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Establishment of a predictive nomogram for differentiated thyroid cancer: an inpatient-based retrospective study

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Abstract

Introduction: Differentiated thyroid cancer (DTC) is the most common malignant tumour of the endocrine system. The aim of this study was to establish a nomogram for simply and effectively predicting DTC.

Material and methods: 464 inpatients who underwent thyroid nodule surgery were retrospectively analysed. Univariate logistic regression and multivariate logistic regression were used to analyse the risk factors of DTC. A nomogram was constructed for predicting DTC.

Results: In this study, multivariate logistic regression found that female sex, age < 55 years, solid composition, hypoechogenicity, irregular margin, microcalcification, taller-than-wide, and cervical lymphadenopathy were independent risk factors for DTC. The area the curve (AUC) of the nomogram model indicated an excellent predictive performance of 0.920 [95% confidence interval (CI): 0.888–0.952]. The best threshold for predicting DTC was 52.4%, with sensitivity and specificity of 91.9% and 81.0%, respectively.

Conclusions: we provided a simple, noninvasive, and accurate model for clinicians to predict DTC. **(Endokrynol Pol 2023; 74 (6): 616–622)**

Key words: *differentiated thyroid cancer; nomogram; screening; risk factor*

Introduction

Thyroid nodule is very common in clinics, and the incidence has been increasing in recent years, but only 7–15% are malignant tumours [1]. Thyroid carcinoma, as the most common malignant tumour of the endocrine system, has been rapidly and continually on the rise in the past decade. Previous research reported that the standardized incidence of thyroid cancer was 6.6 per 100,000 worldwide in 2020, rating as the 5th most common cancer among women [2]. According to the diverse nature of thyroid nodules, the therapeutic options are different, resulting in significant differences in medical expenses, quality of life, and survival prognoses. Thyroid malignant tumour can be divided into differentiated thyroid cancer (DTC), anaplastic thyroid cancer (ATC), and medullary thyroid cancer (MTC), based on its histological origin. Epidemiological studies have shown that the most common type of thyroid carcinoma is differentiated thyroid cancer (DTC), accounting for more than 95% [3], which requires surgical resection and mostly has an excellent prognosis. Therefore, it is of great importance to accurately identify DTC and employ an appropriate treatment method.

Preoperative evaluation of the nature of thyroid nodules plays a crucial role in clinical diagnosis and treatment, and it depends on the medical history, physical examination, laboratory testing, thyroid imaging (such as ultrasound, computed tomography, magnetic resonance imaging, radionuclide imaging, etc.), and fine needle aspiration biopsy (FNAB). For thyroid nodules with high suspicion of malignancy, FNAB is the most sensitive and specific method. However, FNAB is an invasive examination, which cannot be widely carried out due to medical conditions and operator restrictions, and there may be some complications such as bleeding, infection, and metastatic spread [4]. Moreover, FNAB also has some limitations. The cytology of 2–16% of specimens cannot be diagnosed due to insufficient materials [5], and in 5–20% of cases it is not possible to discriminate the nature of follicular neo-plasm [6, 7]. Previous studies [8, 9] have established some models to evaluate the nature of thyroid nodules, but most of them are complicated, and there is still a lack of simple, practical models for predicting DTC. In recent years, the nomogram predictive model has been widely used in clinical cohort studies due to its high accuracy, efficiency, and stability. Therefore, we attempted to establish and evaluate the nomogram model to simply and effectively predict DTC by analysing the pathological and clinical data of cases undergoing thyroidectomy in our hospital.

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Material and methods

Study population

The patients who underwent thyroid nodule surgery in Peking University International Hospital from December 2014 to December 2019 were retrospectively analysed. Inclusion criteria were as follows: (1) adults (age ≥ 18 years old); (2) patients with DTC or benign nodules (including benign adenoma, thyroid cyst, Hashimoto's thyroiditis, etc.) by postoperative pathology; and (3) cases with complete medical records. Exclusion criteria were as follows: (1) patients with MTC or ATC; (2) cases with a history of thyroid surgery or iodine 131 treatment and administration of drugs influencing serum TSH levels, such as MMI (methimazole), PTU (propylthiouracil), levothyroxine, and amiodarone; and (3) cases with other malignant tumours. Finally, a total of 464 patients (124 men and 340 women) with an average age of 47.90 ± 12.66 years were included in this study.

Methods

Demographic and clinical data (age, gender, medical history, etc.) were recorded, and anthropometric parameters, including body weight and height, were measured. Body mass index (BMI) was defined as weight (kg)/square of height (m^2).

