Original Article

Development and validation of a nomogram for preoperative prediction of ipsilateral cervical central lymph node metastasis in papillary thyroid cancer: a population-based study

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Background: The incidence of papillary thyroid cancer (PTC) has increased dramatically, and it is susceptible to cervical lymph node metastasis (LNM), predominantly in the ipsilateral cervical central lymph node metastasis (CLNM). Ipsilateral cervical CLNM affects patients' surgical options and survival rates. In this study, we integrated multiple factors to establish a nomogram-based preoperative prediction model of ipsilateral cervical CLNM in PTC.

Methods: Data were retrospectively collected from 609 patients with PTC admitted to Peking University International Hospital, all of whom underwent ipsilateral cervical lymph node dissection. They were randomly divided into a modeling set and validation set in the ratio of 7:3. Binary logistic regression was used to analyze independent risk factors for ipsilateral cervical CLNM in PTC and to construct a nomogram model. The performance of nomogram CLNM prediction was evaluated by the receiver operating characteristic (ROC) curve and calibration curve.

Results: Binary Logistic Regression showed that age, history of osteoporosis, complicated by Hashimoto's thyroiditis, enlarged lymph nodes in the central neck, and extrathyroidal extension were risk factors for ipsilateral cervical CLNM. Combining these five independent risk factors, a nomogram prediction model was developed. In the modeling set, the area under the curve (AUC) of the nomogram ROC was 0.782 [95% confidence interval (CI): 0.730–0.833], and the sensitivity and specificity of the model were 0.761 and 0.763, respectively, with a well-calibrated curve fit. Moreover, the model presented better discrimination than any of the independent risk factors. The nomogram performed well in the validation set (AUC 0.753; 95% CI: 0.648–0.858).

Conclusions: A non-invasive, and accurate nomogram prediction model for ipsilateral cervical CLNM of PTC was established. It can help physicians identify patients with a high risk of ipsilateral cervical CLNM of PTC preoperative for individualized treatment.

Keywords: Papillary thyroid cancer (PTC); lymph node metastasis (LNM); nomogram; risk factor; validation

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Introduction

Thyroid cancer, as one of the most common malignant tumors, is rapidly increasing in incidence (1), and papillary thyroid cancer (PTC) is the most prevalent subtype of thyroid cancer (2). Lymph node metastasis (LNM) is the main route of PTC metastasis with an incidence of 17–36% (3), and especially cervical central lymph node metastasis (CLNM) is the most common. Understanding the extent and location of LNM is crucial for developing treatment plans. Studies have confirmed that PTC patients with CLNM have a lower survival rate and a higher risk of recurrence (4,5). Therefore, it has been suggested that prophylactic central lymph node dissection can identify lymph node lesions and potentially reduce the risk of disease recurrence (6). However, it has also been suggested that prophylactic central lymph node dissection does not appear to improve the prognosis of patients with low-risk PTC (7), but rather increases the incidence of surgical complications and the risk of long-term postoperative hormone replacement therapy, resulting in overtreatment. Compared to bilateral or distant metastasis, patients with ipsilateral LNM generally have a better prognosis. For patients with ipsilateral cervical CLNM, it may be sufficient to perform ipsilateral lymph node dissection, avoiding intervention on the contralateral side of the neck to reduce surgical risks and complications. Therefore, assessing the risk of ipsilateral cervical CLNM in patients with PTC and treating them with precise surgical procedures have become a hot topic of current research. Currently, clinical suspicion of CLNM requires invasive tests such as fine needle aspiration biopsy of the thyroid and lymph nodes or expensive genetic diagnosis to aid in the evaluation. There is a lack of noninvasive, effective, and convenient assessment tools for the preoperative recognition of CLNM.

Nomogram prediction models are widely used in clinical cohort studies because of their high accuracy, efficiency, and stability. Although studies have identified independent risk factors for constructing predictive models for CLNM in PTC, these studies were more often based on ultrasound (8,9) or computed tomography (CT) images (10,11), with insufficient clinical indicators and thus yielding inconsistent results. Some studies (12,13) used a public database that does not necessarily apply to Asian populations due to ethnicity.

Our study was based on the Chinese population from a practical clinical application scenario, integrating multidimensional factors such as patient demographic characteristics, medical history, preoperative biochemical examination, bone mineral density examination, ultrasound image characteristics, and pathology, to establish and validate a prediction model for early ipsilateral cervical CLNM in PTC based on nomogram. The model is noninvasive, simple, and effective, and can assist physicians in better performing preoperative identification of patients with a high risk of ipsilateral cervical CLNM in PTC and to develop individualized and highly accurate treatment plans. We present this article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-478/rc).

Highlight box

Key findings

- We integrated multiple factors to establish a nomogram-based preoperative prediction model of ipsilateral cervical central lymph node metastasis (CLNM) in papillary thyroid cancer (PTC).

What is known and what is new?

