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Research article

Enhancing clinical decision-making: A novel nomogram for stratifying cancer-specific survival in middle-aged individuals with follicular thyroid carcinoma utilizing SEER data

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ABSTRACT

Background: Thyroid cancer (TC) is the most common malignant tumor in the endocrine system, is also one of the head and neck tumor. Follicular Thyroid Carcinoma (FTC) plays an important role in the pathological classification of thyroid cancer. This study aimed to develop an innovative predictive tool, a nomogram, for predicting cancer specific survival (CSS) in middle-aged FTC patients.

Methods: We collected patient data from the Surveillance, Epidemiology, and End Results (SEER) database. The data from patients between 2004 and 2015 were used as the training set, and the data from patients between 2016 and 2018 were used as the validation set. To identify independent risk factors affecting patient survival, univariate and multivariate Cox regression analyses were performed. Based on this, we developed a nomogram model aimed at predicting CSS in middle-aged patients with FTC. The consistency index (C-index), the area under the receiver operating characteristic (ROC) curve (AUC), and the calibration curve were used to evaluate the accuracy and confidence of the model.

Results: A total of 2470 patients were enrolled in this study, in which patients from 2004 to 2015 were randomly assigned to the training cohort (N = 1437) and validation cohort (N = 598), and patients from 2016 to 2018 were assigned to the external validation cohort (N = 435) in terms of time. Univariate and multivariate Cox regression analysis showed that marriage, histological grade and TNM stage were independent risk factors for survival. The C-index for the training cohort was 0.866 (95 % CI: 0.805–0.927), for the validation cohort it was 0.944 (95 % CI:

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0.903–0.985), and for the external validation cohort, it reached 0.999 (95 % CI: 0.997–1.001). Calibration curves and AUC suggest that the model has good accuracy.
Conclusions: We developed an innovative nomogram to predict CSS in middle-aged patients with FTC. Our model after a rigorous internal validation and external validation process, based on the time proved that the high level of accuracy and reliability. This tool helps healthcare professionals and patients make informed clinical decisions.

1. Background

Thyroid cancer (TC) is the most common clinical endocrine tumour and the most common malignant solid tumour of the head and neck [1]. Unlike other cancers, TC is more likely to occur in middle-aged patients. In 2020, there were 586,000 diagnosed patients of TC worldwide, ranking ninth among malignant tumours. The incidence of TC in developed countries is higher than that in developing countries [2], and it is also one of the tumours with the fastest growing incidence of cancer in the United States [3]. The aetiology of TC is unknown, and the incidence of TC is mainly in women, and the proportion of diagnosed TC in women is about three times that in men. One in 20 women is diagnosed with TC [2]. Well-differentiated thyroid carcinoma (DTC) is the essential thyroid malignant tumour, accounting for more than 90 % of TC [4]. According to histological classification, DTC can be divided into papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) [5]. Papillary and follicular TCs are well differentiated, and there are abundant thyroid-stimulating hormone (TSH) receptors in tumour cells, which greatly depend on TSH receptors secreted by the pituitary gland. Therefore, inhibition of TSH secretion can inhibit the occurrence and development of PTC and FTC. However, TC is also one of the most heterogeneous malignant tumours. Mutation analysis has shown that mutations in different, mutually exclusive genes can cause different types of TCs [6,7].

FTC accounts for 15 % of TC and is more aggressive than PTC. It is also considered an important reason for the increasing incidence of TC year by year [8]. Unlike PTC, which relies on lymphatic diffusion for metastasis, FTC mainly depends on hematogenous metastasis, so PTC mainly metastases to lymph nodes in the neck region. At the same time, PTC is more prone to distant metastasis [9,10]. This is also one of the important reasons for the high malignant degree of FTC. Although it is also in the DTC category, FTC patients have significantly worse overall survival (OS) and cancer-specific survival (CSS) than PTC patients with a good prognosis [11]. In addition, radiation exposure in childhood is considered the only external factor to induce TC [2]. Radiation exposure is significantly correlated with PTC, but studies have shown that this inducing factor does not connect with FTC [12].

Moreover, given the considerable side effects of radioactive iodine, it is routinely used in patients with a poor prognosis of TC. Using I131 for postoperative adjuvant therapy has been highly controversial [13]. In addition, most DTC patients are overdiagnosed and treated. Authoritative reports have found that between 2008 and 2012, 80%-95 % of TC patients in South Korea, Belarus, China, Italy, Croatia, Slovakia and France were overdiagnosed. In countries and regions such as Denmark, the UK and Japan, the ratio is also between 50 % and 70 % [14,15]. Therefore, understanding which patients are at risk for poor prognosis is key to implementing appropriate treatment plans and long-term monitoring. Thus, improving the knowledge of the prediction of FTC and accurately judging the prognosis of FTC patients has become an important topic and has excellent research significance.

The low mortality rate of TC patients makes it difficult to assess the importance of survival-related and other relevant factors using single-center studies [16]. Traditionally, TNM staging has been considered the most important criterion for determining the prognosis of various malignancies. However, it is not sufficient to encompass the biology of various malignancies and control for their survival outcomes [17]. Some essential clinical variables that may significantly impact cancer were not included. More importantly, these critical clinical variables, such as active and passive treatment patterns, sex and age, are still controversial in the predictive value evaluation of TC [18,19]. In addition, no predictive model has been developed for middle-aged PTC patients.

FTC is a relatively rare type of thyroid cancer, which tends to metastasize through vascular invasion and has a relatively poor prognosis compared with papillary thyroid cancer (PTC). Middle-aged patients may exhibit different disease progression and treatment responses due to changes in physiological and psychological status, such as changes in hormone levels and increased life stress [20]. In addition, family and social responsibilities of middle-aged patients may affect their adherence to treatment and continuity of follow-up [21]. Therefore, the need to study FTC in middle-aged adults is to provide more accurate diagnosis, treatment, and follow-up strategies for this population.

