Original Article

Nomograms for predicting cervical central lymph node metastases and high-volume cervical central lymph node metastases in papillary thyroid carcinoma

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Background: Cervical central lymph node metastasis (CLNM) is a known risk factor for recurrent thyroid cancer (TC), and cervical high-volume central lymph node metastases (HVCLNM) are associated with higher recurrence rates and shorter disease-specific survival. The status of CLNM is critical in determining surgical strategies for papillary thyroid carcinoma (PTC). We developed two separate nomograms to predict the probability of CLNM and HVCLNM.

Methods: We retrospectively analyzed 590 PTC patients who underwent total thyroidectomy or lobectomy with central lymph node dissection (CLND) between January 2020 and May 2023. Univariate and multivariate analyses were conducted to identify risk factors associated with CLNM and HVCLNM. The nomograms were internally validated using bootstrapping and evaluated on a temporal validation cohort.

Results: Between January 2020 and May 2023, 1,019 patients were screened, 590 (57.9%) were eligible, and they were divided into development (n=353) and validation (n=237) cohorts. HVCLNM was present in 41 patients (11.6%). The variables with the strongest predictive value for CLNM were younger age (P<0.001), male sex (P=0.045), tumor size (P<0.001), and tumor multifocality (P=0.001). The strongest predictors for HVCLNM were younger age (P=0.001), tumor size (P<0.001), bilateral lesions (P=0.005), and preoperative serum thyroid peroxidase antibody (TPOAb) ≤14.95 IU/mL (P=0.01). The area under the curve (AUC) for the CLNM model was 0.75, with similar results achieved in internal validation (0.74) and external validation (0.68). The AUC for the HVCLNM model was 0.80, with similar values in internal validation (0.79) and external validation (0.79). Both models demonstrated good calibration, with predictions closely aligning with observed outcomes.

Conclusions: Based on the quantified risk stratification offered by our nomograms, clinicians can engage in comprehensive preoperative discussions with PTC patients. Prophylactic CLND and strict postoperative evaluation may be recommended for patients with high nomogram scores.

Keywords: Papillary thyroid carcinoma (PTC); cervical high-volume central lymph node metastases (cervical HVCLNM); thyroid peroxidase antibody (TPOAb); nomogram

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Introduction

Thyroid cancer (TC) is currently the fastest-growing endocrine malignancy worldwide, with papillary thyroid carcinoma (PTC) comprising more than 90% of cases (1,2). Most cases of PTC progress slowly and can achieve a favorable prognosis with appropriate treatment (3). However, the occurrence rate of cervical lymph node metastasis (LNM) in PTC patients ranges from 20% to 90% (4-6), making it a significant risk factor for increased recurrence rates. High-volume lymph node metastasis (HVLNM) is defined as the presence of more than five metastatic lymph nodes (6). Increasing evidence suggests that patients with HVLNM experience poorer outcomes compared to those with low-volume lymph node metastasis, including higher recurrence rates and worse disease-free survival (7,8). The recurrence rates for PTC patients with five or fewer and more than five involved lymph nodes (pN1PTC) are 5% and 20%, respectively. Consequently, the 2015 American Thyroid Association (ATA) guidelines identify more than five pathologic lymph nodes (smaller than 3 cm) as characteristics of intermediate-risk patients in postoperative risk stratification (6). Furthermore, the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for oncology (thyroid carcinoma, version 2.2022) recognize HVLNM as an adverse pathological characteristic, recommending total thyroidectomy and subsequent radioactive iodine (RAI) therapy when HVLNM is identified after lobectomy and ipsilateral central lymph node dissection (CLND) (9). However, the accuracy of ultrasound and cervical computed tomography (CT) scans for detecting preoperative cervical central lymph node metastasis (CLNM) is limited (10). Studies indicate that current clinical examination methods are not sensitive enough to diagnose hidden CLNM, with approximately 60–70% of CLNM cases going undetected by ultrasound or CT scans (11,12).

This study evaluated the clinical factors associated with cervical LNM and aimed to develop a model to predict the development of cervical LNM in PTC patients, including CLNM and high-volume central lymph node metastasis (HVCLNM). Our results may inform the management strategy for PTC patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-237/rc).

Highlight box

Key findings

- The nomograms, based on preoperative ultrasound tumor characteristics and thyroid peroxidase antibody (TPOAb), effectively predict both cervical central lymph node metastases (CLNM) in papillary thyroid carcinoma. The predictive factors include age, sex, tumor size, multifocality, bilateral lesions, and preoperative serum TPOAb levels.

What is known and what is new?

- Several risk factors for cervical CLNM have been identified, such as age, male sex, tumor size, multifocality, and bilateral lesions. Various predictive models have been developed to enhance the accuracy of risk assessment for cervical central lymph node metastases utilizing these factors.
- Our study identified younger age, tumor size, bilateral lesions, and preoperative serum TPOAb ≤14.95 IU/mL as independent indicators for cervical high-volume central lymph node metastases (HVCLNM). Preoperative tumor ultrasound characteristics and TPOAb levels can be readily acquired before surgery, thus aiding in the preoperative assessment of HVCLNM in PTC.

What is the implication, and what should change now?

- TPOAb can serve as an independent predictive factor for HVCLNM. The significance of this study is to provide new insights for clinical doctors in predicting HVCLNM. Further investigations are warranted to elucidate the precise mechanisms through which varying levels of TPOAb influence LNM in PTC.

Methods

Patient identification

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval was granted by the ethics committee of the Guangzhou First People's Hospital (the Second Affiliated Hospital, School of Medicine, South China University of Technology), approval No. K-2023-135-01. The requirement for written informed consent to participate was waived due to the retrospective nature of the study. All patient data were anonymized to protect confidentiality.

Data from 1,019 patients who underwent surgery for TC between 2020 and 2023 at the Department of Thyroid Surgery of the Guangzhou First People's Hospital (Guangzhou, Guangdong, the People's Republic of China) were retrospectively collected. The process of selecting the qualified patients for analysis is illustrated in *Figure 1*. A total of 590 patients diagnosed with PTC were divided into two cohorts: a training cohort (n=353) and a validation cohort (n=237). The training cohort included patients from January 2020 to August 2022, while the validation cohort encompassed patients from September 2022 to May 2023.