- The role of prophylactic central neck dissection in papillary thyroid cancer patients is controversial and it is still a matter of the debate.
- A non-invasive, and accurate nomogram prediction model for ipsilateral cervical CLNM of PTC was established. It can help physicians identify patients with a high risk of ipsilateral cervical CLNM of PTC preoperative for individualized treatment.

What is the implication, and what should change now?

- The preoperative prediction of the risk of central lymph node metastases and the decision on the necessity and the extent of prophylactic lymphadenectomy is crucial.

Methods

Participants

This study is a retrospective cohort study. This study included 609 patients who underwent thyroid lobectomy and ipsilateral central compartment lymph node dissection at Peking University International Hospital from February 2018 to February 2021. Inclusion criteria: (I) age >18 years; (II) pathological diagnosis of PTC; (III) with complete demographic characteristics, biochemical indices, preoperative ultrasound information, and postoperative pathological data. Exclusion criteria: (I) patients with recurrent thyroid cancer; (II) combined with other malignant tumors; (III) preoperative thyroid nodules which had received adjuvant treatment such as oncological radiotherapy and thyroid nodule ablation.

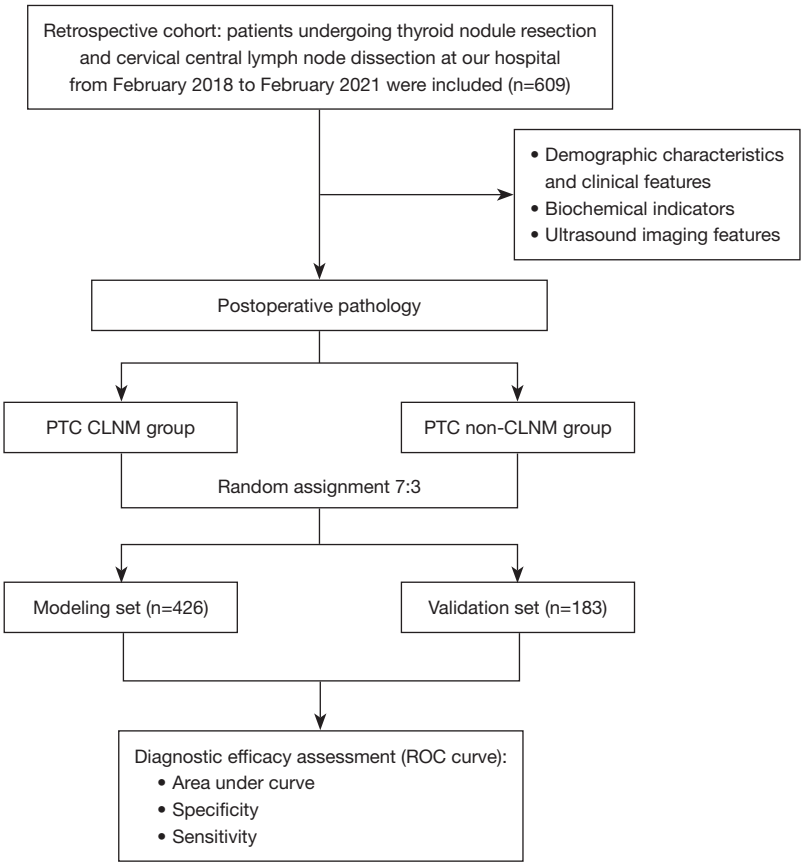

Figure 1 Flow diagram. PTC, papillary thyroid cancer; CLNM, central lymph node metastasis; ROC, receiver operating characteristic.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was retrospective and approved by the Ethics Committee of Peking University International Hospital (No. 2022-KY-0040-01). Because this study used retrospective data and involved no direct contact with study participants, the requirement for informed consent was waived by the Ethics Committee.

Procedures

The following data were collected through the hospital case system: demographic characteristics [sex, age, weight, height, systolic blood pressure (SBP), diastolic blood pressure (DBP)], medical history [Hashimoto's thyroiditis (HT)], biochemical examinations (thyroid function, thyroid antibodies, liver and kidney function, calcium and phosphorus, blood glucose, lipids), bone density examination.

This study retrospectively retrieved and assessed the preoperative thyroid ultrasound images of 609 patients pathologically confirmed with papillary thyroid carcinoma. These images were reevaluated by experienced radiologists (with over 10 years of experience in thyroid imaging). The assessment covered the number of thyroid nodules, size, echo, nature, boundary, shape, location, blood flow signals, microcalcification of the cancerous nodules, enlarged lymph nodes (ELN) in the central neck, and extrathyroidal extension (ETE) in the images. The method of partitioning the cervical lymph nodes followed the American Joint Committee on Cancer (AJCC) seven-part division of the cervical lymph nodes (14). We defined a lymph node with a short axis >0.8 cm as an ELN (15).

All enrolled PTC patients (n=609) were divided into two sets, using a random sampling method in a 7:3 ratio, the modeling set (n=426), and the validation set (n=183). Each data set was divided into two groups based on ipsilateral cervical central compartment lymph node pathology: the CLNM group and the non-CLNM group (as shown in *Figure 1*).