In light of the above, we collected information on middle-aged patients with FTC from the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. Based on these characteristics, we developed and validated a nomogram for the prognosis of CSS in middle-aged patients with FTC.

2. Methods

2.1. Dataset description

The patient data were downloaded from the SEER database and included all middle-aged patients with FTC. At present, there is no clear consensus on the definition of the age range for middle-aged people. In this study, patients aged 40–65 years old were included according to the conclusions of previous studies [22]. The SEER database contains 18 cancer registries, covering approximately 30 % of the US population. This study did not require ethical approval or informed consent from patients because patient records are publicly

available and patients' personal data are not identifiable. Our study methods conform to the study criteria published in the SEER database.

We downloaded basic information about the patient such as age, gender, race, year of diagnosis, and marital status. Also available were the patient's intraoperative status and chemoradiotherapy status. Patient follow-up information, including survival status, cause of death, and survival time, was also collected equally.

Inclusion criteria:(1) age 40–65; (2) the pathologic diagnosis was FTC; (3) patients diagnosed between 2004 and 2018.

Exclusion criteria:(1) tumour size and TNM staging is unknown; (2) unknown surgical method; (3) patients had no (< 1 month) or unknown survival time at follow-up. A detailed screening algorithm is shown in Fig. 1.

Patients are classified as white, black, or other (American Indian/British Indian, Asian/Pacific Islander). Histologic classification is grade I (well-differentiated), grade II (moderately differentiated), grade III (poorly differentiated), and grade IV (undifferentiated). To ensure the consistency of data, TNM staging was unified as (Derived AJCC 6th ed) TNM staging. Surgical procedures included intraoperative thyroid lobectomy, subtotal thyroidectomy, total thyroidectomy, and near total thyroidectomy.

2.2. Nomogram construction and validation

Patients from the SEER database from 2004 to 2015 were randomly assigned to the training and validation cohorts in a 7:3 ratio, while patients from 2016 to 2018 were included in a time-based external validation cohort. We used univariate and multifactorial Cox regression models to identify independent risk factors affecting CSS in patients with FTC. Column plots predicting CSS in middle-aged FTC patients were constructed based on the screened independent risk factors. We used a validation cohort from 2004 to 2015 for cross-validation and a time-based external validation cohort from 2016 to 2018 to test the accuracy and reliability of the nomogram. The accuracy of the model was tested using calibration curves, and the discriminatory power of the model was tested using C-index and AUC.

2.3. Clinical application

We used the decision curve analysis (DCA) algorithm to calculate the benefits of the model. At the same time, we compared the constructed nomogram with the conventional TNM staging to test the clinical utility value of the nomogram. Next, we calculate the risk value of each patient based on the constructed nomogram and select the optimal cut-off value by subject operating characteristic curve (ROC). Patients were divided into high-risk and low-risk groups based on the cutoff values. Finally, the Log-rank test and Kaplan-Meier (K-M) curves were used to compare the survival differences between patients in the low-risk and high-risk groups.

2.4. Statistical analysis

In the statistical analysis, for categorical data, we used frequency to represent. When comparisons between groups were needed, we

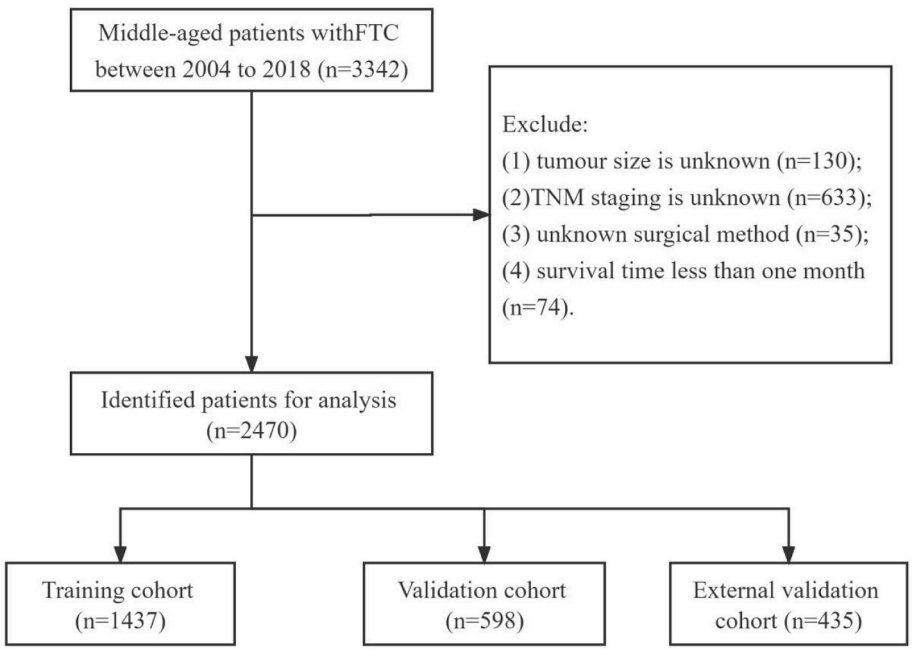

Fig. 1. Flow chart for inclusion and exclusion of all patients with PTC screening.

used the chi-square test. For continuous data, after passing the normal distribution test, we describe them by means and standard deviations. When making comparisons between groups, we used the nonparametric *U* test or the chi-square test. To explore the factors affecting patient survival, Cox regression models were used. Differences in survival between groups were assessed by means of the Log-rank test. We used R software, version 4.1.0, and SPSS software, version 26.0, to perform these statistical analyses. A P value of less than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Clinical features