Thyroid function and thyroid ultrasound were performed in all patients before surgery. Venous blood was drawn after the patient was fasted for 10 hours. Thyroid function, including thyroid-stimulating hormone (TSH), anti-thyroid peroxidase antibody (TPOAb), and anti-thyroglobulin antibody (TgAb), were detected by using a Roche Cobas Elesys 601 analyser (Roche, Basel, Switzerland). The reference ranges of TgAb and TPOAb were 0–115 IU/mL and 0–34 IU/mL, respectively. TPOAb and TgAb positivity were defined as antibody levels exceeding the upper limit of the reference range. Colour Doppler ultra-sound of the thyroid was performed by skilled sonographers using a Philips iU Elite Colour Doppler Ultrasound System (Philips Healthcare, Eindhoven, Netherlands) with a probe frequency of 12 MHz, and the specific imaging of thyroid nodules (including number, size, location, composition, echogenicity, shape, margin, calcification, etc.) and cervical lymph nodes were judged and recorded. Cervical lymphadenopathy was defined as the lymph nodes with abnormal sonographic features including enlargement, loss of the fatty hilum, a rounded rather than oval shape, hyperechogenicity, cystic change, calcifications, and peripheral vascularity [10].

After thyroidectomy, all patients underwent pathological examination of surgical specimens by experienced pathologists.

Statistical analysis

In this study, we used SPSS 20.0 software (provided by IBM, Armonk, NY, United States). Normality was assessed with the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median (Q1, Q3). Categorical variables were expressed as absolute numbers and percentages. To compare the differences between the 2 groups, the independent t-test, Mann–Whitney U test, or chi-square test was employed if appropriate. Univariate logistic regression and multivariate logistic regression were used to analyse the risk factors of DTC. $p < 0.05$ indicated significant differences.

The establishment and validation of nomogram were performed with statistical packages R (http://www.R-project.org) and EmpowerStats (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). In this study, the nomogram was internally validated in cohorts using the bootstrap validation method by 1000 re-samplings. Receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to assess the predictive accuracy of the nomogram.

Results

Characteristics of participants

In this study, 464 patients were divided into a DTC group (359 cases) and a benign group (105 cases) according to the pathological results. The rate of DTC was 77.37%. Compared to the benign group, cases with DTC were more likely to be female, younger, and non-smoking ($p < 0.05$), and more DTC patients had sonographic characteristics including size < 1 cm, solid composition, hypoechogenicity, irregular margin, microcalcification, taller-than-wide, and cervical lymphadenopathy ($p < 0.05$). There were no statistically significant differences in BMI, the levels of TSH, the rate of drinking, Hashimoto's thyroiditis, and TPOAb/TgAb positivity between the 2 groups ($p > 0.05$) (Tab. 1).

In this study, none of the patients had a history of radiation exposure (including head/neck and whole-body radiation) or family history of thyroid cancer. Therefore, these variables were not further analysed.

Table 1. *Characteristics of patients with differentiated thyroid cancer (DTC) and benign nodules*

Variables	Subgroups	DTC group (n = 359)	Benign group (n = 105)	p
Gender	Female	274 (76.32)	66 (62.86	0.006
	Male	85 (23.68)	39 (37.14)	
Age [years]		46.19 ± 12.00	53.73 ± 13.14	0.000
	< 55	259 (72.14)	52 (49.52)	0.000
	≥ 55	100 (27.86)	53 (50.48)	
Smoking	Yes	16(4.46)	10 (9.52)	0.047
	No	343 (95.54)	95 (90.48)	
Drinking	Yes	6 (1.67)	4 (3.81)	0.345
	No	353 (98.33)	101 (96.19)	
BMI [kg/m^2]		24.84 ± 3.93	25.52 ± 3.77	0.117
	< 24	142 (39.55)	36 (34.29)	0.329
	≥ 24	217 (60.45)	69 (65.71)	

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Table 1. *Characteristics of patients with differentiated thyroid cancer (DTC) and benign nodules*

