Original Article

Analysis of the ideal cutoff age as a predictor of differentiated thyroid cancer using the Surveillance, Epidemiology, and End Results database

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Background: It has been discovered that the prognosis of patients with differentiated thyroid cancer (DTC) correlates with age at initial diagnosis. However, there are disagreements over the optimal cutoff age among the numerous staging and risk stratification criteria, which make it inconsistent to predict the clinical prognosis of specific DTC patients. This study aimed to determine the optimum cutoff age for diagnosis in relation to the clinical outcomes of DTC using data from the Surveillance, Epidemiology and End Results (SEER) database.

Methods: The best age cutoff value was determined by the X-tile software. The link between clinical characteristics and cancer-specific survival (CSS) was examined using univariate and multivariate Cox regression models. An additional application of the independent prognostic criteria, such as age stratifications, was applied to construct a nomogram model for predicting the chances of patient survival.

Results: The most accurate diagnosis cutoff age for DTC patients was suggested to be 67 years old. The multivariate analysis, using factors determined by univariate analysis, showed that age [>67 years, hazard rate (HR) =5.049, 95% confidence interval (CI): 4.509–5.653, P<0.001], sex (female, HR =0.651, 95% CI: 0.584–0.727, P<0.001), tumor size (>20 and ≤40 mm, HR =2.296, 95% CI: 1.983–2.658, P<0.001; >40 mm, HR =4.976, 95% CI: 4.304–5.752, P<0.001), lymphadenectomy (HR =1.337, 95% CI: 1.186–1.506, P<0.001), distant metastasis (HR =12.166, 95% CI: 10.749–13.769, P<0.001) and surgical treatment (HR =0.173, 95% CI: 0.144–0.210, P<0.001) were independent factors for CSS. Patients in the high-risk group had worse survival rates, and the C-index for the CSS prediction model with age (cutoff of 67) and other independent clinicopathological variables was 0.906.

Conclusions: Accordingly, the optimal cutoff age for predicting death from DTC specifically is 67 years old at the time of the initial diagnosis. It might be a more suitable factor when used in risk stratification for patients with DTC.

Keywords: Differentiated thyroid cancer (DTC); age; Surveillance, Epidemiology and End Results (SEER); cancer-specific survival (CSS); nomogram

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Introduction

For several decades, the prevalence of thyroid cancer has been rising dramatically (1). Differentiated thyroid cancer (DTC) is made up of the two separate and most common types [papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC)] according to histological categorization, and its incidence accounts for 85–90% of thyroid cancers (2). However, mortality can be significantly higher in patients with aggressive phenotypes (3). Therefore, reliable clinical staging evaluation based on clinical characteristics is crucial for DTC patient prognosis prediction and treatment decision.

The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging method is the current gold standard for DTC prognosis (4,5). According to the AJCC-TNM staging system, age is an independent prognostic predictor for DTC patients (6). In the second edition of the AJCC-TNM staging system, 45 years was regard as the cutoff point value for the initial diagnostic age. While in the eighth edition, a significant change has been made by raising the age cutoff from 45 to 55 years (4,5). Previous researches indicated a superior accuracy of the 55-cutoff age in predicting the disease specific survival disease-specific survival (DSS) rate in patients with DTC, which led to the decision to raise the age cutoff in the TNM system (7-9). A meta-analysis that included six studies and involved 10,850 subjects showed that the AJCC-8 revision improved stratification of DSS among clinical stages of disease compared with the AJCC-7. However, the clinical characteristics of each study population, including DTC subtype, extent of disease, and treatment, varied significantly among the included reports, and differences between studies were seen with respect to the proportion of patients migrating between stages and DSS estimates (10). Therefore, the predictive age needs to be explored and validated in broader populations.

Consequently, this study aimed to establish an ideal prognostic threshold of age using information from the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute of the United States, and construct a competitive nomogram to forecast the incidence of death arising from DTC. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-247/rc).

Highlight box

Key findings

- This study aimed to determine the optimum cutoff age for diagnosis in relation to the clinical outcomes of differentiated thyroid cancer (DTC) using data from the Surveillance, Epidemiology and End Results (SEER) database. The optimal cutoff age for predicting death from thyroid cancer specifically was shown to be 67 years old at the time of the initial diagnosis. It might be a more suitable factor when used in risk stratification for patients with DTC.