A total of 2470 patients with FTC were included in this study. Of these, patients from 2004 to 2015 were randomly assigned to the training (N = 1437) and validation (N = 598) groups in a 7:3 ratio, and patients from 2016 to 2018 were included in the external validation group (N = 435) as temporal external validation. The mean age of the patients included in this study was (52.6 ± 7.26) years. Of these, 1575 cases (77.4 %) were Caucasian. In the gender classification, there were fewer males, 664 cases (32.6 %). Among the marital status, married accounted for the majority, with 1321 cases (64.9 %). There were 375 (18.4 %) patients with grade I, 93 (4.57 %) patients with grade II, 62 (3.05 %) patients with grade III, and 9 (0.44 %) patients with grade IV. There were 508 (25.0 %) patients in T1, 777 (38.2 %) patients in T2, 681 (33.5 %) patients in T3, and 69 (3.39 %) patients in T4. 1960 (96.3 %) patients had

Table 1
Clinicopathological characteristics of middle-age patients with FTC.

	ALL	Training cohort	Validation cohort	
	N = 2035	N = 1437	N = 598	p
Age	52.6 (7.26)	52.6 (7.28)	52.6 (7.23)	0.797
Race				0.125
white	1575 (77.4 %)	1097 (76.3 %)	478 (79.9 %)	
black	268 (13.2 %)	203 (14.1 %)	65 (10.9 %)	
other	192 (9.43 %)	137 (9.53 %)	55 (9.20 %)	
Sex				0.508
Male	664 (32.6 %)	462 (32.2 %)	202 (33.8 %)	
Female	1371 (67.4 %)	975 (67.8 %)	396 (66.2 %)	
Marital				0.233
No	714 (35.1 %)	492 (34.2 %)	222 (37.1 %)	
Married	1321 (64.9 %)	945 (65.8 %)	376 (62.9 %)	
Year of diagnosis				0.967
2004–2009	990 (48.6 %)	700 (48.7 %)	290 (48.5 %)	
2010–2015	1045 (51.4 %)	737 (51.3 %)	308 (51.5 %)	
Grade				0.333
I	375 (18.4 %)	255 (17.7 %)	120 (20.1 %)	
II	93 (4.57 %)	71 (4.94 %)	22 (3.68 %)	
III	62 (3.05 %)	47 (3.27 %)	15 (2.51 %)	
IV	9 (0.44 %)	5 (0.35 %)	4 (0.67 %)	
Unknown	1496 (73.5 %)	1059 (73.7 %)	437 (73.1 %)	
T				0.965
T1	508 (25.0 %)	360 (25.1 %)	148 (24.7 %)	
T2	777 (38.2 %)	547 (38.1 %)	230 (38.5 %)	
T3	681 (33.5 %)	483 (33.6 %)	198 (33.1 %)	
T4	69 (3.39 %)	47 (3.27 %)	22 (3.68 %)	
N				0.018
N0	1960 (96.3 %)	1395 (97.1 %)	565 (94.5 %)	
N1a	42 (2.06 %)	23 (1.60 %)	19 (3.18 %)	
N1b	33 (1.62 %)	19 (1.32 %)	14 (2.34 %)	
M				0.746
M0	1954 (96.0 %)	1378 (95.9 %)	576 (96.3 %)	
M1	81 (3.98 %)	59 (4.11 %)	22 (3.68 %)	
Tumor size	35.9 (24.8)	35.9 (23.0)	35.8 (28.8)	0.965
Surgery				0.290
No	28 (1.38 %)	20 (1.39 %)	8 (1.34 %)	
Lobectomy	392 (19.3 %)	262 (18.2 %)	130 (21.7 %)	
Subtotal or near total thyroidectomy	99 (4.86 %)	68 (4.73 %)	31 (5.18 %)	
Total thyroidectomy	1516 (74.5 %)	1087 (75.6 %)	429 (71.7 %)	
Chemotherapy				1.000
No/Unknown	2019 (99.2 %)	1425 (99.2 %)	594 (99.3 %)	
Yes	16 (0.79 %)	12 (0.84 %)	4 (0.67 %)	
Radiation				0.846
No/Unknown	791 (38.9 %)	561 (39.0 %)	230 (38.5 %)	
Yes	1244 (61.1 %)	876 (61.0 %)	368 (61.5 %)	
Survival months	96.2 (44.9)	96.0 (45.3)	96.7 (43.8)	0.744

stage N0 and 1954 (96.0 %) patients had stage M0. 392 (19.3 %) patients received lobectomy, 99 (4.86 %) received subtotal or near-total thyroidectomy, and 1516 (74.5 %) received total thyroidectomy. Sixteen (0.79 %) patients received chemotherapy, and 1244 (61.1 %) received radiotherapy. There was no significant difference in patients in the training and validation cohorts(Table 1).

3.2. Univariate and multivariate cox regression analysis

In the training set, initial evaluation using univariate Cox regression indicated that several variables -age, race, marital status, Grade grade, tumor size, TNM stage, and treatment including radiation and chemotherapy -were significantly associated with patient survival outcomes. Subsequently, we performed a multivariate Cox regression analysis incorporating factors that showed prognostic significance in the early univariate assessment. This refined analysis identified marital status, Grade grade, and TNM stage as independent predictors of survival. The combined results of univariate and multivariate Cox regression analyses are presented in Table 2.