Statistical analysis

Data were analyzed using SPSS 26.0 software. Normally distributed data were expressed as mean ± standard deviation ($\bar{x}$±s) and non-normally distributed data were expressed as median (interquartile range), respectively. We analyzed the differences between the CLNM and non-CLNM groups using the *t*-test and Mann-Whitney *U* test, and the χ^2 test was used to compare the counting units. P<0.05 was considered a statistically significant difference. Binary logistic regression analysis was used to determine the risk factors for ipsilateral cervical CLNM in PTC, and the odds ratios (OR) and their 95% confidence intervals (CI) were calculated. The nomogram was performed with statistical packages R (http://www.R-proje ct.org) and Empower Stats (www.empowersta ts.com, X&Y Solutions, Inc., Boston, MA, USA) to generate correction curves and calculate the area under the curve (AUC) of the receiver operating characteristic (ROC) curves to evaluate the accuracy, sensitivity, and specificity, and external validation was performed in the validation set.

Results

Clinical characteristics of subjects in the modeling set (Table 1)

Of the 426 patients with PTC included in the study, a total of 109 patients (25.6%) with pathologically confirmed CLNM, 24.8% of whom were males, were included in the CLNM group. A total of 317 patients (74.4%) without CLNM, 20.5% of whom were males, were included in the non-CLNM group.

The age of subjects in the CLNM group was significantly lower than that in the non-CLNM group (P<0.001). The proportion of subjects with osteoporosis (7.3% *vs.* 1.6%, P=0.003) and complicated by HT (33.0% *vs.* 13.6%, P<0.001) was significantly higher in the CLNM group compared with the non-CLNM group. The thyroid stimulating hormone (TSH) level was significantly higher in the CLNM group than in the non-CLNM group (P=0.04). The proportion of thyroid peroxidase antibody (TPOAb) positive was higher in the CLNM group than in the non-CLNM group (20.2% *vs.* 11.4%, P=0.02). The estimated glomerular filtration rate (eGFR) was lower in the CLNM group than in the non-CLNM group (P=0.03). There was no significant difference in body mass index (BMI), history of alcohol consumption, SBP, free tetraiodothyronine (FT4), free triiodothyronine (FT3), DBP, anti-thyroglobulin antibody (TgAb), thyrotropic receptor antibodies (TRAb), fasting blood glucose (FBG), lipids, alanine aminotransferase (ALT), aspartate transaminase (AST), uric acid (UA), calcium (Ca), and phosphorus (P) levels between the two groups.

Ultrasonic characteristics of subjects in the modeling set (Table 2)

Ultrasound imaging showed a higher proportion of nodules >1 cm (71.6% *vs.* 55.2%, P=0.003), blurred borders (82.6% *vs.* 71.0%, P=0.02), irregular shape (86.2% *vs.* 74.8%, P=0.01), microcalcification (56.0% *vs.* 36.9%, P=0.001), ELN in the central neck (43.1% *vs.* 14.8%, P<0.001) and ETE (58.7% *vs.* 29.0%, P<0.001) in the CLNM group compared to the non-CLNM group.

Logistic regression analysis of risk factors of ipsilateral cervical CLNM in the modeling set

In univariate analysis (*Tables 1*,*2*), the following factors were associated with ipsilateral cervical CLNM: age, history of osteoporosis, complicated by HT, TSH level, TPOAb, eGFR level, cancerous nodule size, cancerous nodule boundary, cancerous nodule shape, microcalcification, ELN in the central neck and ETE.

Then, we performed binary logistic regression analysis on the above risk factors, and the results showed that age, history of osteoporosis, complicated by HT, ELN in the central neck and ETE were risk factors for ipsilateral cervical CLNM (as shown in *Figure 2*). The younger the age, the higher the risk of ipsilateral cervical CLNM (95% CI: 0.939–0.979, P<0.001). The risk of ipsilateral cervical CLNM was 4.831 times higher in patients with osteoporosis (95% CI: 1.245–20.531, P=0.03). Patients with PTC who have HT experience a 2.657-fold increase in the risk of ipsilateral cervical CLNM (95% CI: 1.485–4.744, P=0.001). The risk of ipsilateral cervical CLNM was 3.891 times (95% CI: 2.275–6.697, P<0.001) higher in patients with ELN in the central neck than in patients with normal lymph nodes. Patients with PTC who exhibit ETE have a 3.551-fold increased risk of ipsilateral central CLNM (95% CI: 2.164–5.895, P<0.001).