Variables	Subgroups	DTC group (n = 359)	Benign group (n = 105)	p
Nodule size [cm]	≥ 1	198 (55.15)	92 (87.62)	0.000
	< 1	161 (44.85)	13 (12.38)	
Composition	Solid	314 (87.47)	51 (48.57)	0.000
	Cystic or mixed	45 (12.53)	54 (51.43)	
Echogenicity	Hypoechoic	311 (86.63)	43 (40.95)	0.000
	Hyperechoic or isoechoic	48 (13.37)	62 (59.05)	
Margin	Irregular	212 (59.05)	11 (10.48)	0.000
	Regular	147 (40.95)	94 (89.52)	
Shape (taller-than-wide)	Yes	141 (39.28)	4 (3.81)	0.000
	No	218 (60.72)	101 (96.19)	
Calcification	Microcalcification	217 (60.45)	23 (21.90)	0.000
	No or macrocalcification	142 (39.55)	82 (78.10)	
Cervical lymph node	Lymphadenopathy	85 (23.67)	14 (13.33)	0.023
	Normal	274 (76.32)	91 (86.67)	
TSH [uIU/mL]		1.97 ± 1.75	1.90 ± 1.54	0.702
TPOAb	Positive	84 (23.40)	18 (17.14)	0.433
	Negative	275 (76.60)	87 (82.86)	
TgAb	Positive	62 (17.27)	16 (15.24)	0.624
	Negative	297 (82.73)	89 (84.76)	
HT	Yes	118 (32.87)	25 (23.81)	0.077
	No	241 (67.13)	80 (76.19)	

BMI — body mass index; TSH — thyroid-stimulating hormone; TPOAb — anti-thyroid peroxidase antibody; TgAb — anti-thyroglobulin antibody; HT — Hashimoto's thyroiditis

Analysis of risk factors for DTC

As shown in Table 2, results from the univariate logistic regression analysis showed that age < 55 years, female sex, solid composition, hypoechogenicity, irregular margin, microcalcification, taller-than-wide, and cervical lymphadenopathy were significantly associated with DTC ($p < 0.05$). Smoking, Hashimoto's thyroiditis, TPOAb positivity, and TgAb positivity were not associated with DTC ($p > 0.05$).

Multivariate logistic regression analysis was performed with DTC as a dependent variable and with statistically significant variables from univariate regression analysis as independent variables, to analyse the risk factors for DTC. The independent risk factors of DTC included female sex [odds ratio (OR): 2.145, 95% confidence interval (CI): 1.071–4.296], age < 55 years (OR: 2.225, 95% CI: 1.176-4.210), solid composition (OR: 3.708, 95% CI: 1.851-7.430), hypoechogenicity

Table 2. *Logistic regression analysis of risk factors for differentiated thyroid cancer (DTC)*

Variables	Subgroups	Univariable		Multivariable	
		OR (95% CI)	p	OR (95% CI)	p
Gender	Male	Ref.		Ref.	
	Female	1.905 (1.197–3.031)	0.007	2.145 (1.071–4.296)	0.031
Age (years)	≥ 55	Ref.		Ref.	
	< 55	2.640 (1.689–4.127)	0.000	2.225 (1.176–4.210)	0.014
Smoking	No	Ref.			
	Yes	0.443 (0.195–1.008)	0.052		
Solid composition	No	Ref.		Ref.	
	Yes	7.388 (4.508–12.109)	0.000	3.708 (1.851–7.430)	0.000

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Table 2. *Logistic regression analysis of risk factors for differentiated thyroid cancer (DTC)*

Hypoechogenicity	No	Ref.		Ref.	
	Yes	9.342 (5.702–15.305)	0.000	6.228 (3.111–12.469)	0.000
Irregular margin	No	Ref.		Ref.	
	Yes	12.324 (6.376–23.822)	0.000	3.915 (1.819–8.427)	0.000
Microcalcification	No	Ref.		Ref.	
	Yes	5.448 (3.276–9.060)	0.000	5.046 (2.547–9.997)	0.000
Taller-than-wide	No	Ref.		Ref.	
	Yes	16.331 (5.881–45.354)	0.000	8.698 (2.759–27.420)	0.000
Lymphadenopathy	No	Ref.		Ref.	
	Yes	2.016 (1.092–3.722)	0.025	2.480 (1.120–5.490)	0.025
TSH [uIU/mL]		1.027 (0.898–1.174)	0.702		
HT	No	Ref.			
	Yes	1.567 (0.950–2.584)	0.078		
TPOAb-positivity	No	Ref.			
	Yes	1.476 (0.841–2.593)	0.175		
TgAb-positivity	No	Ref.			
	Yes	1.161 (0.638–2.113)	0.625		

TSH — thyroid-stimulating hormone; HT — Hashimoto's thyroiditis; TPOAb — anti-thyroid peroxidase antibody; TgAb — anti-thyroglobulin antibody

(OR: 6.228, 95% CI: 3.111–12.469), irregular margin (OR: 3.915, 95% CI: 1.819–8.427), microcalcification (OR: 5.046, 95% CI: 2.547–9.997), taller-than-wide (OR: 8.698, 95% CI: 2.759–27.420), and cervical lymphadenopathy (OR: 2.480, 95% CI: 1.12025.490) ($p < 0.05$).