3.3. Nomogram construction

Then, a new nomogram was constructed for predicting CSS in middle-aged FTC patients based on multifactorial Cox regression analysis with selected independent risk factors (Fig. 2). TNM stage was the most important factor affecting patient survival. Secondly, the histological grade of the tumor was also considered as an important prognostic factor in our analysis. Finally, our nomogram showed that marital status also had some impact on patient survival.

Table 2
Univariate and multivariate analyses of CSS in training set.

	Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P
Age	1.06	1.02–1.1	0.004			
Race						
white						
black	1.95	1.01–3.74	0.046			
other	1.96	0.91–4.22	0.085			
Sex						
Male						
Female	0.6	0.35–1.01	0.055			
Marital						
No						
Married	0.38	0.23–0.65	<0.001	0.436	0.247–0.772	0.004
Year of diagnosis						
2004–2009						
2010–2015	0.81	0.45–1.46	0.478			
Grade						
I						
II	1.78	0.33–9.69	0.507	0.716	0.124–4.138	0.709
III	15.67	4.91–49.99	<0.001	3.725	1.09–12.729	0.036
IV	139.68	34.64–563.24	<0.001	23.987	4.502–127.791	<0.001
Unknown	2.06	0.73–5.8	0.169	1.401	0.49–4.007	0.529
T						
T1						
T2	2.91	0.63–13.46	0.172	2.969	0.641–13.755	0.164
T3	10.75	2.56–45.19	0.001	8.747	2.07–36.968	0.003
T4	90.31	20.94–389.38	<0.001	18.063	3.878–84.13	<0.001
N						
N0						
N1a	11.33	4.81–26.69	<0.001	6.064	2.339–15.724	<0.001
N1b	13.39	5.7–31.44	<0.001	0.732	0.26–2.057	0.554
M						
M0						
M1	25.57	14.99–43.63	<0.001	12.423	6.437–23.974	<0.001
Tumor size	1.01	1.01–1.02	<0.001			
Surgery						
No						
Lobectomy	0.22	0.02–1.97	0.176			
Subtotal or near total thyroidectomy	0.4	0.04–4.4	0.452			
Total thyroidectomy	0.67	0.09–4.86	0.692			
Chemotherapy						
No/Unknown						
Yes	18.48	6.59–51.76	<0.001			
Radiation						
No/Unknown						
Yes	2.36	1.25–4.47	0.008			

3.4. Validation

We used the C-index to test the discrimination of the prediction model in the training cohort and validated it in the validation cohort. The results showed that the C-index was 0.866 (95 % CI: 0.805–0.927) and 0.944 (95 % CI: 0.903–0.985) for the training cohort and the validation cohort, respectively. Meanwhile, the C-index of the external validation cohort was 0.999 (95 % CI:0.997–1.001), indicating the good predictive ability of the model by the time-based external validation cohort. The calibration curves in the training and validation cohorts show that the observed and predicted values of our constructed prediction model are consistent (Fig. 3). In the training cohort, the 3-, 5-, and 10-year AUCs of the nomogram are 85.4, 86.0, and 87.6. In the validation cohort, they are 97.2, 95.8, and 94.9, respectively; this indicates that the prediction model we constructed has good identification ability (Fig. 4).

3.5. Clinical application

Moving forward, we conducted a Decision Curve Analysis (DCA) across both the training and validation cohorts, which confirmed the robust clinical applicability of our developed nomogram. The predictive accuracy of this nomogram was notably higher compared to the standard TNM staging system (Fig. 5). Furthermore, individual patient risk scores were determined utilizing the nomogram, and the most effective cut-off point was identified through Receiver Operating Characteristic (ROC) analysis. Utilizing this threshold, the patient population was categorized into high-risk (scores ≥89.2) and low-risk (scores <89.2) categories. Kaplan-Meier (K-M) survival analysis for the stratified middle-aged FTC patients revealed that those in the low-risk category exhibited markedly improved survival rates when contrasted with the high-risk group (Fig. 6). The 3-, 5-, and 10-year survival rates of FTC patients in the low-risk group were 99.6 %, 99.4 %, and 99.4 %, respectively. In contrast, the 3-, 5-, and 10-year survival rates for FTC patients in the high-risk group were significantly lower, at 96.7 %, 95.4 %, and 90.5 %, respectively. Finally, in the comparison of surgical modalities, we found that most patients underwent lobectomy and total thyroidectomy, and patients had the highest survival rate after lobectomy (Fig. 7).

4. Discussion

TC is one of the most common endocrine tumours [1] and one of the top ten common malignant tumours in the United States [23]. In 2020, the incidence of TC ranked ninth in the world [2]. Although most TC patients have a good prognosis, some FTC patients have a poor prognosis due to distant metastasis, and the results are heterogeneous [16]. The overall incidence ratio for TC in women/men was approximately 3:1. One plausible explanation is that women are screened for TC earlier and more widely than men. In FTC, the incidence ratio of females to males is 2:1, and the prognosis of male TC patients is generally worse than that of females. Therefore, understanding the changes in the incidence of FTC based on demographic and tumour characteristics can provide information for future analysis and intervention strategies [24].