Nomogram and evaluation of prediction model of ipsilateral cervical CLNM

Based on the independent risk factors for ipsilateral cervical

Table 1 Comparison of baseline characteristics and biochemical indicators between CLNM and non-CLNM groups

Index	CLNM group	Non-CLNM group	$t/U/\chi^2$	P
Patients	109 (25.6)	317 (74.4)		
Gender (male)	27 (24.8)	65 (20.5)	0.872	0.35
Age (years)	40.00 (33.00, 52.50)	47.00 (37.00, 58.00)	–3.420	<0.001*
BMI (kg/m^2)	24.2±2.9	24.2±3.5	–3.910	0.96
Osteoporosis (yes)	8 (7.3)	5 (1.6)	9.103	0.003*
HT (yes)	36 (33.0)	43 (13.6)	20.34	<0.001*
SBP (mmHg)	125.00 (120.00, 135.00)	126.00 (120.00, 136.00)	–1.260	0.21
DBP (mmHg)	78.00 (70.00, 80.00)	75.00 (70.00, 80.00)	–0.887	0.38
TSH (μIU/mL)	2.25 (1.34, 2.93)	1.81 (1.14, 2.57)	–1.933	0.04*
FT4 (pmol/L)	15.50 (14.30, 16.90)	16.06 (14.70, 17.60)	–1.664	0.10
FT3 (pmol/L)	4.71 (4.20, 5.20)	4.70 (4.20, 4.90)	–1.608	0.11
TRAb positive	0	4 (1.3)	1.388	0.24
TgAb positive	46 (42.2)	128 (40.4)	0.112	0.74
TPOAb positive	22 (20.2)	36 (11.4)	5.373	0.02*
FBG (mmol/L)	4.40 (3.70, 4.80)	4.30 (3.70, 4.67)	–0.42	0.67
TC (mmol/L)	4.59 (3.86, 4.65)	4.59 (3.98, 5.11)	–0.45	0.65
TG (mmol/L)	2.04 (0.88, 2.14)	2.02 (0.96, 2.13)	–0.734	0.46
HDL-C (mmol/L)	1.18 (1.00, 1.32)	1.19 (0.88, 1.35)	–0.931	0.35
LDL-C (mmol/L)	2.66 (2.16, 2.72)	2.65 (2.14, 3.18)	–1.573	0.12
ALT (U/L)	18.00 (12.00, 25.50)	18.00 (12.00, 22.00)	–0.107	0.92
AST (U/L)	20.00 (15.00, 24.00)	19.00 (16.00, 22.00)	–0.194	0.85
UA (μmol/L)	314.23 (246.00, 351.50)	313.32 (257.50, 357.00)	–0.219	0.83
eGFR (mL/min×1.73 m^2)	100.18 (98.76, 113.07)	105.20 (100.78, 107.91)	–2.138	0.03*
Ca (mmol/L)	2.33 (2.25, 2.35)	2.31 (2.20, 2.35)	–0.955	0.34
P (mmol/L)	1.21 (1.20, 1.25)	1.22 (1.17, 1.24)	–0.532	0.60

Categorical data are expressed as n (%). Normally distributed data are expressed as mean ± standard deviation and non-normally distributed data were expressed as median (interquartile range). *, P<0.05 *vs.* CLNM group. CLNM, central lymph node metastasis; BMI, body mass index; HT, Hashimoto's thyroiditis; SBP, systolic blood pressure; DBP, diastolic blood pressure; TSH, thyroid stimulating hormone; FT4, free tetraiodothyronine; FT3, free triiodothyronine; TRAb, thyrotropic receptor antibody; TgAb, anti-thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate transaminase; UA, uric acid; eGFR, estimated glomerular filtration rate; Ca, calcium; P, phosphorus.

CLNM, a nomogram of the ipsilateral cervical CLNM risk prediction model for PTC patients was developed (as shown in *Figure 3*), and the total ipsilateral cervical CLNM score for PTC patients was calculated based on the scores corresponding to each predictor to estimate the probability of ipsilateral cervical CLNM. The cutoff value for the nomogram score was obtained from the maximum Youden index, and this value was used to differentiate whether the patient was at high risk for ipsilateral cervical CLNM.

We evaluated the ROC curves for each independent risk factor predicting ipsilateral cervical CLNM separately (as shown in *Figure 4A*), with an AUC of 0.610 (95% CI: 0.547–

Table 2 Comparative of ultrasound imaging features between CLNM and non-CLNM groups

Index	CLNM group (n=109)	Non-CLNM group (n=317)	χ^2	P
Multifocal (yes)	74 (67.9)	191 (60.3)	2.012	0.15
Features of cancerous nodule				
Size (>1 cm)	78 (71.6)	175 (55.2)	8.995	0.003*
Echo			6.344	0.18
Unclear	4 (3.7)	14 (4.4)		
Low	85 (78.0)	260 (82.0)		
Media	7 (6.4)	21 (6.6)		
High	8 (7.3)	7 (2.2)		
Mixed	5 (4.6)	15 (4.7)		
Nature			1.218	0.75
Unclear	1 (0.9)	7 (2.2)		
Capsular	3 (2.8)	7 (2.2)		
Solidity	92 (84.4)	258 (81.4)		
Cystic solidity	13 (11.9)	45 (14.2)		
Boundary (blurred)	90 (82.6)	225 (71.0)	5.656	0.02*
Shape (irregular)	94 (86.2)	237 (74.8)	6.164	0.01*
Location (vertical)	82 (75.2)	258 (81.4)	1.909	0.17
BFS (yes)	76 (69.7)	203 (64.0)	1.161	0.28
Microcalcification (yes)	61 (56.0)	117 (36.9)	12.107	0.001*
ELN (yes)	47 (43.1)	47 (14.8)	37.756	<0.001*
ETE (yes)	64 (58.7)	92 (29.0)	30.813	<0.001*

Data are expressed as n (%). *, P<0.05 *vs.* CLNM group. CLNM, central lymph node metastasis; BFS, blood flow signals; ELN, enlarged lymph nodes; ETE, extrathyroidal extension.