What is known and what is new?

- It has been discovered that the prognosis of patients with DTC correlates with age at initial diagnosis.
- A total of 99,449 DTC patients from the SEER cancer database were examined in the current study. With the lowest P values using log-rank 2 statistics, the ideal cutoff age at diagnosis, which we determined to be 67 years, was the most significant predictive factor of DTC-attributable death based on the X-tile program.

What is the implication, and what should change now?

- The optimal cutoff age for predicting death from thyroid cancer specifically is 67 years old at the time of the initial diagnosis. It might be a more suitable factor when used in risk stratification for patients with DTC. Our work serves as a timely reminder that young and old cancer patients have very varied tumor molecular features and should be treated as having distinct diseases. However, further research is required to determine how to divide thyroid cancer into adolescent, adult, and geriatric types.

Methods

SEER database and study cohort

The SEER database, a population-based program that compiles data from 18 cancer registries in the United States, was used to gather data on the incidence and survival of thyroid cancer (11). Version 8.3.9 of the SEER*Stat program (www.seer.cancer.gov/seerstat) was used to identify 210,045 patients with single primary thyroid cancer (C73.9). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Only the patients whose histology examination revealed DTC were included. The PTC (8050, 8260, 8340–8344, 8350, and 8450–8460) and FTC (8290 and 8330–8335) histological types were classified using the International Classification of Diseases for Oncology, the third edition (ICD-O-3) system. The patients with lacking clinical features and outcomes were excluded (12). *Figure 1* shows the specifics of the evaluation procedure and data on the number of patients included and excluded.