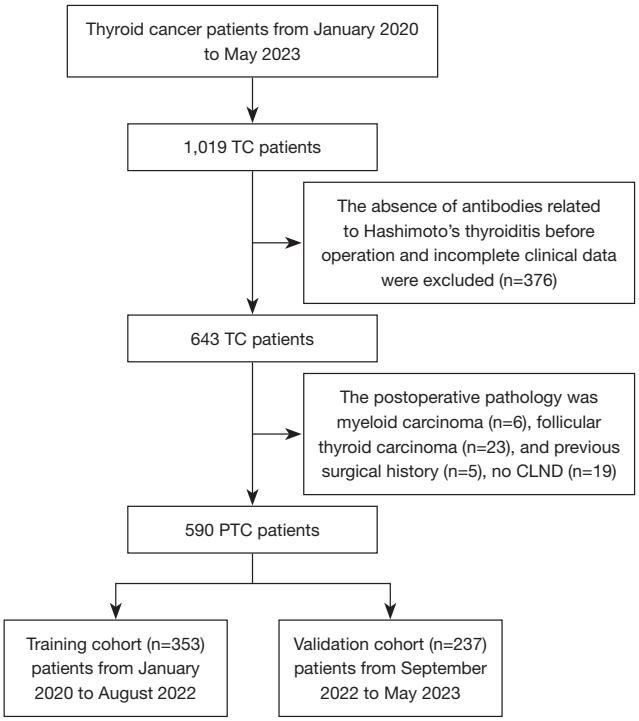

Figure 1 PTC patients exclusion flowchart. CLND, central lymph node dissection; PTC, papillary thyroid carcinoma; TC, thyroid cancer.

Variables such as demographic information, preoperative serum autoantibody levels, ultrasound tumor characteristics, pathological diagnosis, and treatment modalities were extracted from medical records. Patients with follicular, medullary, or anaplastic thyroid carcinoma, those who underwent a second surgery, experienced disease recurrence, or had incomplete examination records were excluded. Additionally, patients who did not undergo CLND were excluded from this study. General demographic information including age, sex, and body mass index (BMI), was recorded. Ultrasound reports were prepared by at least two ultrasound physicians, and tumor characteristics such as size, multifocality, and extrathyroidal extension (ETE) were documented. Surgical pathology reports documented the pathological type, the number of central/lateral lymph nodes removed, and the number of lymph nodes with metastatic carcinoma. Serum antithyroglobulin and antithyroid peroxidase levels were measured within 30 days before surgery using the immune-electrochemiluminescence method. The normal ranges for serum levels of thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) were 0–115 and 0–34 IU/mL, respectively. The presence of diffuse lesions was confirmed by ultrasound, and the diagnosis of Hashimoto's thyroiditis was supported by elevated serum levels of TgAb or TPOAb. Age was categorized as ≤45 or >45 years, and tumor size was defined by its largest dimension. Multifocality was defined as the presence of more than one suspected malignant lesion in the same lobe, while ETE was determined by suspected ETE observed on ultrasound. Suspicious malignant lesions were defined as having an American College of Radiology (ACR) score greater than 4. All scores were calculated using the 2017 ACR Thyroid Imaging-Reporting and Data System (TI-RADS) standard (13). Central lymph nodes included the central compartment, paratracheal, and laryngeal/Delphian lymph nodes (equivalent to pathologic stage N1a). Lateral lymph nodes included unilateral, bilateral, or contralateral cervical (levels I–V), retropharyngeal, or superior mediastinal (level VII) lymph nodes (equivalent to pathologic stage N1b).

Surgical strategy

According to the guidelines for the diagnosis and management of thyroid nodules and differentiated TC in China, nearly all patients at our institution with TC routinely undergo CLND. Lobectomy combined with isthmectomy and ipsilateral CLND was typically performed as the initial surgical treatment for PTC patients with malignant lesions confined to a single lobe. When malignant lesions were present in both thyroid lobes, a total thyroidectomy and bilateral CLND were performed. Lateral lymph node dissection (LLND), encompassing levels II–V, was performed exclusively only in cases with clinically confirmed lateral neck lymph node metastasis (LLNM).

Statistical analysis

This study utilized the Statistical Package for the Social Sciences (SPSS) for Windows, Version 25.0 (SPSS Inc., Chicago, IL, USA) and R version 4.3.1. Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as frequencies (%). The Student's *t*-test or one-way analysis of variance (ANOVA) was used to analyze normally distributed continuous variables, while non-normally distributed variables were analyzed using non-parametric tests. The Pearson Chi-squared test was employed to analyze categorical variables. In this study, risk factors for CLNM and HVCLNM were assessed, and preoperative laboratory data (blood

