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Predicting central lymph node metastasis in papillary thyroid carcinoma combined with Hashimoto's thyroiditis: a preoperative study

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Abstract

Background Current studies have reported a high association between the Hashimoto's thyroiditis (HT) and papillary thyroid cancer (PTC). However, studies on the characteristics of central lymph node metastasis (CLNM) in PTC patients with HT are scarce. Therefore, this study aims to evaluate the risk factors of CLNM in PTC and HT patients.

Methods We retrospectively collected clinical data from 933 PTC patients with HT who underwent thyroid surgery. Of these, 653 patients were categorized into a training cohort for constructing the nomogram, and 280 patients formed a validation cohort to verify the performance of the model. Least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression analyses were used to select risk factors. A nomogram model for predicting CLNM was developed and internally validated. We subsequently evaluated thyroid function within 3 years after surgery and estimated the prevalence and incidence of postoperative complications between the CLNM (+) and CLNM (-) groups.

Results LASSO regression revealed that 19 nonzero variables were associated with CLNM. Multivariate logistic regression analysis revealed that younger, patients of low body mass index (BMI), drinking, intranodular hyperechoic (IH) status, diameter ≥ 1 cm, multifocality, extrathyroidal extension (ETE), enlarged central lymph nodes (ECLNs) and lateral lymph node metastasis (LLNM) were at higher risk of CLNM ($P < 0.05$). A nomogram to predict CLNM in PTC patients with HT was constructed and internally validated on the basis of risk factors. The areas under the ROC curve (AUCs) of nomogram were 0.768 (95% CI, 0.723–0.812) and 0.773 (95% CI, 0.705–0.841) in training and validation groups, respectively. Moreover, the nomogram data showed a good discrimination and calibration ability to training and validation groups. Postoperative follow-up revealed that TGAb levels and the incidence of hypothyroidism were significantly greater in CLNM (+) group than CLNM (-) group, respectively.

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Conclusions Our nomogram schedule developed and validated with a comprehensive set of preoperative risk factors showed a high benefit in predicting CLNM in PTC patients with HT. Postoperative follow-up of thyroid function allow to clarify the trend, as well as prevalence and incidence of common thyroid complications.

Keywords Central lymph node metastasis, Hashimoto's thyroiditis, Nomogram, Papillary thyroid carcinoma, Postoperative complications, Risk factors

Introduction

With the annual increase to 4.5–6.6%, thyroid cancer has become the fastest-growing disease in the world [1]. PTC accounts for 80–90% of all new thyroid cancer cases [2, 3], which mostly coexist with other benign thyroid diseases such as HT, adenoma and nodular goitre [4]. HT is one of the most common thyroidal autoimmune diseases which inflict a progressive injury to thyroid tissue resulting in clinically evident hypothyroidism [5]. Notably, current studies have reported that the average coexistence rate between HT and PTC is quite high, approximately 23% [6].

The relationship between PTC and HT has been controversial since its first description by Dialey et al. in 1955 [7]. Ehlers et al. [8] suggested that HT and PTC may be associated with immunological factors. However, this viewpoint has not been confirmed in more other studies, and the pathogenesis underlying the coexistence of PTC and HT remains controversial [9, 10]. When PTC coexists with HT, pathology reveals that many lymphocytes infiltrate the cancer parenchyma within and adjacent to the cancer tissue [11]. Many studies have focused on evaluating the prognoses of patients with PTC coexisting with HT [4]. Some studies have demonstrated that PTC with HT tends to have decreased tumour aggressiveness, such as a lower frequency of central lymph node metastases (CLNM) or recurrence rates, the absence of extrathyroidal extension, a smaller tumour size and a lower stage [12, 13]. In contrast, some researchers have reported that CLNM is more likely to occur in PTC patients with HT [14, 15]. The significance of how to assess CLNM in PTC patients with HT remains debated because the molecular mechanisms by which chronic thyroid lymphocytic infiltration affects CLNM in patients with PTC are unclear.

The American Thyroid Association (ATA) guidelines for differentiated thyroid cancer state that central lymph node dissection (CLND) should be considered if metastatic lymph nodes (cN1) are evident on preoperative ultrasound or palpable on examination [16]. The 2015 ATA management guidelines for PTC do not recommend routine prophylactic CLND for noninvasive, T1 or T2, or clinical node-negative PTC (cN0) [17]. The Chinese and Japanese PTC guidelines recommend that prophylactic CLND should appropriately protected against the parathyroid gland and the recurrent laryngeal nerve [18, 19]. The need for routine prophylactic CLND in patients without clinical evidence of CLNM, especially those with unilateral lesions, remains controversial [20]. Approximately 28.0%-33.0% of PTC patients do not have CLNM detected on preoperative ultrasound, but the diagnosis is confirmed by pathology after prophylactic CLND [21]. Studies have shown that neck lymph node metastasis in PTC patients may increase the recurrence rate and thus affect the prognosis [22, 23]. Therefore, accurately assessing the risk of CLNM in patients with PTC with HT to determine the appropriate lymph node dissection modality is particularly important.

PTC patients undergoing surgical treatment are prone to complications such as hypothyroidism and hyperthyroidism. Although some researchers have analysed trends in postoperative thyroid function and the incidence of hyperthyroidism and hypothyroidism, no studies have compared differences in thyroid function indicators between the CLNM (+) group and the CLNM (-) group of PTC patients with HT during postoperative follow-up, which is an issue needs to be clearly elucidated.