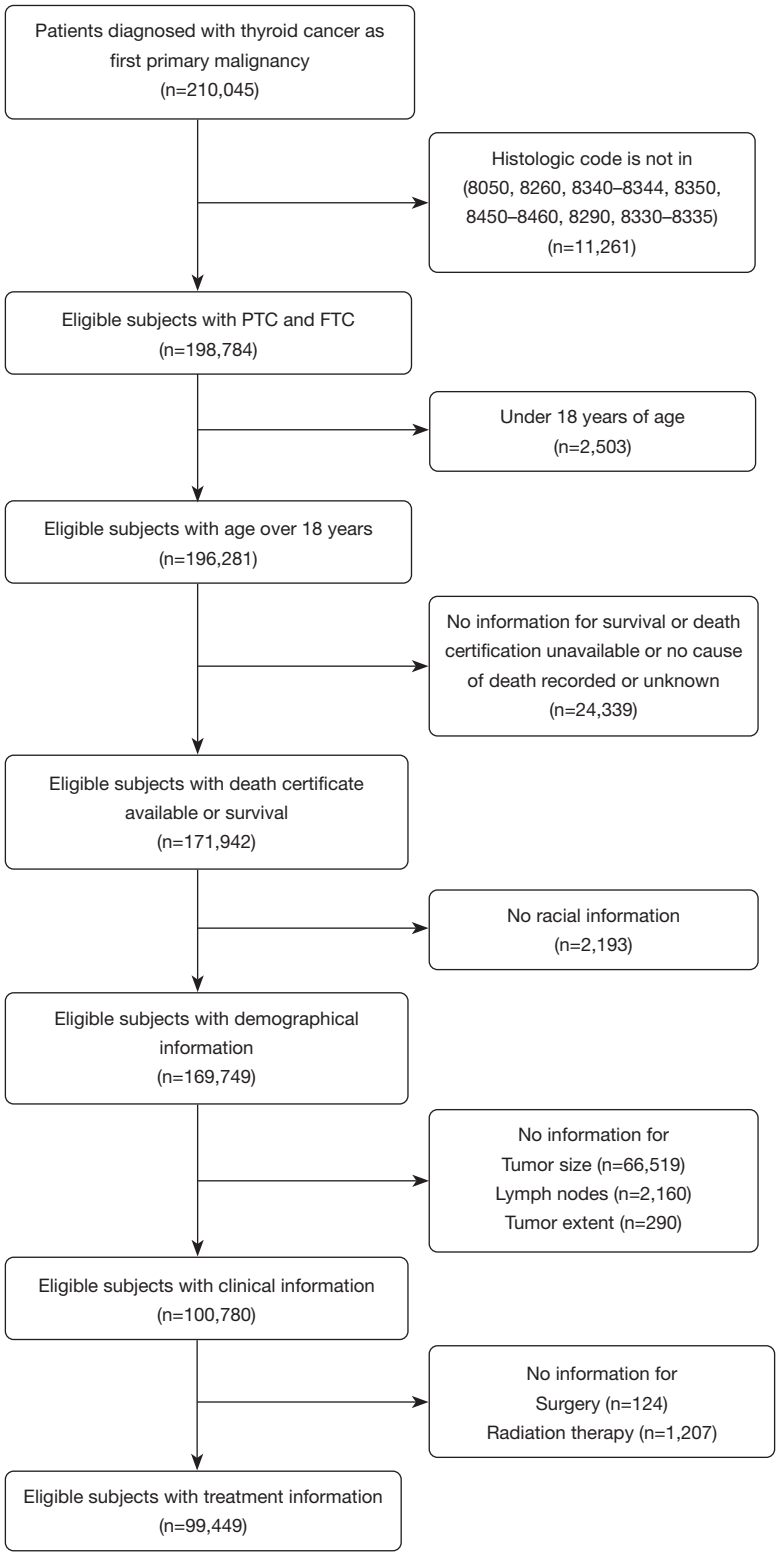

Figure 1 Data collection flowchart. PTC, papillary thyroid cancer; FTC, follicular thyroid cancer.

Clinicopathological variable assessment

The demographic characteristics (age at diagnosis, sex, and race), tumor characteristics (size, extent of tumor, lymphadenectomy), treatment specifics [surgeries, radiation therapy (including beam radiation, combination of beam with implants or isotopes, radiation with method or source not specified, radioactive implants, radioisotopes)], and follow-up data (survival time, vital status, cause-specific death, and other cause of death) were all retrieved from the SEER database. The treatment specifics collected in the SEER database refer to the patients' initial treatment. Whites, blacks, and others (including Asian or Pacific Islanders, American Indians, and Alaska Natives) were the three categories for race. Cancer-specific survival (CSS) was the endpoint.

Statistical analysis

For variables that were categorical, Chi-squared analysis was performed. The Kaplan-Meier (KM) curve represented the survival rate, and the log-rank test was used to analyze survival disparities. Using the X-tile program (http://www.tissuearray.org/rimmlab/), the cutoff points for age at diagnosis were investigated. This program determined the cutoff values with the smallest P values from log-rank χ^2 statistics for the variable in terms of CSS. The relationship between covariables and cancer mortality was evaluated using both univariate and multivariate Cox regression. Based on the outcomes of the multivariate analysis, a predictive nomogram was created using the rms package in R version 2.14.1 (http://www.r-project.org/). The concordance index (C-index) and calibration, which compare nomogram-predicted and observed KM estimations of overall survival probabilities, were used to measure and evaluate the nomogram's predictive accuracy (13). Regression analysis was used to obtain the C-index and calibration curve. P values were all two-sided. Statistics were judged significant at P<0.05.

Results

Baseline characteristics of the entire cohort

In this retrospective study, a total of 99,449 DTC patients were included, with 22,110 (22.2%) men and 77,339 (77.8%) women and a median age of 48.0 (range, 18–105) years. White patients made up the majority (82.0%), followed by other patients (11.2%) and black patients (6.8%). A total of 66.9% of these patients had tumors that were under 20 mm in size, whereas 9.7% of patients had tumors that were beyond 40 mm in size. *Table 1* lists the specific clinicopathological characteristics of these patients. A total of 99.0% of patients underwent surgery, and lymph node dissection was required in 50.0% of cases in the cohort (n=49,748). A total of 4,853 patients (4.88%) died during the study period, and 1,386 (28.56%) of the deaths were related to DTC.

