patients who were older; had distant metastasis, larger tumors, and N1 and M1 stage disease; and did not undergo thyroidectomy had a poorer prognosis. Therefore, we constructed separate nomograms for OS and CSS (*Figure 2*) in order to predict the 1-, 3- and 5-year survival probability in HCTC patients.

### Validation of nomogram

To assess the discrimination value of the nomograms, we calculated c-indexes. The c-index of the OS and CSS nomogram was 0.822 (95% CI: 0.803–0.841) and 0.893 (95% CI: 0.866–0.920), respectively. Calibration curves showed a good consistency between the predicted and actual values of 1-, 3-, and 5-year OS and CSS in patients with HCTC (*Figure 3*). These findings were consistent with those of AUC analysis. The AUCs were 0.888, 0.841, and 0.834 for 1-, 3-, and 5-year OS and 0.970, 0.949, and 0.933 for 1-, 3-, and 5-year CSS, respectively (*Figure 4*). In addition, DCA indicated that the nomogram provided better clinical utility than individual clinical features (*Figure 5*). These results showed that the nomograms were accurate and reliable for the prediction of survival outcomes in HCTC.

### Discussion

HCTC is now independently classified and is considered separate from FTC (17). HCTC is more aggressive than FTC and is associated with a worse prognosis (18,19). HCTC patients also show a higher metastasis rate and

**Table 1** Characteristics of patients from SEER database

Variables	Total (N=3,264)
Sex	
Female	2,228 (68.3%)
Male	1,036 (31.7%)
Age (years)	
Mean (SD)	57.5 (15.5)
Median [min, max]	58.0 [11.0, 85.0]
Age group (years)	
<55	1,351 (41.4%)
≥55	1,913 (58.6%)
Race	
Black	273 (8.4%)
Other	223 (6.8%)
White	2,768 (84.8%)
Summary stage	
Distant	132 (4.0%)
Localized	2,749 (84.2%)
Regional	383 (11.7%)
Tumor size (mm)	
Mean (SD)	36.6 (23.2)
Median [min, max]	31.5 [0, 420]
T stage	
T1	821 (25.2%)
T2	1,164 (35.7%)
T3	1,141 (35.0%)
T4	138 (4.2%)
N stage	
N0	3,080 (94.4%)
N1	184 (5.6%)
M stage	
M0	3,174 (97.2%)
M1	90 (2.8%)

**Table 1** (continued)**Table 1** (continued)

Variables	Total (N=3,264)
AJCC stage	
I	1,328 (40.7%)
II	886 (27.1%)
III	830 (25.4%)
IV	220 (6.7%)
Thyroidectomy	
No	41 (1.3%)
Yes	3,223 (98.7%)

SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer.