Establishment and validation of the predictive nomogram for DTC

In this study, the predictive nomogram was constructed based on risk factors of DTC. The total score, which was calculated according to the corresponding score of each predictive factor, can be used to estimate the incidence probability of DTC (Fig. 1). ROC curve analysis was performed to evaluate the accuracy of the nomogram model. As shown in Figure 2, the AUC of model was 0.920 (95% CI: 0.888–0.952, $p < 0.05$), which showed good discrimination ability. The best threshold for predicting DTC was 52.4%. The sensitivity, specificity, positive predictive value, and negative predictive value were 0.919, 0.810, 0.943, and 0.746, respectively.

Discussion

Thyroid nodules are focal lesions of the thyroid gland due to abnormal growth of thyroid cells, including benign nodules (such as adenoma) and malignant tumours [11]. Because benign and malignant thyroid nodules are treated in completely different ways, it is essential to distinguish benign and malignant nodules and conduct timely and correct clinical intervention for malignant tumours. DTC, including papillary carcinoma, follicular carcinoma, and Hürthle cell carcinoma, is the most common histological type of thyroid carcinoma, and most thyroid cancer deaths are from DTC [12]. Therefore, our research subjects were patients with DTC. In this study, the incidence of DTC was 77.37%, which was higher than reported in previous studies [13]. The discrepancy may be caused by the difference of the study population. In those studies, the prevalence was in the general population without a history of thyroid disease. While in this study, the population were selected after thyroidectomy. In clinical practice, most thyroid nodules requiring surgical treatment are malignant, because benign pathology can be treated in most cases with alternative approaches.

Previous studies have suggested that both thyroid nodule and thyroid cancer are more common in women than in men [14, 15], but the reason for this difference is not clear, which may be related to the proliferation of thyroid cells stimulated by oestrogen [15]. This study showed that the frequency of women was significantly higher in patients with thyroid nodules and DTC, and female gender was the independent risk factor for DTC ($p < 0.05$), which was consistent with the above findings.

In this study, the results showed that the mean age and the proportion of age ≥ 55 years in the DTC group were significantly lower than those in benign group ($p < 0.05$). DTC occurred 2.225-fold more often in patients < 55 years old than in cases ≥ 55 years old