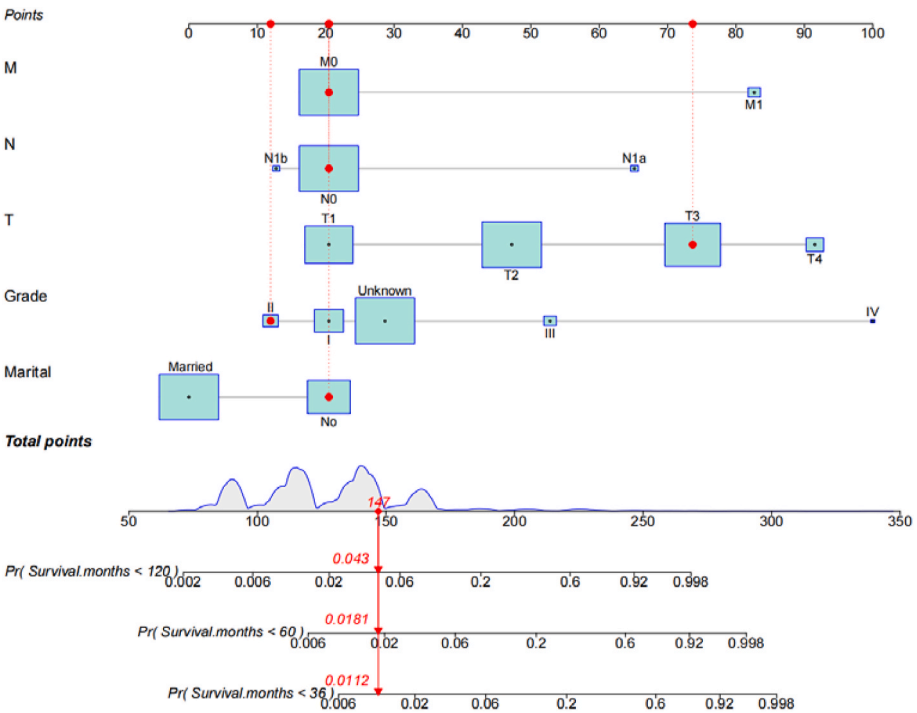

Fig. 2. Nomogram predicting CSS in middle-aged patients with FTC.

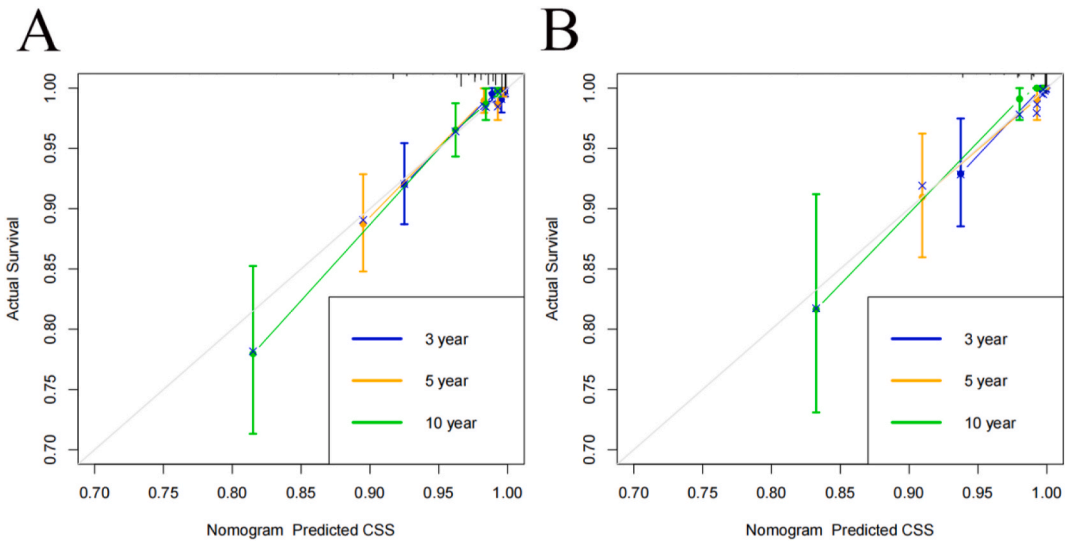

Fig. 3. The calibration curves of the Nomogram constructed in this study were in the training cohort (A) and the validation cohort (B).

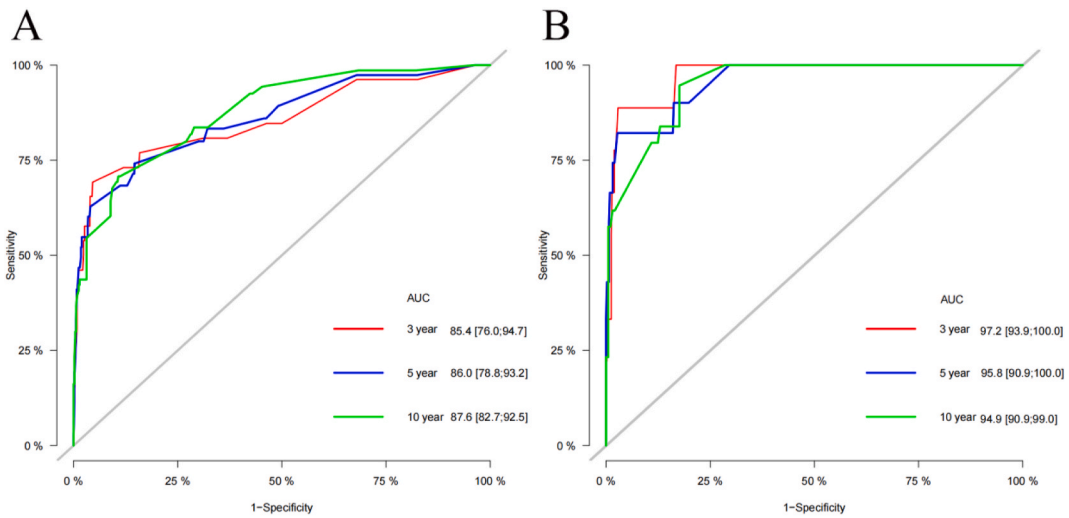

Fig. 4. AUC curves predicting CSS in middle-aged FTC patients in the training cohort (A) and validation cohort (B).