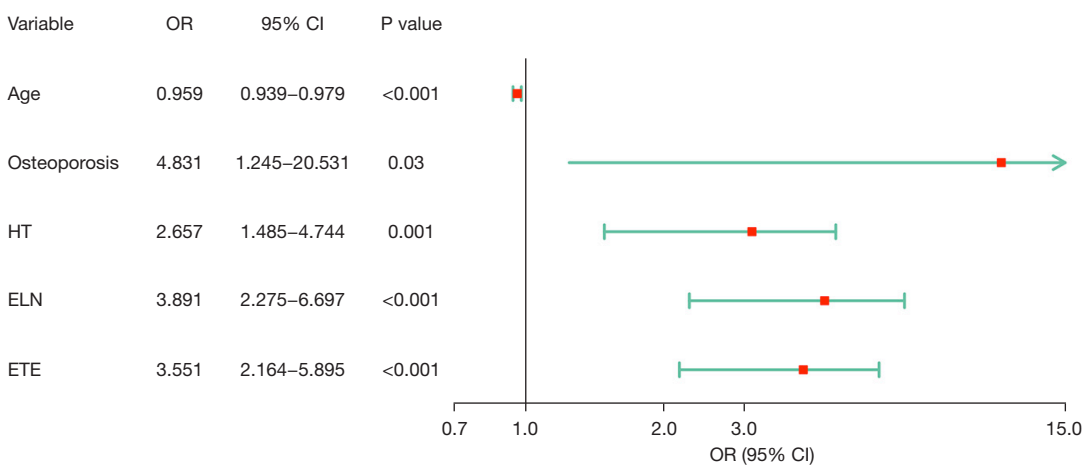

Figure 2 Forest plot of multivariable analysis for ipsilateral cervical central lymph node metastasis in papillary thyroid carcinoma. OR, odds ratio; CI, confidence interval; HT, Hashimoto's thyroiditis; ELN, enlarged lymph nodes; ETE, extrathyroidal extension.

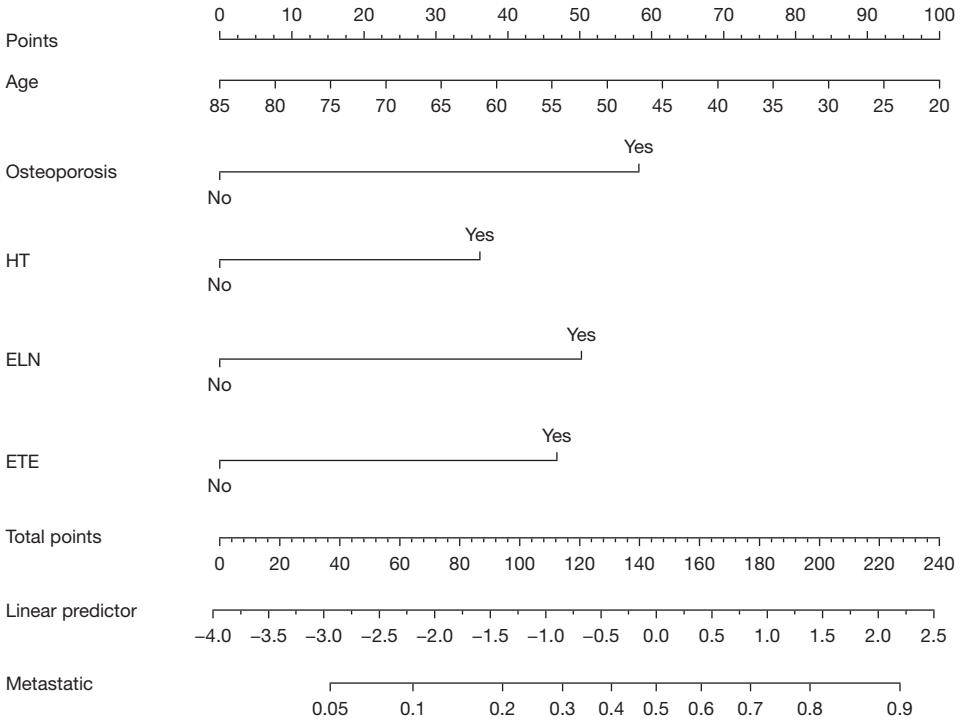

Figure 3 Nomogram for predicting the risk of ipsilateral cervical central lymph node metastasis in papillary thyroid carcinoma. HT, Hashimoto's thyroiditis; ELN, enlarged lymph nodes; ETE, extrathyroidal extension.