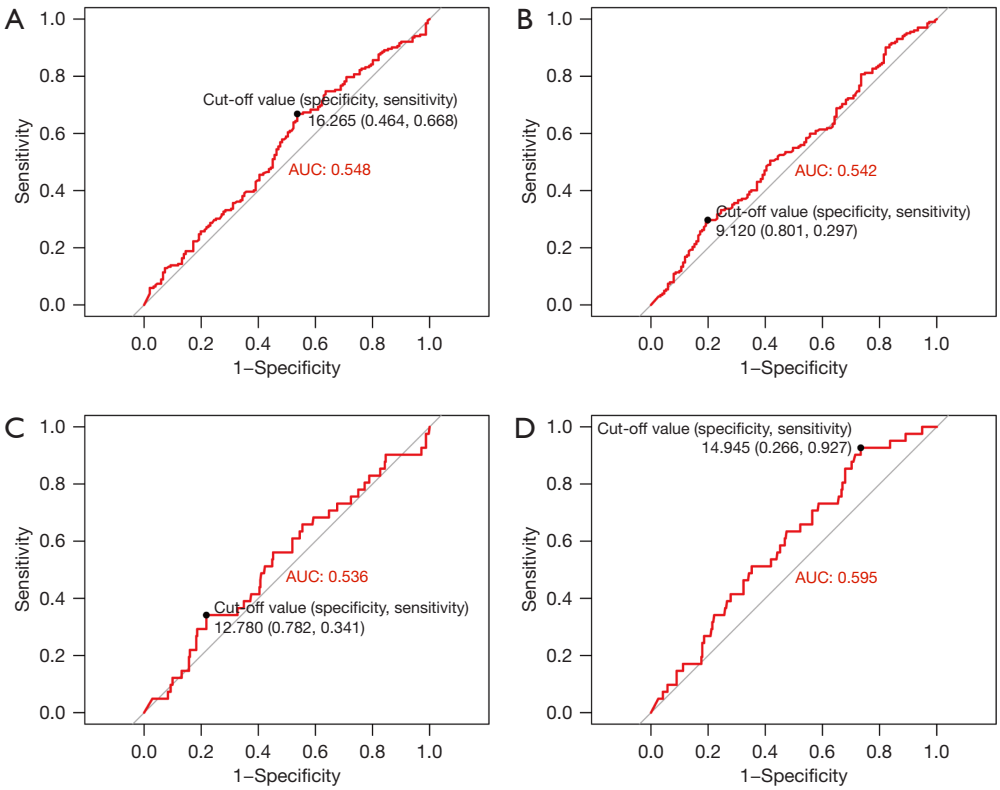

Figure 2 ROC curve and optimal cut-off value of TgAb-CLNM (A), TPOAb-CLNM (B), TgAb-HVCLNM (C), TPOAb-HVCLNM (D). AUC, area under the curve; CLNM, central lymph node metastasis; HVCLNM, high-volume central lymph node metastasis; ROC, receiver operating characteristic; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

chemistry analysis) for serum TPOAb and TgAb were treated as continuous variables. Receiver operating characteristic (ROC) curves for TPOAb-CLNM, TPOAb-HVCLNM, TgAb-CLNM, and TgAb-HVCLNM were initially plotted (*Figure 2*). Continuous variables were then transformed into categorical variables using optimal cutoff values for analysis. Subsequently, variables were categorized and screened for risk factors for CLNM and HVCLNM using univariate analysis along with other risk factors. Multivariate logistic regression was employed to construct two nomogram models that separately predict the contributing factors of CLNM and HVCLNM, based on statistically significant variables from univariate analysis. The performance of the logistic regression model was internally validated using bootstrapping, with temporal validation (external validation) performed using data collected from patients between September 2022 and May 2023. To evaluate the nomogram's predictive ability, a ROC curve was plotted, and the area under the curve (AUC) was calculated. A calibration plot was generated to show the difference between the nomogram's predicted outcomes and actual results, demonstrating the model's accuracy. Finally, decision curve analysis (DCA) was conducted to provide a more comprehensive evaluation of the model. During the validation process, the data of patients in the internal validation cohort and the external validation dataset were input into the nomograms of the training cohort. Predicted probabilities were calculated, and corresponding ROC curves, calibration plots, and DCA curves were then generated to assess the predictive value of the model in practical applications. The model training and validation were both implemented using R version 4.3.1. Statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

Characteristics of PTC patients

The training cohort of this study comprised 353 patients

Table 1 Clinical and ultrasound tumour characteristics of patients

Characteristics	Training cohort (N=353)
Age (years)	
>45	156 (44.2)
≤45	197 (55.8)
Gender	
Male	110 (31.2)
Female	243 (68.8)
Tumor size (cm)	
≤1	224 (63.5)
>1	129 (36.5)
ETE	
Absent	297 (84.1)
Present	56 (15.9)
Bilateral lesions	
Absent	302 (85.6)
Present	51 (14.4)
Multifocality	
Absent	231 (65.4)
Present	122 (34.6)
HT	
Absent	311 (88.1)
Present	42 (11.9)
CLNM	
Absent	151 (42.8)
Present	202 (57.2)
HVCLNM	
Absent	312 (88.4)
Present	41 (11.6)
TPOAb (IU/mL)	22.7±66.9
TgAb (IU/mL)	85.2±336.3
BMI (kg/m^2)	23.8±3.6

Data are presented as n (%) or mean ± standard deviation. BMI, body mass index; CLNM, central lymph node metastasis; ETE, extrathyroidal extension; HT, Hashimoto thyroiditis; HVCLNM, high-volume central lymph node metastasis; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

who were diagnosed with PTC through definitive histological examination. Among these patients, 68.8% were female (243 cases) and 31.2% were male (110 cases). Furthermore, 44.2% of the patients were aged >45 years (156 cases). Tumor size greater than 1 cm was observed in 36.5% of patients (129 cases), and ETE was observed in 15.9% of tumors (56 cases). Multifocality was present in 34.6% of patients (122 cases), bilateral lesions were present in 14.4% of patients (51 cases), and Hashimoto's thyroiditis was detected in 11.9% of patients (42 cases). Among them, CLNM was present in 57.2% of cases (202 cases), while the incidence of HVCLNM was 11.6% (41 cases) (*Table 1*).

Univariate and multivariate analyses on CLNM risk factors

In the univariate analysis, age (P<0.001), gender (P=0.005), tumor size (P<0.001), bilateral lesions (P=0.007), and multifocality (P<0.001) were closely related to CLNM. Logistic regression modeling identified several variables significantly associated with CLNM, including age ≤45 years [odds ratio (OR) =2.67, 95% confidence interval (CI): 1.645 to 4.333; P<0.001], male sex (OR =1.745, 95% CI: 1.012 to 3.009; P=0.045), tumor size >1.0 cm (OR =3.888, 95% CI: 2.3 to 6.57; P<0.001), multifocality (OR =2.797, 95% CI: 1.514 to 5.168; P=0.001) (*Table 2*).

Univariate and multivariate analyses on HVCLNM risk factors

In the univariate analysis, age (P=0.001), tumor size (P<0.001), bilateral lesions (P<0.001), multifocality (P=0.006), and TPOAb (P=0.047) were closely related to HVCLNM. Logistic regression modeling identified variables to be significantly associated with HVCLNM, including age ≤45 years (OR =3.968, 95% CI: 1.651 to 9.539; P=0.001), tumor size >1 cm (OR =5.979, 95% CI: 2.731 to 13.092; P<0.001), bilateral lesions (OR =4.287, 95% CI: 1.51 to 12.165; P=0.005) and TPOAb (OR =5.443, 95% CI: 1.498 to 19.775; P=0.01) (*Table 3*).