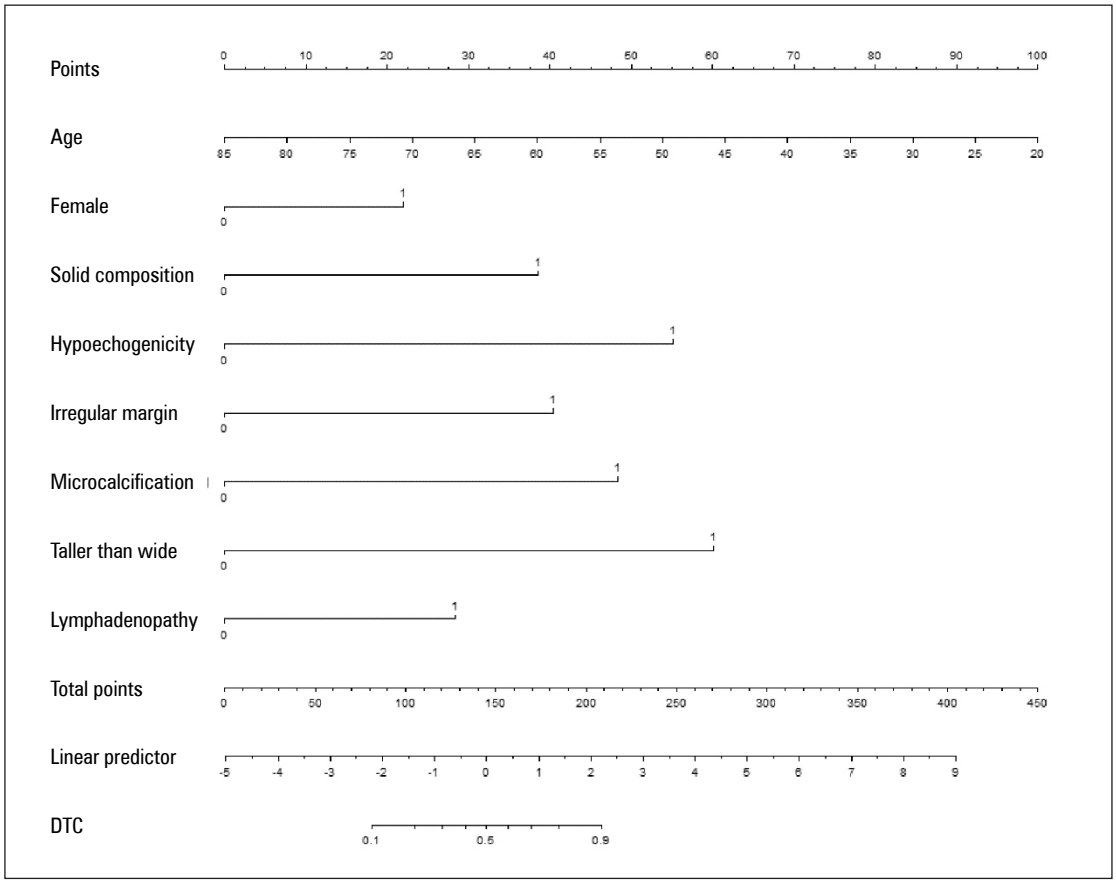

Figure 1. *Nomogram for predicting differentiated thyroid cancer. Instructions: The corresponding score of each predictor can be obtained separately on the point scale axis. The total score was calculated by adding the point score from each variable. Then, we can estimate the incidence probability of differentiated thyroid cancer (DTC) by projecting the total point onto the bottom axis*

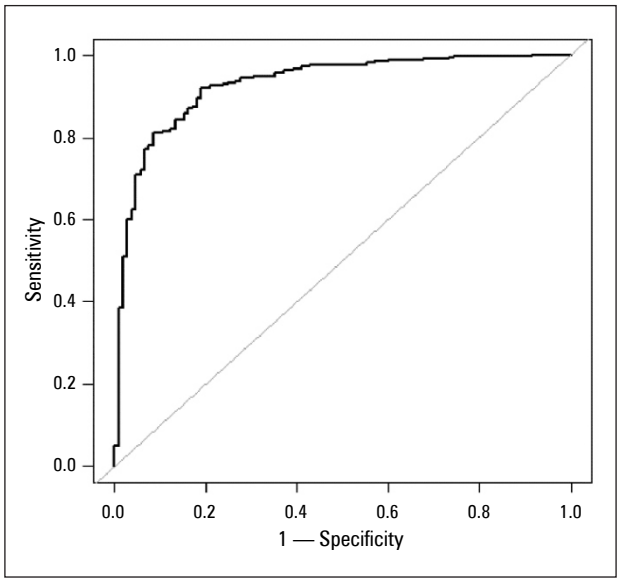

Figure 2. *Receiver operating characteristics (ROC) curve of the predictive nomogram for differentiated thyroid cancer. The predictive accuracy [area under the curve (AUC)] was 0.920 [95% confidence interval (CI): 0.888–0.952]*

(95% CI: 1.176–4.210, $p < 0.05$). Many previous studies also support that young patients with thyroid nodules comprise the high-risk population of DTC [8, 16].

The malignant risk of thyroid nodules is raised with the increase of serum TSH concentration, and previous studies have shown that TSH is an independent predictor of thyroid cancer [17, 18]. In this study, the median level of TSH in the DTC group was higher than that in the benign group (1.97 *vs*. 1.90 uIU/mL), but the difference was not statistically significant, which was not consistent with previous research.

A pooled analysis of 5 prospective studies in the United States by Kitahara found that smoking was associated with reduced risk of thyroid cancer [hazard ratio (HR) = 0.68, 95% CI: 0.55–0.85] [19]. The mechanism may be that smoking can reduce TSH concentration. Our study also showed that the proportion of smoking was lower in the DTC group than in the benign group (4.46% *vs*. 9.52%, $p < 0.05$), but there was no negative correlation between smoking and DTC ($p > 0.05$).