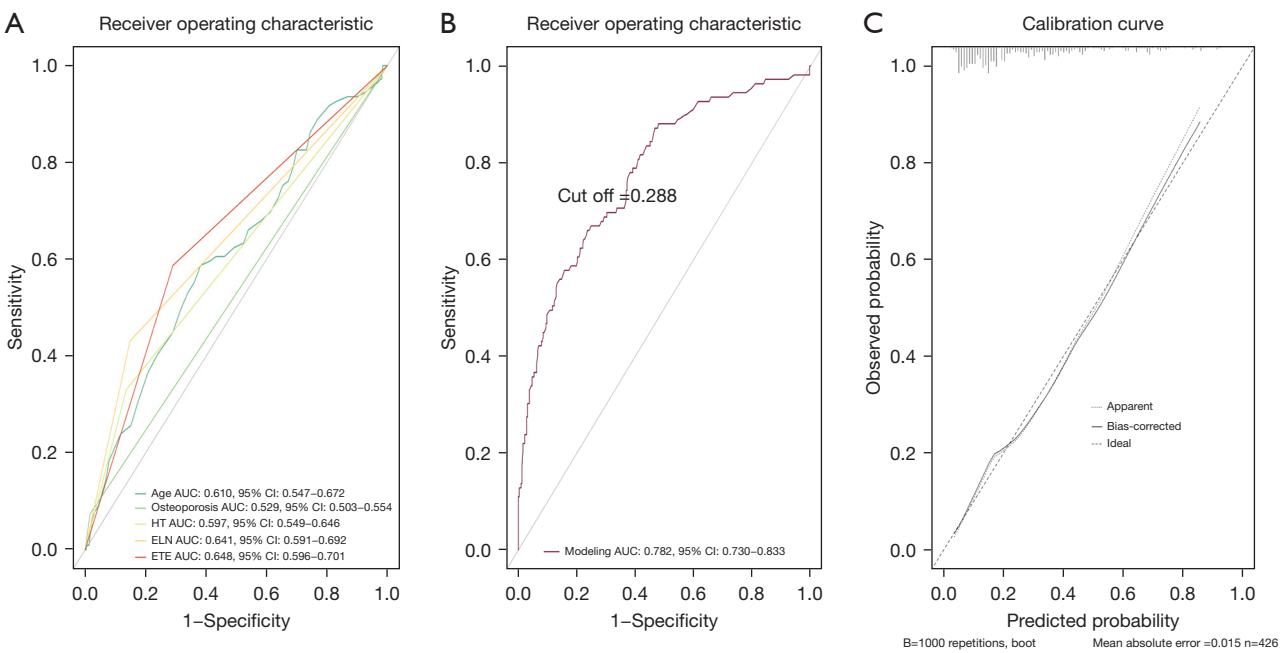

Figure 4 Evaluation of predictive models' performance. (A) The receiver operating characteristic curve at every single factor, respectively. (B) The receiver operating characteristic curve in the modeling set, the sensitivity and specificity were 0.761 and 0.763, respectively. (C) Calibration curves for the modeling set. AUC, area under the curve; CI, confidence interval; HT, Hashimoto's thyroiditis; ELN, enlarged lymph nodes; ETE, extrathyroidal extension.

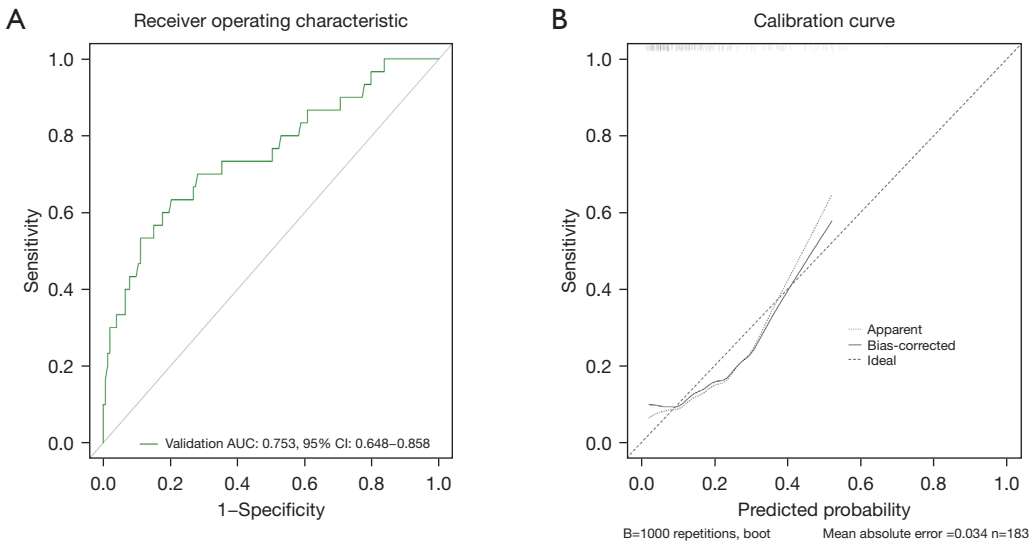

Figure 5 Validation of the predictive model. (A) The receiver operating characteristic curve in the validation set, the sensitivity and specificity were 0.661 and 0.863, respectively. (B) Calibration curves for the validation set. AUC, area under the curve; CI, confidence interval.