Nomograms for predicting CLNM and HVCLNM in PTC patients

To delve deeper into the proportion of each risk factor

Table 2 Univariate and multivariate analyses of risk factors associated with CLNM in PTC patients

Characteristics	All patients (N=353)		P value	Multivariate analysis adjusted OR (95% CI)	$P_{adj.}$ value
	Non-CLNM (n=151)	CLNM (n=202)			
Age (years)					
Mean ± SD	46.7±11.8	41.6±12.4	<0.001		
>45	87 (57.6)	69 (34.2)	<0.001	Reference	
≤45	64 (42.4)	133 (65.8)		2.67 (1.645–4.333)	<0.001
Gender					
Male	35 (23.2)	75 (37.1)	0.005	Reference	
Female	116 (76.8)	127 (62.9)		1.745 (1.012–3.009)	0.045
Tumor size (cm)					
Mean ± SD	0.80±0.6	1.2±0.9	<0.001		
≤1	120 (79.5)	104 (51.5)	<0.001	Reference	
>1	31 (20.5)	98 (48.5)		3.888 (2.3–6.57)	<0.001
Extrathyroidal extension					
Absent	130 (86.1)	167 (82.7)	0.38	–	
Present	21 (13.9)	35 (17.3)		–	
Multifocality					
Absent	117 (77.5)	114 (56.4)	<0.001	Reference	
Present	34 (22.5)	88 (43.6)		2.797 (1.514–5.168)	0.001
Bilateral lesions					
Absent	138 (91.4)	164 (81.2)	0.007	Reference	
Present	13 (8.6)	38 (18.8)		1.562 (0.667–3.66)	0.30
HT					
Absent	127 (84.7)	184 (91.1)	0.045	Reference	
Present	24 (15.9)	18 (8.9)		1.021 (0.448–2.328)	0.96
BMI (kg/m^2)				–	
Mean ± SD	23.9±3.6	23.7±3.8	0.83		
BMI <24	81 (53.6)	114 (56.4)	0.68	–	
BMI ≥24	70 (46.4)	88 (46.3)			
TgAb (IU/mL)					
Mean ± SD	83.2±28.0	86.7±331.0	0.92		
TgAb >16.27	70 (46.4)	67 (33.2)	0.01	Reference	
TgAb ≤16.27	81 (53.6)	135 (66.8)		1.644 (0.952–2.838)	0.08
TPOAb (IU/mL)					
Mean ± SD	26.1±74.7	20.2±60.5	0.41		
TPOAb >9.12	121 (80.1)	142 (70.3)	0.04	Reference	
TPOAb ≤9.12	30 (19.9)	60 (29.7)		1.507 (0.854–2.66)	0.16

Data are presented as n (%) unless otherwise specified. The P value <0.05, which is statistically significant. BMI, body mass index; CI, confidence interval; CLNM, central lymph node metastasis; HT, Hashimoto thyroiditis; OR, odds ratio; SD, standard deviation; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

Table 3 Univariate and multivariate analyses of risk factors associated with HVCLNM in PTC patients

Characteristics	All patients (N=353)		P value	Multivariate analysis adjusted OR (95% CI)	$P_{adj.}$ value
	Non–HVCLNM (n=312)	HVCLNM (n=41)			
Age (years)					
Mean ± SD	44.58±12	37.95±10	0.001		
>45	140 (44.9)	8 (19.5)	0.002	Reference	
≤45	172 (55.1)	33 (80.5)		3.968 (1.651–9.539)	0.001
Gender					
Male	92 (29.5)	18 (43.9)	0.06	–	
Female	220 (70.5)	23 (56.1)		–	
Tumor size (cm)					
Mean ± SD	0.97±0.7	1.60±1.0	<0.001		
≤1	211 (67.6)	11 (26.8)	<0.001	Reference	
>1	101 (32.4)	30 (73.2)		5.979 (2.731–13.092)	<0.001
Extrathyroidal extension					
Absent	256 (82.1)	30 (73.2)	0.17	–	
Present	56 (17.9)	11 (26.8)		–	
Multifocality					
Absent	212 (67.9)	19 (46.3)	0.006	Reference	
Present	100 (32.1)	22 (53.7)		1.543 (0.632–3.767)	0.34
Bilateral lesions					
Absent	274 (87.8)	27 (65.9)	<0.001	Reference	
Present	38 (12.2)	14 (34.1)		4.287 (1.51–12.165)	0.005
HT					
Absent	272 (87.2)	39 (95.1)	0.20	–	
Present	40 (12.8)	2 (4.9)			
BMI (kg/m^2)				–	
Mean ± SD	23.8±3.7	23.2±3.7	0.24		
BMI <24	173 (55.4)	22 (53.7)	0.83	–	
BMI ≥24	139 (44.6)	19 (46.3)			
TgAb (IU/mL)				–	
Mean ± SD	74.0±15.3	170.3±101	0.35		
TgAb >12.78	68 (21.8)	14 (34.1)	0.08	–	
TgAb ≤12.78	244 (78.2)	27 (65.9)			
TPOAb (IU/mL)					
Mean ± SD	24.2±4.0	11.1±0.7	0.047		
TPOAb >14.95	83 (26.6)	3 (7.3)	0.007	Reference	
TPOAb ≤14.95	229 (73.4)	38 (92.7)		5.443 (1.498–19.775)	0.01

The P value <0.05, which is statistically significant. Data are presented as n (%) unless otherwise specified. BMI, body mass index; CI, confidence interval; HT, Hashimoto thyroiditis; HVCLNM, high-volume central lymph node metastasis; OR, odds ratio; SD, standard deviation; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