Baseline traits of groups based on the ideal cutoff age

Based on the ideal criterion selected by the X-tile software, all patients were separated into two subgroups: ≤67 years (n=88,796, 89.29%) and >67 years (n=10,653, 10.71%) (*Figure 2*, *Table 2*). In comparison to the group of patients aged ≤67 years, the percentage of patients in the >67 years group by sex (male), tumor diameter greater than 40 mm, and distant metastasis was considerably higher. The incidence of laterality, however, was comparable across age-based groupings. Younger patients had surgery more frequently than the elderly (99.2% *vs.* 96.8%, P<0.001) when compared to those who had surgery. Furthermore, 51.5% of patients aged ≤67 years had lymph node dissection compared to 37.7% of patients aged >67 years (P<0.001). A total of 4,853 (4.9%) documented deaths were taken into account in the analysis, of which 2,495 (2.8%) affected people ≤67 years and 2,358 (22.1%) affected those above the age of 67 years. Patients who were >67 years had 10- and 15-year overall survival rates of 68.7% and 52.2%, respectively, as opposed to patients who were ≤67 years, who had 96.1% and 93.3%, respectively (P<0.001). Additionally, we can confirm that DTC was directly responsible for 1,386 deaths in total. In the two groups, DTC-related fatalities were 0.8% and 6.5%, respectively. The 10-year thyroid CSS rates were 98.9% and 90.9% in patients aged ≤67 years and >67 years, respectively (P<0.001).

Analysis of subgroups and the overall effect of age on survival in DTC

We used univariate and multivariate Cox regression analyses to determine the strength of the relationship between mortality and increasing age in comparison to known DTC risk factors (*Table 3*). Age >67 years, sex (male), large tumor size (>20 mm), distant metastasis, no surgery, and treatments including lymph node dissection and radiation therapy were found to be significant risk factors for poor

Table 1 The SEER database contains the clinicopathological features of 99,449 DTC patients

Characteristics	Number (%) or median [range]
Age at diagnosis (years)	48.0 [18–105]
Gender	
Male	22,110 (22.2)
Female	77,339 (77.8)
Race	
White	81,526 (82.0)
Black	6,736 (6.8)
Others	11,187 (11.2)
Tumor size, mm	
≤20	66,517 (66.9)
>20 and ≤40	23,288 (23.4)
>40	9,644 (9.7)
Lymphadenectomy	
No	49,701 (50.0)
Yes	49,748 (50.0)
Distant metastasis	
No	96,911 (97.4)
Yes	2,538 (2.6)
Laterality	
Unilateral	98,944 (99.5)
Bilateral	505 (0.5)
Surgical treatment	
No	1,017 (1.0)
Yes	98,432 (99.0)
Radiation therapy	
No	49,747 (50.0)
Yes	49,702 (50.0)
Cause of death	
Death resulting from thyroid cancer	1,386 (1.4)
Death resulting from other cause	3,467 (3.5)

SEER, Surveillance, Epidemiology and End Results; DTC, differentiated thyroid cancer.

clinical prognosis of DTC cases, according to the results of the univariate Cox proportional hazard regression models. We conducted subgroup analyses for the effects of age on survival in DTC stratified by these important characteristics to evaluate the influence of age itself by limiting interference from conventional risk factors. KM curves using proportional hazards regression models showed that older age (>67 years) was connected to lower survival in each factor subgroup (Figure S1). Multivariate analysis (*Table 3*) revealed that older age [>67 years, hazard rate (HR) =5.049, 95% confidence interval (CI): 4.509–5.653, P<0.001], tumor size (>20 and ≤40 mm, HR =2.296, 95% CI: 1.983–2.658, P<0.001; >40 mm, HR =4.976, 95% CI: 4.304–5.752, P<0.001), lymphadenectomy (HR =1.337, 95% CI: 1.186–1.506, P<0.001), and distant metastasis (HR =12.166, 95% CI: 10.749–13.769, P<0.001) were all independently associated with worse CSS, while female sex (HR =0.651, 95% CI: 0.584–0.727, P<0.001), and surgical treatment (HR =0.173, 95% CI: 0.144–0.210, P<0.001) were associated with better CSS.