Whether sex can be used as an independent risk factor to predict the prognosis of TC has been controversial. Existing data are from single-centre retrospective or population-based studies, without specific analysis of the role of sex in TC [22]. According to histological classification, Studies have shown that sex hormones regulate growth and modulate the function of the thyroid gland [25]. This difference also exists in cancer and adjacent tissues of TC patients [26]. This may be related to the fact that estrogen can promote TSH release from the pituitary, while TSH can inhibit the development of TC. Studies on TC tumour tissues also found that TC tissues contain many estrogen receptors, but there is still a lack of precise mechanisms [27].

Whether marital status is one of the important factors influencing tumor survival is controversial. Merrill RM et al. conducted a large sample population survival analysis after collecting data on 779,978 men and 1,032,868 women diagnosed with one of the 13 cancers between 2000 and 2008. It was found that for less fatal cancers, such as thyroid cancer, married status significantly prolonged the survival time of patients with these cancers [28]. The results of an Italian study, however, showed no substantial association between marital status and cancer risk [29]. In a study related to thyroid cancer, Shi RL et al. evaluated the impact of marriage on survival outcomes in patients with DTC through a retrospective analysis, and they found that being unmarried and especially widowed increased the risk of cancer death in patients with DTC [30]. Not coincidentally, Tang J et al. also found that unmarried and widowed patients tended to predict a poor prognosis compared to married middle-aged PTC patients [31]. The underlying rationale for this phenomenon may be that married people have better mood and receive more social support, including practical support and financial resources, so that they can focus on therapy [30]. Studies have shown that married status can even enable patients to obtain higher

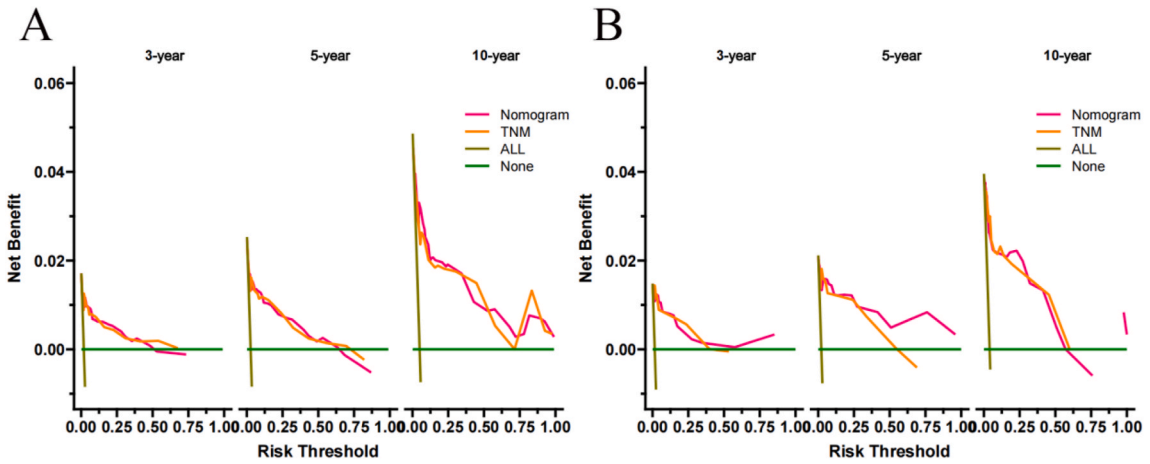

Fig. 5. The DCA of Nomogram constructed in this study is in the training cohort (A) and the validation cohort (B).

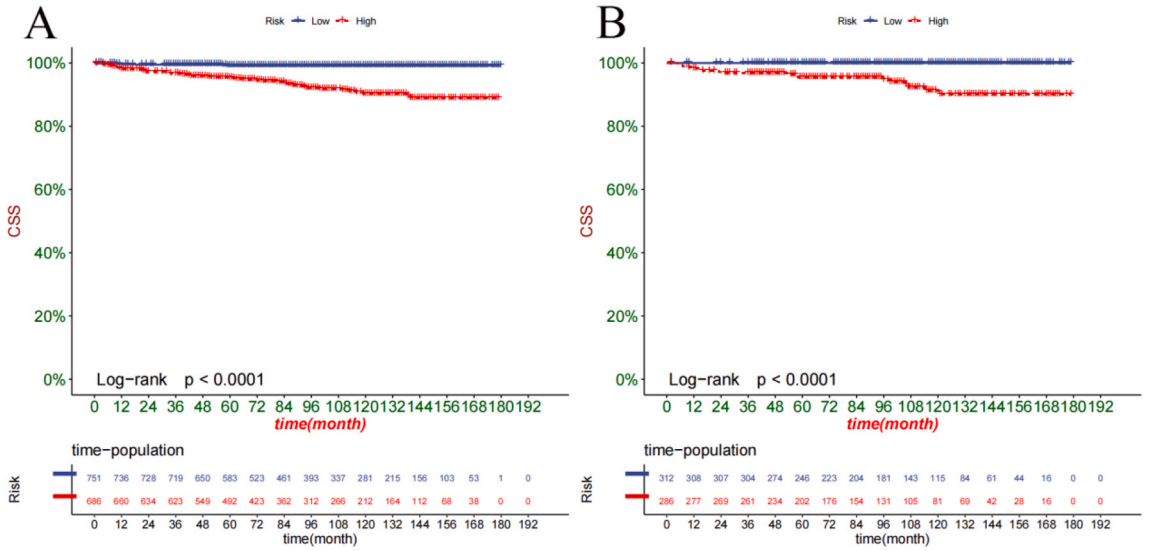

Fig. 6. Kaplan-Meier curves for middle-aged FTC patients in the low-risk and high-risk groups in the training cohort (A) and the validation cohort (B).

benefits than chemotherapy [32]. In the present study, we found that married middle-aged FTC patients reflected a longer survival time and better prognosis, consistent with previous studies related to thyroid cancer. Exploring the underlying reasons, in terms of psychosocial, economic or treatment adherence, we found that married patients may have a better prognosis due to better social support and mental health status [33]. Unmarried or divorced patients may face more psychological stress and less social support, which may affect their adherence to treatment and, thus, overall health [34]. In addition, marital status may also be associated with patient's economic status, health insurance coverage, and access to health information, all of which may indirectly influence the prognosis of FTC as mediated by marital status [31].