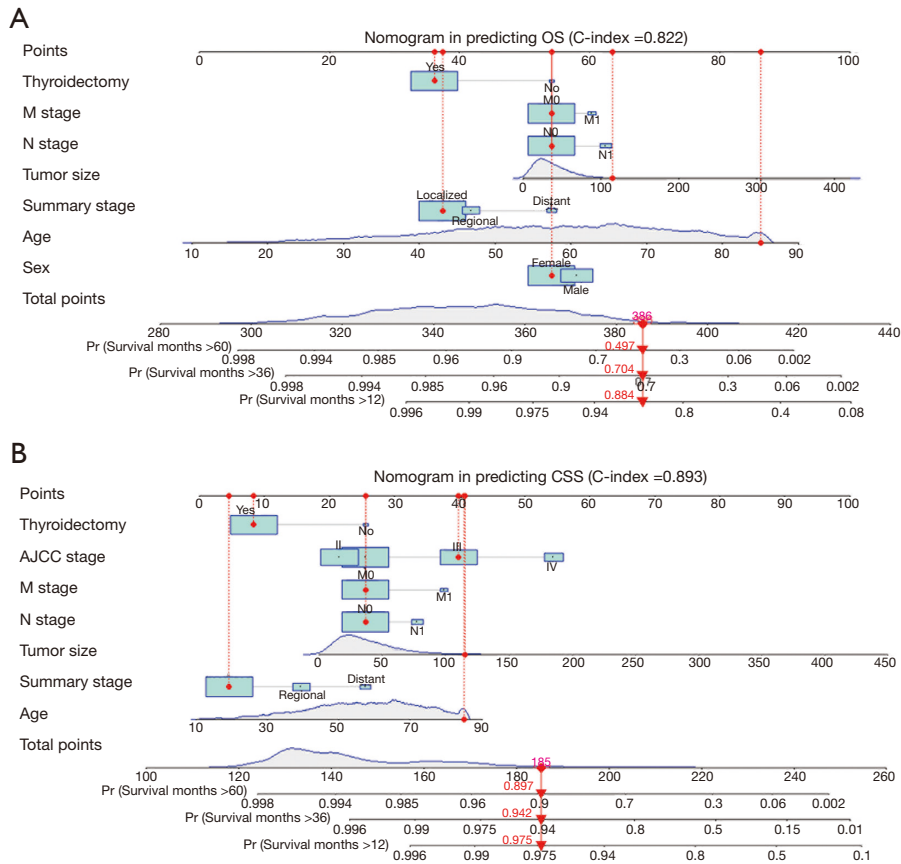
lower OS and disease-specific survival (20–22). HCTC is more common than other types of differentiated thyroid cancers among men (31.1% *vs.* 23.0%,  $P < 0.001$ ) and older patients (mean age, 57.6 years *vs.* 48.9 years,  $P < 0.001$ ) (8). Despite the prognostic difference between HCTC and FTC, HCTC cannot be considered a highly aggressive carcinoma. In the present study, a small proportion of HCTC patients were diagnosed at an advanced stage (T4 stage, 4.2%; N1 stage, 5.6%; and M1 stage, 2.8%), and most of them underwent surgery.

The present study showed that age, sex, treatment with thyroidectomy, summary stage, tumor size, N stage, and M stage are associated with the prognosis of HCTC. The link between older age and a worse survival has been proven by many studies (23). In a cohort of 89 HCTC patients from the United States, age >45 years was found to be correlated with reduced survival. However, age was not identified as an independent risk factor for poor survival in the multivariate analysis (24). By dividing HCTC patients into different age groups (<45 years, 45–64 years, and ≥65 years), one study (8) found that age was negatively correlated with disease-specific survival and was an independent prognostic factor in the last two groups. In the present study, age was identified as an independent risk factor, and the median age in the study cohort was 58 years. This suggested that most HCTC patients in the cohort would require aggressive

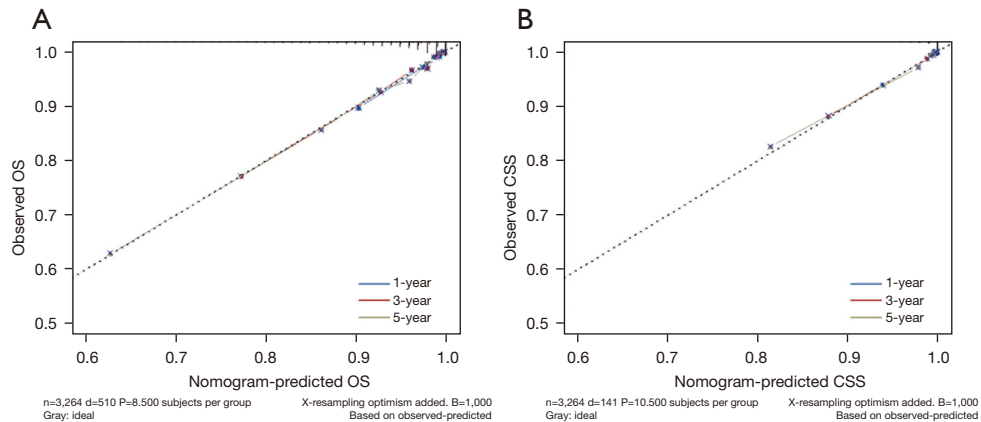
**Table 2** Univariate and multivariate Cox analysis of OS and CSS