CSS prognostic nomogram

According to our knowledge, the TNM classification is one of the most widely used methods for cancer staging, and it uses an age cutoff of 45 or 55 years to divide patients with DTC into groups with a high or low chance of dying from cancer. Age (three categories, with cutoffs of 67 years or binary classification with the traditional cutoff of 45/55 years), sex, and clinicopathological features were chosen as the final model's independent components with the highest predictive accuracy for the risk of cancer-specific mortality (*Figure 3*, Figures S2,S3). For example, a patient with age >67 years (1:64 points), male (0:18 points), tumor size >20 and ≤40 mm (1:32 points), underwent lymphadenectomy (1:12 points), without metastasis (0:0 points), without surgery (0:70 points). Thus, the total score is 196 points; the patient's 5-year survival rate is about 85%, and the 10-year survival rate is about 55%. With cutoff ages of 67, 45, and 55 years, the C-index for CSS prediction was 0.906, 0.907, and 0.915, respectively. The calibration plot for the likelihood of survival at 5- or 10-year following surgery revealed the best possible concordance between the nomogram's forecast and the actual observations

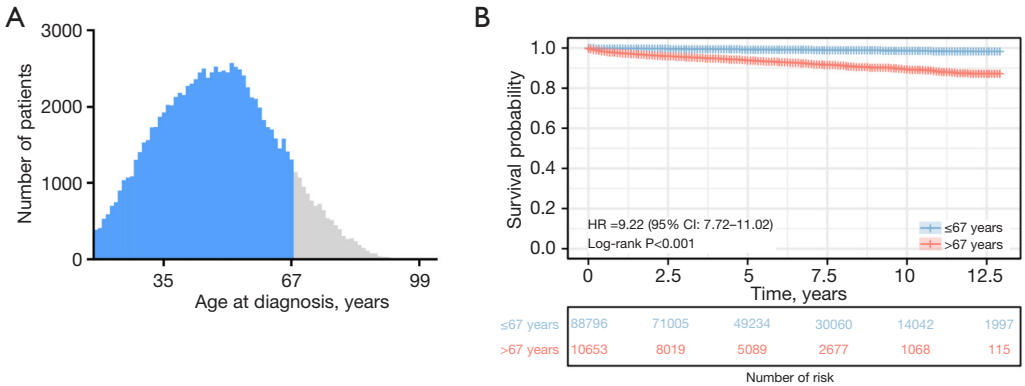

Figure 2 X-tile analysis was used to determine the SEER registry's ideal cutoff age for DTC. The ideal cutoff point is displayed on a cohort-wide histogram (A) and KM plot (B). Age is divided in the graphs at the ideal cut-point (67, P<0.001). SEER, Surveillance, Epidemiology and End Results; DTC, differentiated thyroid cancer; HR, hazard ratio; KM, Kaplan-Meier.

(*Figure 3B,3C*). Patients were classified into two groups, high-risk and low-risk, based on their risk scores (cutoff =0.121466). The KM curves were used to compare the CSS of the two groups (*Figure 3D*). When compared to patients in the low-risk group, patients from the high-risk group had considerably poorer survival rates (P<0.001). The model could identify the individuals in the high-risk category who had poorer survival outcomes and had a reasonably strong prognosis-predictive capacity. *Figure 3E,3F* illustrates ROC curves demonstrating the effectiveness of prognosis prediction for 5 and 10 years in the cohorts.

Discussion

Key findings, comparison with similar researches and explanations of findings

The ideal age upon diagnosis to predict clinical outcomes for DTC was found to be 67 years old, according to the first retrospective population-based observational cohort study. Additionally, to estimate the cause-specific mortality of each patient, we created a model that incorporates the ideal cutoff age as well as other common characteristics, which may be helpful to distinguish high-risk patients and follow-up management.

Even though the prognosis of patients with DTC is good, up to 10% of them still have a recurrence, get distant metastases, and eventually pass away (14,15). Numerous researchers have developed risk prediction algorithms to categorize individuals as high- or low-risk based on either demographic characteristics or clinicopathological variables. Age at diagnosis is incorporated into most staging systems for DTC since it is thought to be a significant prognostic factor (16). The second edition of the TNM staging system used a cutoff value of 45 years for diagnosis, which has been raised to 55 years in the eighth edition (6). Uncertainty exists regarding the precise rationale for the decision to make 45 years of age the cutoff age in the previous seventh TNM staging. According to the current studies, the median age in numerous earlier investigations was 45 years (4,5,17), and the increased age threshold for the eighth edition of the TNM system was based on three earlier studies that showed that patients with DTC could have superior DSS predictions with an age cutoff of 55 years (7-9). The majority of the main thyroid cancer staging systems have all used the age threshold of 45 for many years (18-21). In contrast, in other prognostic scoring systems [such as those used by the European Organization for Research and Treatment of Cancer (EORTC) (22); Age, Grade, Extent, Size (AGES) (23); etc.], the age at the time of diagnosis has been regarded as a continuous variable. Meanwhile, Adam *et al.* suggested that patient age is significantly associated with death from PTC in a linear fashion, without an apparent age cut point demarcating survival difference (24). Our findings clearly show that older age has a proportionate impact on the cancer-specific mortality of DTC. The age threshold of 45/55 years now in use enables higher-risk patients to be appropriately assigned to high-stage groups, but it leads to a sizable proportion of low-risk patients being overstaged and overtreated. Our findings imply that the prognostic prediction power of the cutoff age (45, 55, or 67 years) is equivalent. It has been proven that 20% of patients assigned to a high disease stage (stage III or IV) will pass away from