Age is positively correlated with many types of cancer. Studies have shown that the OS of TC starts to decline steadily from age 40 [35]. A population study in Germany found that when comparing the all-cause mortality of well-differentiated TC patients with the general population, there was a moderate decline in survival in patients aged >45 years and a significant decrease in patients aged over 60 years [36]. Yang et al. conducted a population-based study that evaluated and predicted the probability of death due to TC and other causes in patients with TC and found a continuous positive correlation between age and TC survival [37]. Age was not an independent risk factor for CSS in FTC patients aged 40–65 years in this study. This may be related to FTC maintaining a lower mortality rate in this age group.

Our study also found that TNM staging remains the primary prognostic criterion for middle-aged FTC, although it is insufficient to cover all critical clinical factors. This study found that the prognosis of middle-aged FTC patients with tumours> 4 cm and minimal invasion (stage T3-4) was worse, while confined within the thyroid capsule and tumour < 4 cm suggested an excellent prognosis was

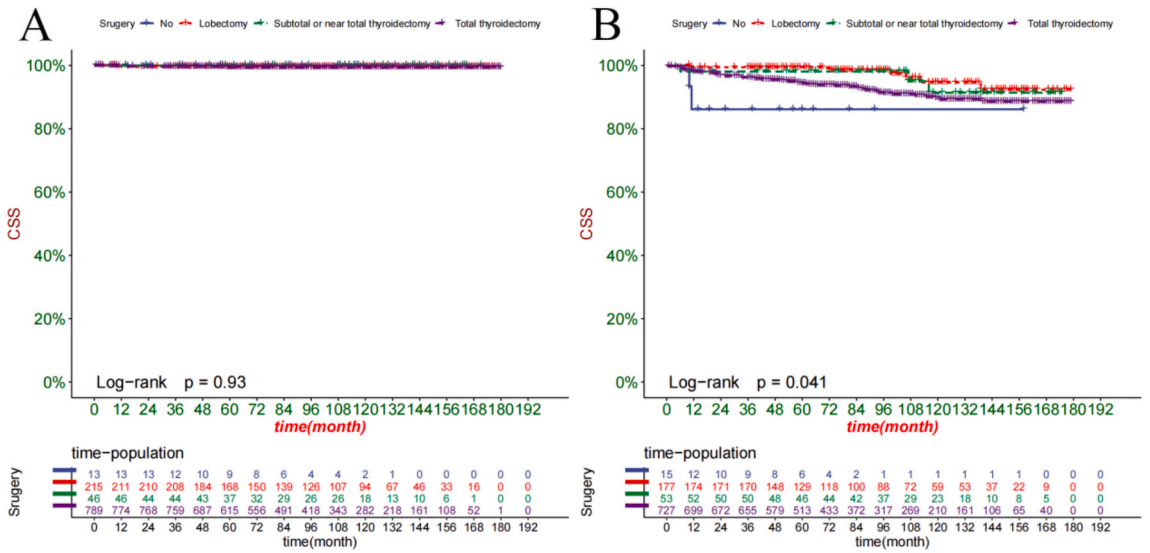

Fig. 7. Kaplan-Meier curves for different surgical approaches in middle-aged FTC patients: low-risk group (A); high-risk group (B).

consistent with relevant reports. It is worth noting that Aschebrook et al. analyzed the incidence of FTC in the United States from 1980 to 2009 and found that patients newly diagnosed with FTC had larger tumour volume accompanied by more regional lymph node metastasis [11]. That means the 4 cm threshold may need to be updated. We believe that traditional TNM staging in FTC patients may need to be updated by the latest trends. Onitilo et al. developed a new simplified and quantified TNM staging system (QTNM) after updating the TNM system. The comparison with the traditional TNM system revealed better discrimination of QTNM, which was maintained when such risk stratification was applied to external validation [38].

Surgery is the primary way to treat DTC. The critical factor in deciding whether or not to operate and the scope of the operation is the results of a fine needle aspiration biopsy (FNAB) combined with an intraoperative frozen section. However, whether to use I-131 for postoperative treatment and the specific dosage are the most significant controversies in diagnosing and treating TC. Although as a single therapeutic effect, I-131 can kill residual tumour tissue and effectively prevent tumour recurrence. However, from the overall perspective of adjuvant therapy, I-131 will also affect the normal thyroid tissue remaining after injury [13]. For high-risk TC, such as undifferentiated thyroid carcinoma (ATC) and medullary thyroid carcinoma (MTC), the benefits of adjuvant therapy with I-131 have been demonstrated in patients with TC [39]. However, in the low-risk group of patients represented by PTC and FTC, I-131 adjuvant therapy did not benefit patients. In a systematic review of multivariable correction analysis of low-risk TC patients, Lamartina et al. did not find that I-131 use significantly impacted patients' CSS [40]. I-131 has been infrequently used in low-risk FTC in recent years because of its effects on pregnancy, young children in the family, and potential risk of secondary malignancies [41]. In contrast, thermal ablation (TA), including radiofrequency ablation (RFA), laser thermal ablation (LTA), microwave ablation (MWA), and high-intensity frequency ultrasound (HIFU), involves the delivery of energy to target lesions and destruction of their constituent cells. This treatment does not cause hypothyroidism and does not cause significant maternal and child toxic side effects. It has gradually become the mainstream trend of non-surgical treatment [42]. The latest joint statement of thyroid associations and Societies of Nuclear Medicine in the United States and Europe believes that there is probably no "right" treatment for DTC, and individual assessment and treatment are needed for the specific situation of each patient [13]. Our study can provide a basis for evaluating CSS in middle-aged FTC patients.