0.672) for age, 0.529 (95% CI: 0.503–0.554) for the history of osteoporosis, 0.597 (95% CI: 0.549–0.646) for complicated by HT, 0.641 (95% CI: 0.591–0.692) for ELN in the central neck and 0.648 (95% CI: 0.596–0.701) for ETE.

The AUC of the ipsilateral cervical CLNM risk prediction model in the modeling set population was 0.782 (95% CI: 0.730–0.833), with a sensitivity and specificity of 0.761 and 0.763, respectively (as shown in *Figure 4B*), which had a good diagnostic performance. The model presented better discrimination than any of the independent risk factors. The calibration curve for the risk of ipsilateral cervical CLNM showed good agreement between the predicted and actual observations in the nomogram (as shown in *Figure 4C*). The diagnostic cutoff value of this nomogram prediction model for distinguishing a PTC population at high risk of CLNM was 0.288.

The AUC of the ipsilateral cervical CLNM risk prediction model in the internal validation set population was 0.753 (95% CI: 0.648–0.858), and the sensitivity and specificity of the validation model were 0.661 and 0.863, respectively, with good discriminatory power (as shown in *Figure 5A*). The calibration curves of the validation set also showed good agreement (as shown in *Figure 5B*).

Discussion

In this study, a variety of factors such as patient demographic characteristics, medical history, preoperative biochemical examinations, bone mineral density examinations, and imaging features were fully integrated for more accurate modeling to assess the risk of ipsilateral cervical CLNM in PTC. A total of five independent risk factors were identified, and patients with younger age, history of osteoporosis, complicated by HT, ELN in the central neck and ETE had a greater risk of CLNM. ETE (AUC 0.648) had the highest predictive value for ipsilateral cervical CLNM of PTC, followed by ELN in the central neck (AUC 0.641), complicated by HT (AUC 0.597), age (AUC 0.610) and history of osteoporosis (AUC 0.529).

ETE refers to the phenomenon where thyroid cancer cells spread beyond the thyroid capsule and invade surrounding tissues. Numerous studies (16-18) have shown that ETE is an independent risk factor for LNM in PTC. Consistent with previous research findings, we observed that PTC patients with ETE face a higher risk of ipsilateral cervical CLNM. ETE can increase the likelihood of tumor cells spreading through the lymphatic system, thereby elevating the risk of LNM. Consequently, for PTC patients with ETE, more aggressive treatment strategies may need to be considered, such as extensive cervical lymph node dissection and adjuvant therapy post-surgery.

Previous studies have identified ELN (19,20) as a risk factor for CLNM, and we obtained the same results. Tumor cells can spread from the primary thyroid tumor site to the

central lymph nodes through the lymphatic system, and ELN is often considered a direct clinical sign of LNM in PTC. However, not all ELN are attributable to metastasis from PTC; ELN can also be due to infections, inflammation, or other types of cancer. In cases of micrometastases, patients with LNM may not exhibit significant ELN. Therefore, the specificity of ELN in the central neck for predicting CLNM in PTC is not high and it needs to be combined with other predictors.

HT is an autoimmune thyroid disease characterized by chronic lymphocytic thyroiditis. In recent years, researchers have extensively explored the relationship between HT and PTC, particularly the potential impact of HT on LNM in PTC, yet the findings have been inconsistent. Some studies have found a significant effect of HT on the risk of LNM in PTC (21-23). Our findings are in line with this, indicating an increased risk of ipsilateral cervical CLNM among PTC patients with concurrent HT, although the specific mechanisms remain unclear. Other studies have indicated that patients with HT present with lower aggressiveness at onset and better prognosis in PTC (24,25), suggesting that the chronic inflammatory environment induced by HT may limit cancer cell invasion and metastasis through enhanced local immune surveillance. A study found (26) that in PTC patients with the BRAF wild-type, the presence of HT appears to offer a more pronounced protective factor against the risk of disease recurrence, a protective effect that seems less significant in patients with BRAF mutations. Unfortunately, our study lacks genetic data, preventing stratified analysis. Therefore, future prospective studies are needed to further explore these relationships.

Consistent with previous studies (16,22,27,28), our study found that youth was a risk factor for CLNM in patients with PTC. In addition, it has been confirmed (29) that the survival rate of PTC patients combined with CLNM was significantly lower in those under 45 years of age, and the diagnostic threshold for age in our study was 42 years. This might be because young individuals have higher basal metabolic rates and are more likely to have things like genetic abnormalities (30). In older patients, although the risk of LNM may be lower, once metastasis occurs, the prognosis could be poorer. Therefore, age and other relevant factors should be considered comprehensively when formulating treatment plans and prognostic assessments.