Table 2 Clinicopathological traits of DTC patients from the SEER database are compared by age groupings

Variable	≤67 years (n=88,796)	>67 years (n=10,653)	P value
Gender			<0.001
Male	19,020 (21.4)	3,090 (29.0)	
Female	69,776 (78.6)	7,563 (71.0)	
Race			
White	72,643 (81.8)	8,883 (83.4)	
Black	6,079 (6.8)	657 (6.2)	
Others	10,074 (11.3)	1,113 (10.4)	<0.001
Tumor size, mm			
≤20	60,000 (67.6)	6,517 (61.2)	
>20 and ≤40	20,834 (23.5)	2,454 (23.0)	
>40	7,962 (9.0)	1,682 (15.8)	<0.001
Lymphadenectomy			
No	43,069 (48.5)	6,632 (62.3)	
Yes	45,727 (51.5)	4,021 (37.7)	<0.001
Distant metastasis			
No	87,028 (98.0)	9,883 (92.8)	
Yes	1,768 (2.0)	770 (7.2)	<0.001
Laterality			0.68
Unilateral	88,348 (99.5)	10,596 (99.5)	
Bilateral	448 (0.5)	57 (0.5)	
Surgical treatment			<0.001
No	674 (0.8)	343 (3.2)	
Yes	88,122 (99.2)	10,310 (96.8)	
Radiation therapy			<0.001
No	43,740 (49.3)	6,007 (56.4)	
Yes	45,056 (50.7)	4,646 (43.6)	
Cause of death			<0.001
Death resulting from thyroid cancer	696 (0.8)	690 (6.5)	
Death resulting from other cause	1,799 (2.0)	1,668 (15.7)	

SEER, Surveillance, Epidemiology and End Results; DTC, differentiated thyroid cancer.

the disease (7). Therefore, the prognostic accuracy of the method is preserved, and a considerable number of patients are suitably downstaged by raising the cutoff age for DTC patients in our dataset from 55 to 67 years of age.

Although it is common knowledge that age has a significant role in determining clinical outcomes, an ideal cutoff age has not been clearly determined, and an increasing number of studies are looking at it. After correcting for age at diagnosis, sex, and TNM stage, Jonklaas *et al.* (25) proposed a cutoff number based on the average age at which women reached menopause and speculated that the age of 55 years was suitable for

Table 3 Applying the Cox proportional hazards model, univariate and multivariate analysis of the determinants predicting cancer-specific survival in patients with differentiated thyroid cancer

Variable	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age at diagnosis, years				
≤67	Reference		Reference	
>67	9.280 (8.351–10.313)	<0.001	5.049 (4.509–5.653)	<0.001
Gender				
Male	Reference		Reference	
Female	0.372 (0.334–0.414)	<0.001	0.651 (0.584–0.727)	<0.001
Race				
White	Reference			
Black	1.007 (0.881–1.250)	0.95	–	
Others	1.307 (1.120–1.525)	<0.01		
Tumor size, mm				
≤20	Reference		Reference	
>20 and ≤40	3.479 (3.017–4.001)	<0.001	2.296 (1.983–2.658)	<0.001
>40	13.021 (11.412–14.857)	<0.001	4.976 (4.304–5.752)	<0.001
Lymphadenectomy				
No	Reference		Reference	
Yes	1.254 (1.128–1.394)	<0.001	1.337 (1.186–1.506)	<0.001
Distant metastasis				
No	Reference		Reference	
Yes	37.273 (33.526–41.438)	<0.001	12.166 (10.749–13.769)	<0.001
Laterality				
Unilateral	Reference			
Bilateral	0.630 (0.203–1.955)	0.42	–	
Surgical treatment				
No	Reference		Reference	
Yes	0.046 (0.039–0.054)	<0.001	0.173 (0.144–0.210)	<0.001
Radiation therapy				
No	Reference		Reference	
Yes	1.779 (1.529–1.988)	<0.001	1.106 (0.982–1.245)	0.10

CI, confidence interval.