Since Virchow proposed a link between chronic inflammation and cancer in 1863, a large amount of clinical and epidemiological evidence has confirmed that chronic inflammation, which may be a kind of precancerous lesion, can eventually lead to cancer [20, 21]. Hashimoto's thyroiditis (HT) is one of the most common chronic inflammatory thyroid diseases, which is characterized by lymphocytic infiltration in thyroid tissue. Many studies [22–25] have found a significant association between HT and TC, especially follicular thyroid cancer (FTC). The coexistence rate of HT and PTC was 12.1–72.7% [22]. A retrospective analysis of 7545 patients undergoing thyroidectomy by Konturek A et al. reported that the incidence of DTC in patients with HT was 3 times higher than that in patients without HT [23]. Data from a meta-analysis showed that, compared with cases with benign nodules, PTC patients were more likely to have HT [24]. However, recently a retrospective longitudinal cohort study suggested that patients with chronic autoimmune thyroiditis were not at higher risk for developing clinically thyroid cancer during a 10-year median follow-up period [25]. Anti-thyroid antibodies, especially TPOAb and TgAb, are often significantly elevated in patients with HT. Some studies demonstrated that TgAb and TPO positivity were risk factors for DTC [26, 27]. The present research showed that the rate of HT, and TPOAb/TgAb positivity in the DTC group, were slightly higher than those in the benign group, but the differences were not statistically significant ($p > 0.05$). In this study, HT and TPOAb/TgAb positivity were not associated with the occurrence of DTC by logistic regression analysis ($p > 0.05$).

Patients with thyroid cancer usually have no symptoms or non-specific symptoms. Therefore, early diagnosis is a major problem and a challenge for every clinical worker. Fine needle aspiration biopsy is the gold standard for preoperative diagnosis of thyroid cancer. However, because it is an invasive examination with risks such as wound infection and bleeding, patient acceptance is low, and given its high professional requirements, it is not widely performed in clinics. Thyroid ultrasound plays a key role in the detection of thyroid nodules and the differential diagnosis of benign and malignant nodules because of its advantages such as economy, convenience, non-invasive damage, and non-radioactive exposure [28]. Similarly to previous studies [10, 29], this research showed that thyroid nodule patients with the following ultrasonic features: solid composition, hypoechogenicity, irregular margin, microcalcification, taller-than-wide, and cervical lymphadenopathy, were at higher risk of DTC ($p < 0.05$). Although ultrasound is a primary tool used for screening of thyroid cancer, the accuracy of the identification only based on ultrasonic manifestations is slightly poor when other risk factors are ignored. A nomogram can combine multiple indicators to predict the occurrence and development of diseases. In the current study, a nomogram model for predicting DTC was established based on the clinical parameters and sonographic features of the patients, which can improve the accuracy of screening and can intuitively and individually display the incidence probability of DTC, which help clinicians and patients to more easily access and understand the risk of DTC. In our study, the nomogram model had an excellent predictive accuracy of 92.0%, and the best cut-off value for prediction was 52.4%, with sensitivity and specificity of 91.9% and 81.0%, respectively, which indicated that patients with the risk rate greater than 52.4% should undergo further FNAB or surgical evaluation.

There were several strengths to this study. Firstly, the predictive model of this study was established by integrating the risk factors of DTC including clinical data and ultrasonic images, which effectively improved the accuracy of prediction. Secondly, compared with previous mathematical prediction models, the nomogram enabled the visualization of predictive results, which can help clinicians more easily distinguish benign and malignant thyroid nodules. This study also had some limitations. Firstly, this was a single-centre retrospective study, the subjects were inpatients with postoperative pathologic data, and the sample size was relatively small, which may result in selection bias. Secondly, the model was only internally validated. Therefore, multi-centre and larger sample studies with external validation are necessary to confirm the predictive effectiveness of this model in the future.

Conclusions

Accurate differentiation between benign and malignant thyroid nodules and timely intervention for malignant nodules are critical clinical priorities in the management of thyroid nodules. In this study, we developed a simple, noninvasive, and reliable method for predicting DTC, and we found that the best threshold for predicting DTC was 52.4%. Based on this finding, it is recommended that patients with a risk rate exceeding the threshold should undergo further evaluation, such as FNAB or surgical assessment.

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Authors' contributions

J.D., W.L., and X.Z. (Xiaomei Zhang) contributed to conception and design of the study. J.D., W.L., X.Z. (Xin Zhao), and C.S. or-

ganized the database. J.D., W.L., and X.Z. (Xin Zhao) performed the statistical analysis. J.D. wrote the first draft of the manuscript. J.D., W.L., and X.Z. (Xiaomei Zhang) finally revised the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Peking University International Hospital. This is an observational and retrospective study with no potential damage to the subjects. Individual identifiable information and privacy of the subjects were not involved in the study. For this study it was sanctioned that the informed consent of the participant was not required by the Ethics Committee of Peking University International Hospital.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

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