Variables	OS				CSS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.09 (1.08, 1.10)	<0.001	1.08 (1.07, 1.09)	<0.001	1.07 (1.05, 1.08)	<0.001	1.04 (1.02, 1.05)	<0.001
Sex								
Female	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Male	1.86 (1.56, 2.21)	<0.001	1.27 (1.06, 1.53)	0.011	1.73 (1.24, 2.42)	0.001	0.86 (0.61, 1.23)	0.409
Race								
Black	1 (ref)				1 (ref)			
White	0.97 (0.71, 1.32)	0.822			1.69 (0.79, 3.62)	0.178		
Other	0.78 (0.48, 1.26)	0.305			2.17 (0.86, 5.52)	0.103		
Summary stage								
Distant	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Localized	0.11 (0.08, 0.14)	<0.001	0.46 (0.24, 0.85)	0.014	0.02 (0.01, 0.03)	<0.001	0.31 (0.13, 0.78)	0.012
Regional	0.24 (0.18, 0.32)	<0.001	0.62 (0.36, 1.08)	0.091	0.14 (0.09, 0.21)	<0.001	0.64 (0.31, 1.29)	0.207
Tumor size (mm)	1.01 (1.01, 1.01)	<0.001	1.01 (1.00, 1.01)	<0.001	1.01 (1.01, 1.01)	<0.001	1.01 (1.01, 1.02)	<0.001
T stage								
T1	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
T2	1.21 (0.93, 1.59)	0.162	0.82 (0.44, 1.54)	0.536	1.07 (0.48, 2.38)	0.872	0.87 (0.32, 2.37)	0.780
T3	2.13 (1.65, 2.75)	<0.001	1.25 (0.70, 2.24)	0.452	5.54 (2.85, 10.76)	<0.001	1.58 (0.63, 3.94)	0.325
T4	7.42 (5.41, 10.16)	<0.001	1.77 (0.95, 3.33)	0.074	38.97 (19.71, 77.06)	<0.001	1.96 (0.78, 4.96)	0.153
N stage								
N0	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
N1	3.45 (2.67, 4.48)	<0.001	1.71 (1.22, 2.39)	0.002	10.52 (7.37, 15.00)	<0.001	1.73 (1.12, 2.66)	0.013
M stage								
M0	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
M1	9.90 (7.50, 13.07)	<0.001	2.03 (1.19, 3.49)	0.009	34.36 (23.87, 49.46)	<0.001	2.80 (1.44, 5.47)	0.003
AJCC stage								
I	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
II	2.40 (1.83, 3.16)	<0.001	1.39 (0.73, 2.63)	0.313	1.39 (0.54, 3.60)	0.498	0.97 (0.29, 3.30)	0.965
III	3.51 (2.71, 4.55)	<0.001	0.76 (0.43, 1.34)	0.34	7.72 (3.76, 15.86)	<0.001	1.93 (0.73, 5.10)	0.183
IV	13.22 (9.99, 17.49)	<0.001	0.81 (0.41, 1.59)	0.535	82.40 (41.34, 164.27)	<0.001	4.74 (1.57, 14.32)	0.006
Thyroidectomy	0.10 (0.06, 0.16)	<0.001	0.29 (0.18, 0.49)	<0.001	0.06 (0.03, 0.10)	<0.001	0.30 (0.15, 0.60)	<0.001

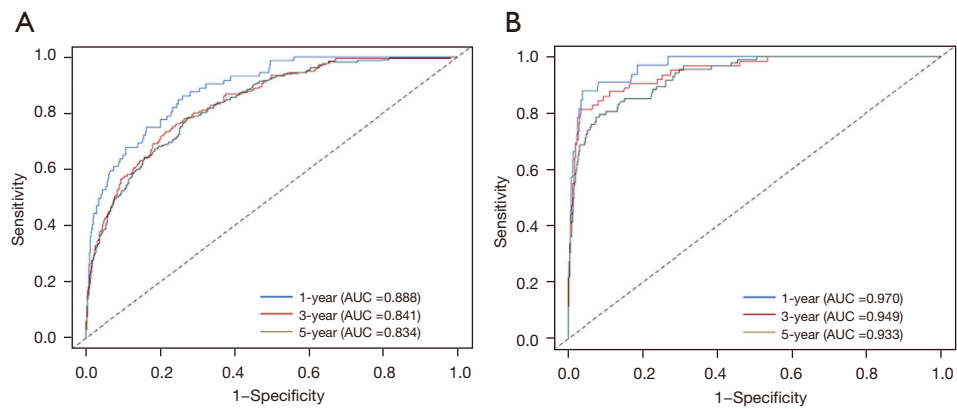
OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; AJCC, American Joint Committee on Cancer.