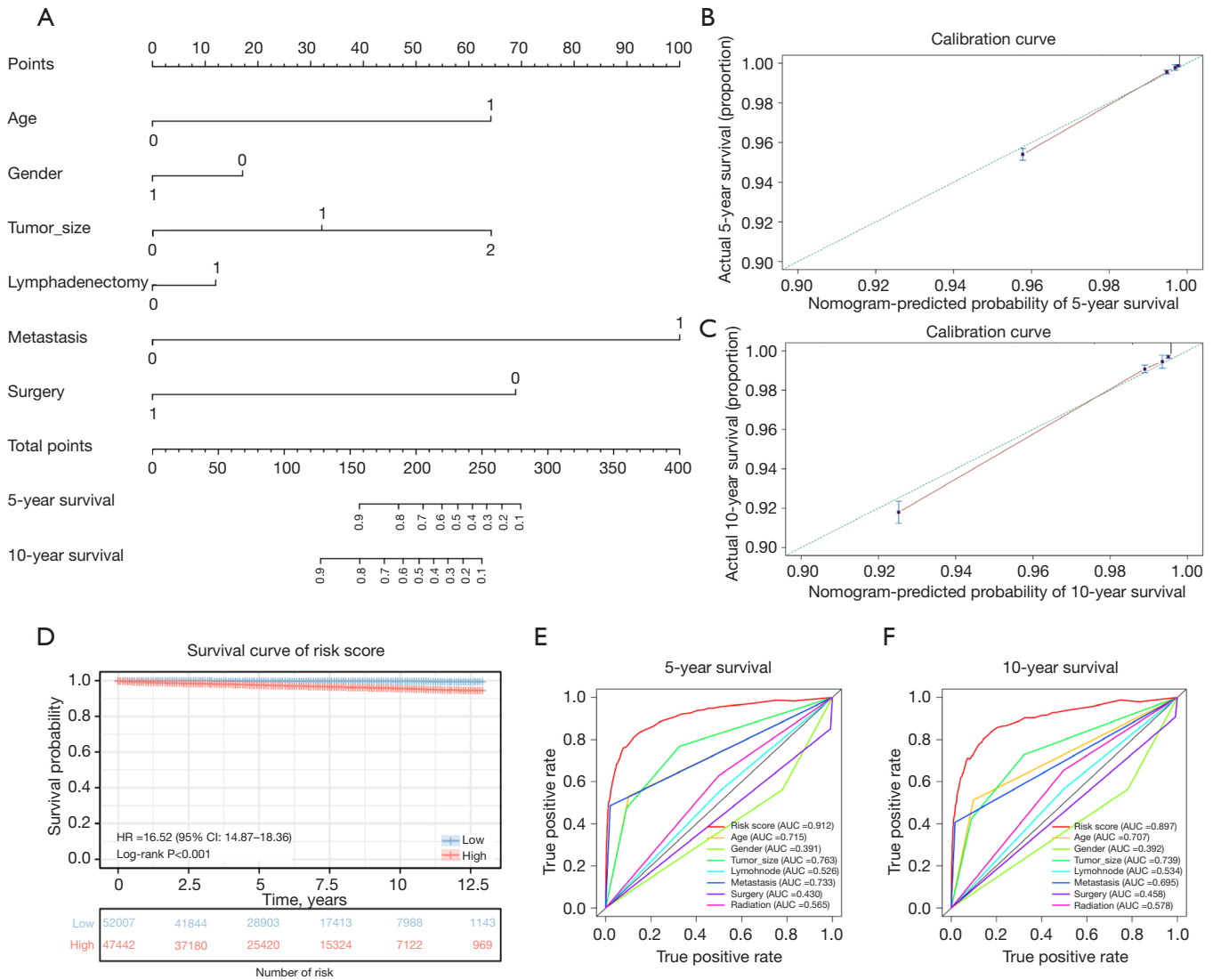

Figure 3 Establishment of CSS nomograms of patients with a cutoff age of 67 years. (A) Nomogram for predicting the 5- and 10-year CSS in DTC patients with a cutoff age of 67 years. Age, 0: ≤67 years; 1: >67 years. Gender, 0: male; 1: female. Tumor size: 0: ≤20 mm; 1: >20 and ≤40 mm; 2: >40 mm. Lymphadenectomy: 0: no; 1: yes. Metastasis: 0: no; 1: yes. Surgery: 0: no, 1: yes. (B,C) Plots of calibration for the 5- and 10-year CSS in DTC. The performance of the nomogram is represented as a solid red line, with a tighter fit to the green line indicating better prediction using the nomogram that we created. (D) CSS Kaplan-Meier curves for risk assessment. (E,F) The ROC curve for the cohort's 5- and 10-year CSS. CSS, cancer-specific survival; DTC, differentiated thyroid cancer; HR, hazard ratio; AUC, area under the curve; ROC, receiver operating characteristic.

DTC staging systems. To determine the ideal cutoff age, Mazurat *et al.* (26) separated the research population into smaller age groups. He also proposed that when using a multivariate Cox proportional hazard model to stratify risk in DTC patients, 55 years old was preferable to 45 years old. Researchers are looking into other cutoff years to categorize age disparities. One study found that each decade of age, starting at 30 years, was independently associated with a worse prognosis (27). Furthermore, there is no turning point in the survival curve at age 45 years, and the 5-year survival rate dropped with each rising age category (28). Analyzing the likelihood of cancer-specific

death in individuals is quite difficult because most DTC cases have an indolent course and a low mortality rate. However, because the population cohort size for the study was so small, there was little room for generalization in the findings.

As a result, the SEER database has offered researchers the chance to examine a number of prognostic markers in a sizable patient population free from selection or referral biases (29). A total of 99,449 DTC patients from the SEER cancer database were examined in the current study. With the lowest p values using log-rank 2 statistics, the ideal cutoff age at diagnosis, which we determined to be 67 years, was the most significant predictive factor of DTC-attributable death based on the X-tile program.