In addition, the present study adequately evaluated preoperative clinical indicators and found that a history of osteoporosis was an independent risk factor for CLNM in patients with PTC, which has rarely been mentioned in previous studies. This may be because most of the indicators in previous studies were measured postoperatively, and patients were not evaluated for osteoporosis preoperatively. However, due to study sample size limitations, subsequent larger and more case-cohort studies are needed to assess the relationship and application of skeletal health impairment and CLNM in PTC. PTC is usually inert, however, 4% of patients with PTC present with distant lesions at the time of diagnosis (31). Bone is a common site of distant tumor localization and bone metastases have a potential negative impact on the bone microenvironment and bone strength (32). Therefore, a preoperative assessment of bone mineral density should be necessary for patients with PTC.

Furthermore, previous studies (18,22,33) have identified several risk factors for cervical CLNM in PTC, such as microcalcifications, nodule size, and multifocality. Microcalcifications are an important ultrasonographic feature in the diagnosis of PTC. Moreover, microcalcifications may be associated with aggressive tumor features, such as the risk of LNM. However, it is important to note that not all PTC patients with microcalcifications will develop LNM. Therefore, the presence of microcalcifications should be considered in conjunction with other clinical and radiological features to assess the patient's risk comprehensively. Typically, larger thyroid nodules are associated with a higher risk of LNM. Larger tumors may imply a higher tumor burden, thereby increasing the chances of LNM. However, this relationship is not absolute, as even micro-PTCs smaller than 1 cm can undergo LNM. In this study, we found that even for thyroid nodules <1 cm, 17.9% (31/173) of patients still developed CLNM. While nodule size is an important indicator for assessing the risk of LNM, this relationship is influenced by various factors, including the biological characteristics of the tumor and other clinical features. Therefore, when assessing the risk of LNM in thyroid cancer patients, nodule size should be considered in conjunction with other diagnostic indicators. Multifocality of nodules may increase the risk of LNM, as multifocal PTC is often associated with a higher tumor burden, possibly making patients more susceptible to aggressive cancer behaviors, such as LNM. Additionally, multifocality may reflect underlying genetic predispositions or environmental factors, promoting carcinogenesis in multiple areas of the thyroid. However, this study did not find an association between microcalcifications, nodule size, and multifocality with CLNM in patients with PTC. This may be influenced by various factors, including a

small sample size, the study being of a retrospective cohort design, differences in population characteristics, data analysis methods, and differences in the study setting.

The nomogram is a graphical computational ruler that has been widely used in medicine in recent years by combining important parameters of regression analysis. The prediction model built on the nomogram in this study integrated multiple risk factors with an AUC of 0.782 (95% CI: 0.730–0.833), which was higher than any of the independent risk factors, and had a higher discriminatory and validation ability to identify the risk of PTC combined with neck CLNM more effectively. The ROC best cut-off values showed sensitivity and specificity of 76.1% and 76.3%, respectively. In the external validation group, the nomogram also performed well with an AUC of 0.753 (95% CI: 0.648–0.858). The present nomogram model can help clinicians screen the high-risk group of ipsilateral cervical CLNM in this group of patients to help develop individualized treatment strategies.

However, this study does have some limitations. The thyroid ultrasound examinations were not standardized across operators, potentially introducing bias. Owing to the retrospective and non-randomized nature of this study, many significant data were not included in the analysis. For instance, all patients underwent only ipsilateral central neck lymph node dissection, leaving the status of the contralateral central lymph nodes unknown. This study was unable to specifically identify which nodules in multifocal presentations were malignant, with scenarios potentially involving either a single malignant nodule or multiple malignant nodules. Data on patients' previous thyroid disease history, such as the presence of Graves' disease, were also incomplete. Enhanced cervical CT and fine-needle aspiration were not routinely used in this study and were limited to a very small number of patients, restricting the possibility of in-depth analysis. Important information, such as genetic data, was also missing from our study data. Additionally, this study had a small sample size and lacked external validation. Therefore, large-scale prospective studies are needed to further analyze these issues and validate the clinical value of the model.

Conclusions

In conclusion, age, history of osteoporosis, complicated by HT, ELN in the central neck, and ETE were found to be risk factors for ipsilateral cervical CLNM in PTC in this study. A nomogram prediction model was created by combining these five independent risk factors to more accurately predict the likelihood of ipsilateral cervical CLNM. This model has good diagnostic efficacy, which can assist doctors in better preoperative identification of high-risk groups of PTC ipsilateral cervical CLNM.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-478/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was retrospective and approved by the Ethics Committee of Peking University International Hospital (No. 2022-KY-0040-01). Because this study used retrospective data and involved no direct contact with study participants, the requirement for informed consent was waived by the Ethics Committee.

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