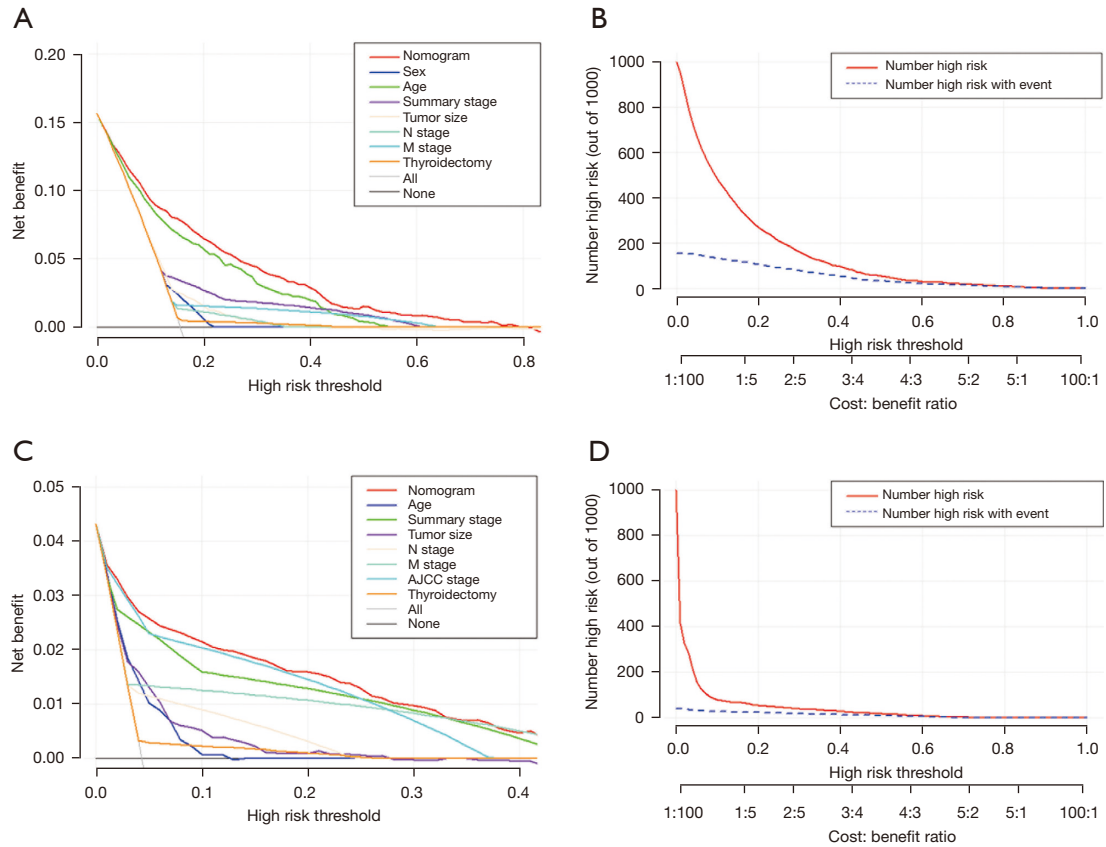
**Figure 2** The nomograms of 1-, 3- and 5-year OS (A) and CSS (B) in thyroid HCTC patients. OS, overall survival; CSS, cancer-specific survival; HCTC, Hürthle cell carcinoma.