While 67 years was determined as an age threshold for differentiating prognosis based on DTC-specific death in our study, 65 years is the age at which elderly individuals are distinguished in the US (30), and the results in senior patients are poorer when compared to younger patients. This shows that the etiology may differ between young patients and elderly people. Comorbidities and mortality concerns that are unrelated to DTC must be taken into account when analyzing why older individuals with DTC do worse (31). Another factor is that tumor diagnoses made while people are younger are frequently limited to thyroid disorders or have a propensity to spread locally, primarily to local lymph nodes (31). Our work serves as a timely reminder that young and old cancer patients have very varied tumor molecular features and should be treated as having distinct diseases. However, further research is required to determine how to divide thyroid cancer into adolescent, adult, and geriatric types.

As a prognostic statistical model, a nomogram can not only visually display the relevant indicators that affect the outcome in multifactor regression analyses but also predict the survival probability through a simple graphical representation, making the prediction simpler and more convenient (32). Our results show that when predicting the CSS, the model has high degrees of discrimination and calibrated accuracy. Since the model can predict the risk of death well it has a certain value for clinical applications.

Limitations

There are still a number of limitations to this study. Firstly, as a retrospective study rather than a prospective cohort study, inherent selection biases cannot be avoided and could limit the external validity of this study. Secondly, there could be coding mistakes in the SEER-provided code, patients with incomplete data were omitted, and confounding by indication might exist. Additionally, we were unable to validate whether this nomogram's cutoff age of 67 for DTC-specific death was a more accurate predictive model than the TNM staging system's cutoff age of 45/55 years. This is because thyroid cancer TNM staging information was not included in the SEER database before 2004.

Conclusions

Overall, the age at diagnosis is the most significant predictive factor for patients with DTC, and the age cutoff value of 67 years may be more accurate in risk stratification and predicting cancer-specific death for DTC patients, according to our research of the SEER database. To identify patients at high risk for cancer-specific mortality, age stratification can be utilized in conjunction with sex and other traditional risk indicators (tumor size, lymph node dissection, distant metastases, and treatment).

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-247/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-247/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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