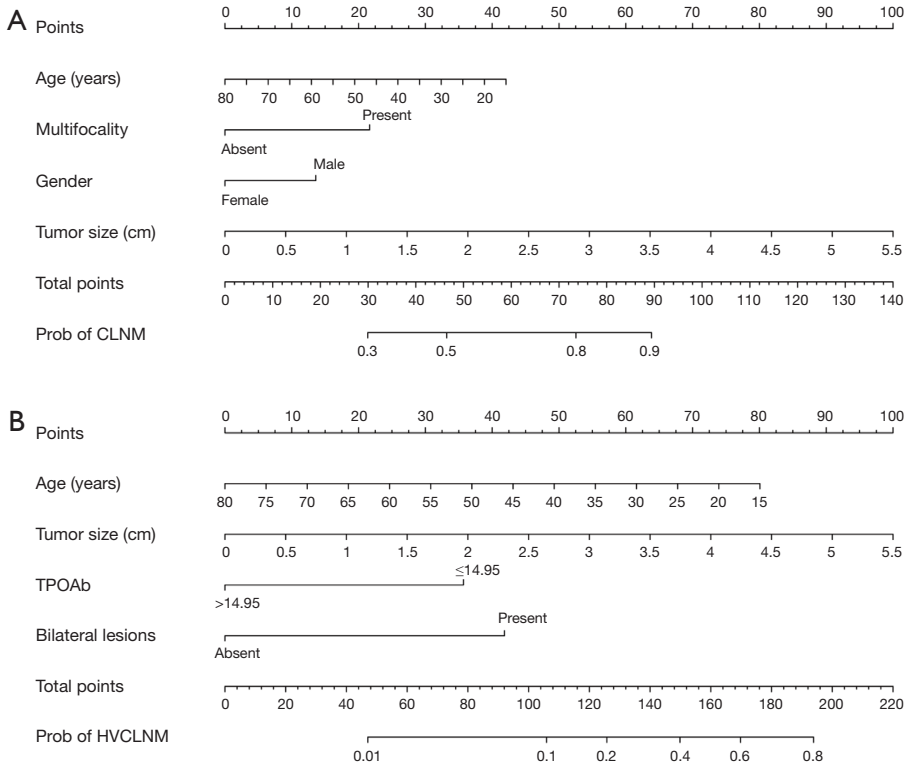

Figure 3 Nomograms based on clinical characteristics present the risk factors for CLNM (A) and HVCLNM (B). CLNM, central lymph node metastasis; HVCLNM, high-volume central lymph node metastasis; TPOAb, thyroid peroxidase antibody.

for CLNM or HVCLNM, we visualized each factor as a line and created the corresponding nomogram. *Figure 3* showcases two new nomograms, with each variable represented as a point ranging from 0 to 100 based on its regression coefficient for CLNM or HVCLNM. We drew a straight line for each variable according to its appropriate score, and the resulting scores were added up and placed on the total score axis to represent the variable value. The nomograms demonstrated that the maximal tumor size was the primary factor for both CLNM and HVCLNM. In clinical practice, the TPOAb value and ultrasound-related tumor characteristics are obtained preoperatively. Subsequently, the corresponding variable values were inputted into the nomogram model to derive the scores for each variable. The total score was calculated by summing these individual scores, which was then positioned on the total score axis to ascertain the probability of HVCLNM or CLNM occurrence.

Calibration and validation of the nomograms

The efficiency of the model was evaluated through ROC analysis on both the training and verification cohorts, with the acquisition of AUCs (also known as C-statistic). In the training cohort, the AUC value was 0.752 (sensitivity: 0.624, specificity: 0.795), in the internal validation, the AUC value was 0.738 (sensitivity: 0.573, specificity: 0.751), and in the temporal validation cohort, the AUC value was 0.680 (sensitivity: 0.593, specificity: 0.702) (*Figure 4A*,*4B*). These results provide conclusive evidence of the reliability of the CLNM prediction model in making accurate predictions. Similarly, in the HVCLNM prediction model, the AUC value was 0.805 (sensitivity: 0.756, specificity: 0.763) in the training cohort, 0.785 (sensitivity: 0.978, specificity: 0.851) in the internal validation cohort, and 0.786 (sensitivity: 0.750, specificity: 0.810) in the temporal validation cohort (*Figure 4C*,*4D*). These AUC values serve as unequivocal evidence of the prediction capabilities of the HVCLNM nomogram.

Furthermore, calibration plots were conducted to verify the accuracy and repeatability of our nomogram models. Positive agreements were observed between the actual and predicted probabilities of CLNM in both the training cohort [mean absolute error (MAE) =0.009] and the validation cohort (MAE =0.015) (*Figure 5A*,*5B*). Similarly, for HVCLNM, the