**Figure 3** Calibration curves in predicting the 1-, 3- and 5-year OS (A) and CSS (B). The x-axis shows the predicted survival probability and the y-axis shows the actual survival probability. The 45-degree dotted line shows that the prediction agrees with actuality. OS, overall survival; CSS, cancer-specific survival.



**Figure 4** ROC curves and AUCs of 1-, 3- and 5-year OS (A) and CSS (B) were used to estimate the prognostic accuracy of the nomogram. ROC, receiver operator characteristic; AUC, area under the curve; OS, overall survival; CSS, cancer-specific survival.



**Figure 5** DCA of nomogram in predicting 1-, 3- and 5-year OS (A and B) and CSS (C and D). DCA, decision curve analysis; OS, overall survival; CSS, cancer-specific survival.

clinical management and surveillance.

Many studies show that male sex is predictive of worse outcomes in HCTC (16,25). In the present study, almost one-third of all patients were men. Male sex was an independent predictor of OS, but it did not influence CSS. Thyroidectomy is recommended for HCTC patients (15,26,27), and our multivariate analysis also indicated that thyroidectomy was the strongest protective factor in HCTC. It is widely accepted that tumor size can increase the risk of poor outcomes. Using multivariate analysis, a study (8) demonstrated that a tumor size  $\geq 4$  cm was associated with a higher disease specific mortality (HR =1.89, P=0.039). Another study (24) that used 4 cm as the cutoff indicated that a larger tumor size was associated with a worse outcome. The results of this study confirmed that tumor size was an independent predictor of both OS and CSS.

Nomograms are considered a graphical tool that can be used to calculate individual risk by integrating and quantifying prognostic factors (28). Accordingly, they are widely applied to assess indicators of cancer prognosis, including recurrence, metastasis, and OS (29-31). To our knowledge, this study is the first to construct an integrated prognostic nomogram for HCTC. In the study, all prognostic factors identified using multivariate Cox regression analysis were weighted and scored. The nomogram illustrated that age, tumor size, N stage, and M stage were the most significant predictors of prognosis, while sex showed a limited influence on outcomes. This implies that clinical characteristics of patients could be used to predict 1-, 3-, and 5-year OS and CSS without any expensive tests.

The accuracy and net benefits of the developed model were also assessed in the present study. The c-index, calibration curves, and time-dependent AUC analysis were used for this purpose. The c-index of the OS and CSS nomograms was 0.822 (95% CI: 0.803–0.841) and 0.893 (95% CI: 0.866–0.920), respectively, indicating its excellent value. Calibration plots demonstrated a great consistency between nomogram-predicted and actual survival probabilities, which confirmed the reliability of the nomograms. Moreover, the AUCs for 1-, 3-, and 5-year OS were 0.888, 0.841, and 0.834, respectively, and those for 1-, 3-, and 5-year CSS were 0.970, 0.949, and 0.933, respectively. Hence, near-perfect agreement was observed between predicted and actual outcomes. Additionally, the nomogram exhibited a better net benefit than individual clinical characteristics. These results showed that the nomogram possessed excellent discrimination ability and

accuracy.

Nevertheless, there were some limitations to this study. First, some significant clinical parameters were not included in the model. Widely invasive HCTC had quite different prognosis compared with minimally. Tumor multifocality can increase risk of recurrence. Additionally, treatments including hemithyroidectomy, total thyroidectomy and radioactive iodine were not acquired in this study, which might function as confounders. Second, given that the study was retrospective in nature, selection bias may have occurred. Finally, the lack of external validation cohorts could have led to over-fitting effects. Therefore, efforts should be made to perform more comprehensive and prospective studies in this field.

## Conclusions

The study demonstrated that age, sex, tumor size, summary stage, N stage, and M stage are independent prognostic factors for HCTC. Additionally, a novel predictive model was developed to predict the survival probability in patients with HCTC. This nomogram could be helpful for avoiding unnecessary tests and medical expenses and for identifying high-risk patients with HCTC. Therefore, the nomogram could allow improved decision-making in HCTC treatment.

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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-21-781/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gS-21-781/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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