The application of the nomogram constructed in this study in clinical practice is mainly to help doctors and patients predict treatment outcome and disease progression based on specific clinical parameters. In the treatment of midlife FTC, first, physicians can use nomograms to assess the expected effects of different treatment options, such as surgery, radioiodine therapy, or targeted therapy. Second, the nomogram can also help to develop a personalized follow-up strategy to adjust the frequency of follow-up and examination items according to the patient's prognostic risk. Avoid situations that result in delay or overtreatment. In addition, the nomogram can be used as a communication tool in patient counseling to help patients understand their disease status and treatment options so that they can better participate in the decision-making process and improve patient adherence to treatment according to their specific situation.

In recent years, molecular markers also play an essential role in predicting the prognosis of FTC patients. Studies have found that there are a variety of gene mutations and rearrangements in FTC, and these molecular events are closely related to the pathogenesis, clinical manifestations, and prognosis of tumours. PAX8-PPARγ rearrangement is the most common in FTC, with an incidence between 30 and 35 %, and has also been reported in benign adenomas of FTC. This rearrangement results in the fusion of the paired domain transcription factor of the PAX8 gene with the PPARγ gene, producing a fusion protein whose overexpression has been implicated in the occurrence of FTC [43]. In addition, RAS gene family mutations are also relatively common in FTC, especially in follicular adenoma and follicular carcinoma; the incidence of RAS mutations is about 20 %. These mutations usually affect the GTPase activity of the RAS

gene, leading to the continuous activation of the RAS protein, which in turn promotes the proliferation and survival of FTC tumor cells through MAPK and PI3K/AKT signaling pathways [44]. At the same time, other gene changes have been found in FTC, such as PIK3CA gene mutation and amplification, which activate the PI3K/AKT signaling pathway and have an important impact on the development and prognosis of FTC [45]. In addition, β-catenin mutations are also common in FTC. These mutations usually occur in exon 3 of the CTNNB1 gene, leading to abnormal nuclear expression of β-catenin, which is associated with tumor aggressiveness and poor prognosis [46]. By studying these molecular markers, physicians may be able to assess patients' prognostic risk more accurately and provide patients with more personalized treatment recommendations. Through the study of these molecular markers, more accurate diagnostic tools and therapeutic targets may be developed in the future.

However, there are some deficiencies in this study. First of all, middle-aged patients with FTC were included in the SEER database for analysis. Considering that the clinical information in the SEER database is all previous information, this study is a retrospective study, and selection bias may be unavoidable. Secondly, the SEER database did not include some clinical variables, such as smoking, alcohol consumption, BMI and other factors that might affect the CSS of middle-aged FTC patients, and also lacked follow-up information. This missing information may have influenced the results. Third, the SEER database includes patients from the United States. Therefore, after considering the influence of different factors such as race and region, the reference value of the conclusions of this study for clinicians in Europe, Africa, Oceania, and Asia may be limited. But we included vital elements such as age, surgery, radiation and chemotherapy, so the results were not significantly different. Finally, although we separately screened patients updated from 2016 to 2018 for external validation in terms of time, the results were more convincing. However, external validation of the nomogram in different populations does need to be considered when conducting prognostic studies in middle-aged FTC patients. Although external time-based validation was performed with data from the SEER database, other cohorts are warranted because thyroid cancer incidence, treatment, race and ethnicity, and patient survival may vary substantially across regions and health systems. Future studies should focus on validating the generalizations of the nomogram in a diverse patient population to provide more accurate prognostic assessment and personalized treatment recommendations for thyroid cancer patients worldwide.

5. Conclusion

In summary, in this study we discovered that marital standing, tumor grade, and TNM staging are predictors of CSS in middle-aged patients with FTC. We have formulated a novel predictive tool, a nomogram, specifically designed for this patient demographic. This prediction model underwent internal validation and external validation based on time, demonstrating commendable precision and dependability. It serves to assist middle-aged individuals with FTC in selecting the most appropriate clinical treatment strategy and offers valuable insights and substantiation for medical professionals in their diagnostic and therapeutic processes.

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Ethics approval and consent to participate

The data of this study is obtained from the SEER database. The patients' data is public and anonymous, so this study does not require ethical approval and informed consent.

Methods

The methods used in this study comply with the regulations and guidelines of the SEER database.

Consent for publication

None.

Data availability statement

The SEER data analyzed in this study is available at https://seer.Cancer.gov/.

CRediT authorship contribution statement

Chenghao Zhanghuang: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jinkui Wang:** Writing – original draft, Formal

analysis, Data curation, Conceptualization. **Fengming Ji:** Methodology, Investigation, Data curation, Conceptualization. **Zhigang Yao:** Data curation, Conceptualization. **Jing Ma:** Project administration, Investigation, Formal analysis, Data curation. **Yu Hang:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jinrong Li:** Validation, Supervision, Formal analysis. **Zipeng Hao:** Validation, Methodology. **Yongqi Zhou:** Validation, Data curation, Conceptualization. **Bing Yan:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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