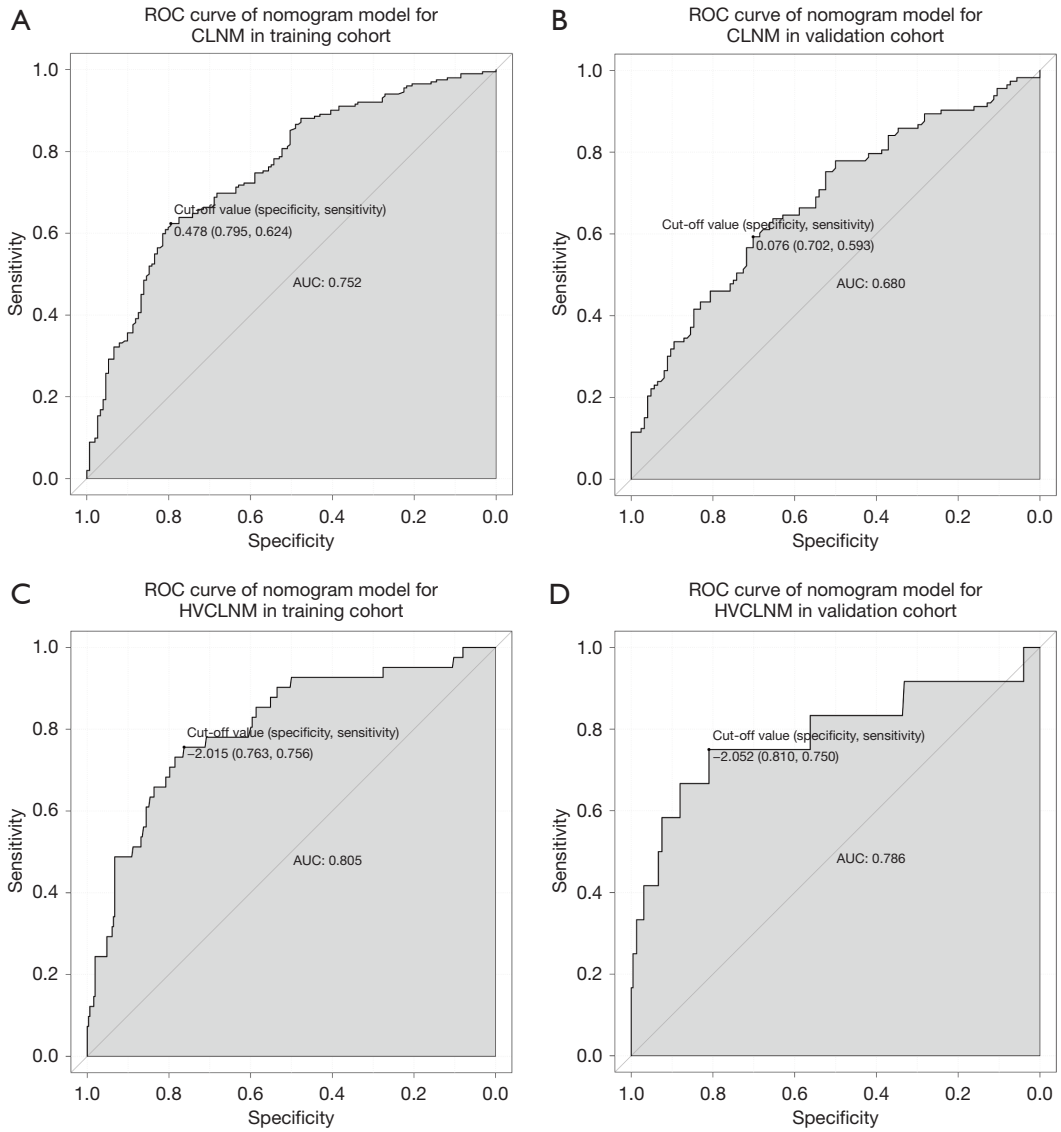

Figure 4 ROC curve shows nomogram predication model for CLNM in training cohort (A), and in validation cohort (B), in addition to the predication model for HVCLNM in training cohort (C), in validation cohort (D). AUC, area under the curve; CLNM, central lymph node metastasis; HVCLNM, high-volume central lymph node metastasis; ROC, receiver operating characteristic.

training cohort (MAE =0.012) and internal validation cohort (MAE =0.015) showed encouraging agreements between observation and prediction, with minimal variation shown in the calibration plots (*Figure 5C*,*5D*). Overall, these findings provide strong support for the accuracy and reliability of the nomogram model.

DCA for clinical decision

To further analyze the clinical application of the nomogram model, we established decision curves to verify its efficiency. *Figure 6* shows how the decision curves indicate the superiority of predictive models in clinical decisions with risk threshold, a dynamic variable that changes according to the characteristics of each patient.

The risk nomogram presented in *Figure 6* was analyzed using DCA to determine its effectiveness in predicting CLNM and HVCLNM. The results indicated that using the risk nomogram would be beneficial for predicting CLNM if the threshold probability was between 0.3

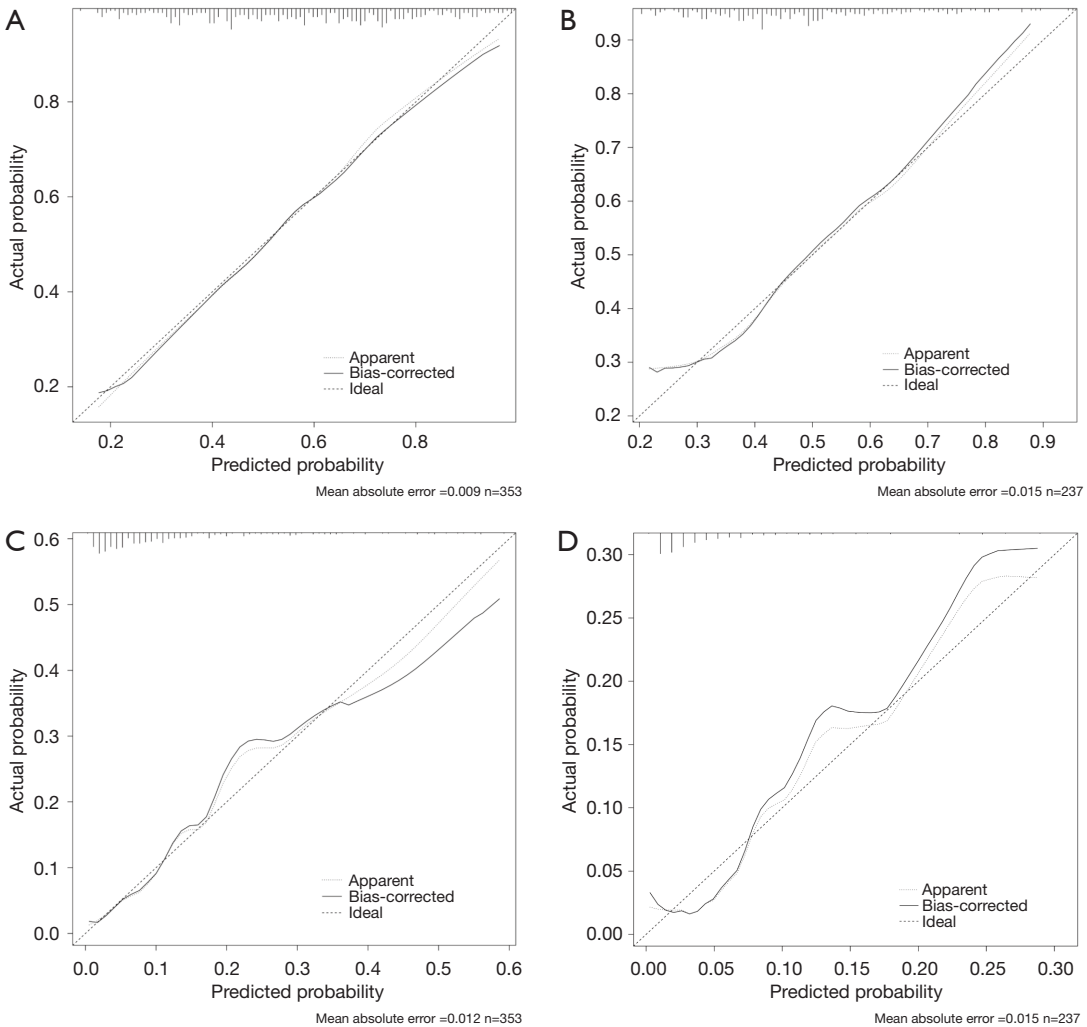

Figure 5 Calibration curve of the predication model for CLNM in training cohort (A) and validation cohort (B), in addition to nomogram prediction model for HVCLNM in training cohort (C) and validation cohort (D). The closer the two lines are, the higher the accuracy of the model. CLNM, central lymph node metastasis; HVCLNM, high-volume central lymph node metastasis.

and 0.8 (*Figure 6A*). Similarly, using the risk nomogram for predicting HVCLNM would be beneficial if the threshold probability was between 0.2 and 0.8 (*Figure 6C*). Furthermore, the net return of the prediction model for CLNM or HVCLNM was found to be larger than that of a none-treat or all-treat approach when the risk threshold was between 0.3 and 0.8 in the validation cohort. This confirms the effectiveness of our models in this range. The risk nomogram also demonstrated comparable net benefits with several overlaps in this range.

Discussion

There is ongoing debate regarding the necessity of CLND in PTC cases. Unnecessary dissections can cause complications such as recurrent laryngeal nerve damage and decreased parathyroid function, which can diminish patients' quality of life (14). Conversely, inadequate lymph node dissection increases the risk of recurrence (15), adding further burden on patients (9). Therefore, developing predictive models to anticipate the presence of CLNM

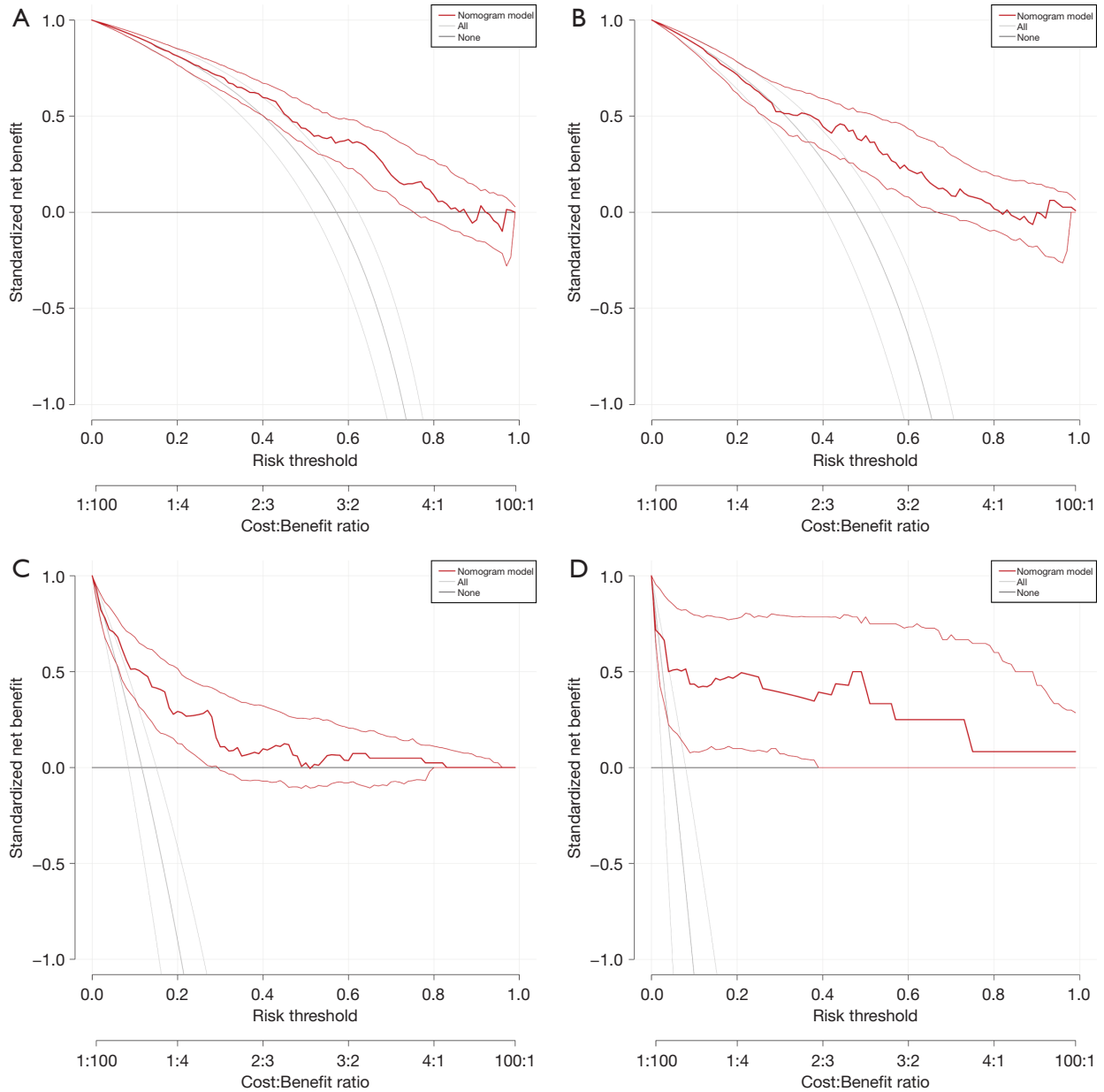

Figure 6 The decision curve of the nomogram model and single factors of CLNM in training cohort (A) and validation cohort (B), in addition to the nomogram prediction model for HVCLNM in training cohort (C) and validation cohort (D). Decision curves of CLNM/HVCLNM risk factors present in the training cohort respectively. The gray line represents CLNM or HVCLNM positive and the horizontal black line represents CLNM or HVCLNM negative. When the red line is above the gray and black lines, the nomogram model possesses a net return at this very risk threshold. CLNM, central lymph node metastasis; HVCLNM, high-volume central lymph node metastasis.

and HVCLNM in PTC could provide significant benefits for both surgeons and patients by enabling personalized treatment plans and reducing the need for subsequent surgeries.

We systematically reviewed existing studies on HVCLNM in PTC. Oh *et al.* (16) conducted a study with 2,329 patients and concluded that male gender, younger age, multifocal tumors, and ETE were risk factors for

HVCLNM in PTC. However, they did not develop a nomogram model, making it difficult to apply their findings in clinical practice. Feng *et al.* (17) developed a nomogram for patients with chronic lymphocytic thyroiditis (CLT) and PTC, achieved internal and external validation with AUCs of 0.854 and 0.825, respectively. However, because CLT is often diagnosed postoperatively, preoperative prediction remains challenging. Wei *et al.* (18) created a nomogram with AUCs of 0.702 and 0.811, but it focused on HVCLNM in papillary thyroid microcarcinoma (PTMC). Lin *et al.* (19) reported an AUC of 0.821, but their model relied on internal validation via bootstrapping, which might lead to overfitting of the model.

Our nomogram model for predicting HVCLNM applies to most classical PTC cases, and through internal and temporal validation cohorts, it can be employed to predict HVCLNM in classical PTC patients. It also confirms the role of TPOAb in predicting HVCLNM, which was not fully emphasized in previous studies. Initially, several studies (16,17,19) omitted the consideration of TPOAb in their analysis of LNM. Although some studies (20) did incorporate TPOAb, they failed to provide clear details on the reagents used and the timing of the tests, potentially resulting in discrepancies. In addition, compared to diagnostic models (16-19) based on postoperative pathological tumor characteristics, our clinical prediction model incorporates ultrasound tumor characteristics as a research variable. These ultrasound findings can be readily obtained through preoperative ultrasound examinations, thus enhancing the clinical applicability of our model.

In this study, the rate of CLNM in our population was 57.2%, which is consistent with previous reports ranging from 38% to 64% (21-24). Multivariate analysis identified younger age (≤45 years), male sex, tumor size (>1 cm), and multifocality as independent predictors of CLNM, which aligns with earlier findings (21-23). The incidence of HVCLNM was 11.6%, which is comparable to prior studies reporting rates ranging from 4% to 13.4% (16,19,25). Our analysis further identified TPOAb (≤14.95 IU/mL), bilateral lesions, younger age (≤45 years), and tumor size (>1 cm) as independent predictors of HVCLNM in PTC patients.

Age and tumor size were identified as independent predictive factors for both CLNM and HVCLNM. Patients >45 years old had a lower risk of CLNM (43.2% *vs.* 67.3%) and HVCLNM (5.4% *vs.* 16.1%) compared to those ≤45 years old. This finding is consistent with previous studies (20,23,26,27) that have shown younger patients are more susceptible to LNM. Additionally, Wang *et al.* (28) found a linear relationship between increasing age and a decreased risk of CLNM, and that patients over 45 years old with HVCLNM had significantly shorter cancer-specific survival rates. Tumor size has been identified as a crucial predictor of LNM in PTC. Thompson *et al.* (21) and Lin *et al.* (27) also concluded that tumor size is an independent predictor of CLNM. Similarly, Lin *et al.* (19) and Zhang *et al.* (25) demonstrated a significant positive correlation between tumor size and the occurrence of HVCLNM. Our study reached similar conclusions, identifying tumor size >1.0 cm as an independent predictor of both CLNM and HVCLNM.

Multifocality is also considered an important risk factor for CLNM in PTC patients, and is consistent with previous studies (20,29,30). In this study, tumors with bilateral lesions had a significantly higher incidence of LNM than tumors with unilateral lesions, with incidence rates of 27.0% and 8.9%, respectively. In addition, it is notable that multivariate analysis confirmed bilateral lesions as an independent predictive factor for HVCLNM, which had not been considered in previous studies (16-19) on HVCLNM. However, unlike other studies (22,23), we did not find ETE to be an independent risk factor for CLNM. Further analysis suggests that this may be due to the low proportion of ETE cases included in our study, which accounted for only 15.7%. Furthermore, postoperative pathology revealed that a significant proportion of ETE identified by ultrasound was actually minimal extrathyroidal extension (mETE). Previous studies have shown poor overall consistency in identifying mETE, which may be attributed to differences in interpretation by individual pathologists and discrepancies in histological criteria for mETE (31,32). Studies (33-35) have demonstrated that mETE has no impact on LNM and prognosis in patients with PTC. Therefore, the utility of mETE in PTC staging and treatment has been questioned, leading to its exclusion from the 8th edition of the TNM staging system.

Regarding laboratory examinations, this study found that low levels of TPOAb were associated with a higher incidence of CLNM and HVCLNM. Subsequent multivariable analysis confirmed TPOAb as an independent predictor of HVCLNM. TPOAb may play a more substantial role in the process of lymph node metastasis (LNM) compared to the occurrence of CLNM. We speculate that the following reasons may exist: (I) TPOAb antibody levels are highly correlated with the degree of inflammation in thyroiditis (36). Thyroiditis exerts its anti-cancer effect through complement-mediated cell death,

antibody-dependent cell-mediated cytotoxicity, and T cell-mediated immune responses (37,38). Zhang *et al.* showed that the infiltration of lymphocytes promotes the formation of tertiary lymphoid organs or ectopic lymphoid structures, potentially limiting the progression of LNM (39). (II) Magri *et al.* and Liu *et al.* have demonstrated a direct positive correlation between the hardness of the surrounding tissue of thyroid nodules and the levels of TPOAb antibodies (40,41). Song *et al.* (42) demonstrated that Patients with positive preoperative TPOAb presented with fewer LNM compared to patients with negative preoperative and can independently predict the recurrence in patients undergoing surgery for PTC. However, further research is needed to determine the specific mechanism by which different levels of TPOAb affect LNM in PTC.

In summary, we have developed and validated a nomogram that predicts CLNM and HVCLNM in PTC patients, based on several independent risk factors. This tool can help predict CLNM on an individual level. The nomogram was internally and temporally validated and showed good discrimination and calibration. DCA demonstrated that the nomogram is effective in predicting HVCLNM within a threshold probability range of 20% to 80%. Similarly, the nomogram for predicting CLNM is beneficial when the threshold probability range is between 30% and 80%. The development of this prediction model allows for personalized predictions of CLNM for most PTC patients, with a particularly noteworthy predictive value for HVCLNM, which can aid surgeons in achieving precise CLND and optimize patient treatment outcomes. The nomogram demonstrates a high level of usability and convenience for clinicians in facilitating decision-making processes.

Nevertheless, several limitations of this study should be acknowledged. First, the retrospective design may introduce inherent selection bias. Second, although ultrasound examinations were reviewed by experienced senior clinicians, the model's practical application may not completely eliminate subjectivity and variability among ultrasound practitioners. Third, model validation was based solely on a single-center cohort, which restricts its external generalizability. Finally, the developed model specifically targets classical PTC and may not be applicable to other histopathological subtypes of TC.

Conclusions

In conclusion, our study identified younger age, tumor size, bilateral lesions, and preoperative serum TPOAb ≤14.95 IU/mL as independent indicators for HVCLNM. Younger age, male sex, tumor size, and multifocality were identified as independent predictors of CLNM. We developed two nomograms to visually represent the independent risk factors associated with CLNM in PTC patients. In addition, clinical decision curves and impact curves were constructed to aid clinicians in optimizing the management and treatment of PTC patients.

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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-24-237/rc

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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). Ethics approval was granted by the ethics committee of the Guangzhou First People's Hospital (the Second Affiliated Hospital, School of Medicine, South China University of Technology), approval No. K-2023-135-01. The requirement for written informed consent to participate was waived due to the retrospective nature of the study.

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