In clinical oncology, nomograms have been widely used as a reliable tool to estimate the numerical probability of an individual patient by incorporating and illustrating important risk factors [4, 24]. This has been demonstrated in several types of cancers, including breast, lung, and gastric cancers, and the predictive results of these nomograms may be more accurate than those based on traditional TNM staging systems [25–27]. Furthermore, we found relatively few nomograms for predicting CLNM in PTC patients with HT. Traditional regression techniques are limited in the analysis and synthesis of large numbers of covariates, including multicollinear variables; however, the least absolute shrinkage and selection operator (LASSO) is a regression-based methodology where a large number of covariates can be present in the model, with an emphasis on its unique feature of penalizing the absolute value of the regression coefficients; thus, the effect of the coefficients on the overall regression can be moderated [28]. The stronger the penalty is, the greater the reduction in the coefficients, with some reaching 0, thus automatically removing unnecessary/uninfluential

covariates [29, 30]. In recent years, LASSO regression has been used to screen for factors associated with tumours [31]. This study used LASSO regression to initially screen for CLNM risk factors in PTC patients with HT.

Our study aimed to establish a practical nomogram that predicts the likelihood of developing CLNM on the basis of clinical, haematological, and ultrasound images strategies. Patients were subsequently followed up for thyroid function within 3 years after surgery, and the prevalence and incidence of postoperative complications were compared between the CLNM (+) and CLNM (-) groups. This study provides a reference for doctors and patients in the formulation of treatment plans for further understanding the development of this disease.

Materials and methods

Study design and participants

This study retrospectively collected the clinical data of patients diagnosed with PTC combined with HT after thyroid surgery at the Hospital of Traditional Chinese Medicine Affiliated with Xinjiang Medical University between January 2015 and December 2022. The inclusion criteria for collection were as follows: (1) the primary lesion was located in the thyroid gland; (2) postoperative pathological examination confirmed PTC with HT; and (3) clinicopathological and USG imaging features were recorded comprehensively. The exclusion criteria were as follows: (1) patients who underwent secondary or more thyroid surgeries; (2) patients who did not undergo radical surgery or CLND; (3) patients who received radiofrequency and microwave ablation preoperatively; (4) patients who were previously diagnosed with tumours in other organs; (5) patients with other pathological types of TC; and (6) patients whose clinical information was incomplete.

Medical information on eligible PTC patients with HT was collected according to the strict inclusion and exclusion criteria of this study. A total of 7005 patients underwent thyroid surgery at the Hospital of Traditional Chinese Medicine Affiliated with Xinjiang Medical University between January 2015 and December 2022. The 2810 patients with benign lesions who were excluded were diagnosed with the following: 1896 patients with nodular goitre, 264 patients with Hashimoto's thyroiditis, 111 patients with benign thyroid tumours, 90 patients with subacute thyroiditis, 47 patients with other benign lesions, and 402 patients with mixed benign lesions. The other pathological types among the 78 patients with cancers were: 38 patients with folic carcinoma, 25 patients with medullary carcinoma, 8 patients with anaplastic carcinoma, and 7 patients with other types. Among the 4117 PTC patients, 3079 (74.79%) had PTC without HT, and 1038 (25.21%) had PTC with HT, with a ratio of approximately 3:1. The final number of PTC patients with HT who met the study criteria was 933, accounting for 22.66% of the PTC patients. Among the 933 PTC patients with HT, 216 (23.15%) had CLNM, and 717 (76.85%) did not have CLNM. We randomly divided the PTC patients with HT into a training group of 653 patients and a validation group of 280 patients at a ratio of 7:3. The detailed results are shown in Fig. 1. This study was approved by the Medical Ethics Committee of Traditional Chinese Medicine Hospital Affiliated with Xinjiang Medical University (IRB No. 2022XE0171). All of the participants provided informed consent to participate in this study after the purpose and nature of all of the procedures used were fully explained.

Information collection

The clinical information collected from PTC patients with HT included 43 variables that could be classified into 4 categories: patient demographics, blood biochemical indicators, thyroid ultrasound reports and pathological diagnosis findings.

The general clinical conditions included age, gender, body mass index (BMI), ethnicity, marital status, hypertension, diabetes, heart disease, smoking, drinking, family history of cancer, and family history of thyroid disease. This information was obtained from the patients' electronic medical records.

The following biochemical variables were used: (1) blood fat: triglyceride (TG), cholesterol (CHOL), high-density lipoprotein (HDL), and low-density lipoprotein (LDL); (2) thyroid function: triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH); (3) thyroid antibodies: thyrotropin receptor antibody (TRAb), anti-thyroglobulin antibodies (TGAb), and thyroid peroxidase antibodies (TPOAb); and (4) tumour markers: thyroglobulin (Tg), alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), and calcitonin (CT). The above blood test indicators of the patients were directly obtained from the hospital information system.

Ultrasound images were acquired using a GE-E11 ultrasound system (GE Medical Systems, USA) with a linear array probe in the frequency range of 9–11 MHz. All patients were placed in the supine position with the lower shoulder-occipital neck extended to better expose the inferior border of the thyroid gland. Scans of both the thyroid lobes and the isthmus were acquired in the transverse and longitudinal planes. Longitudinal and transverse images of the thyroid were obtained according to American College of Radiology accreditation standards. Ultrasound images of the thyroid nodules were prequalified by two experienced sonographers. The following

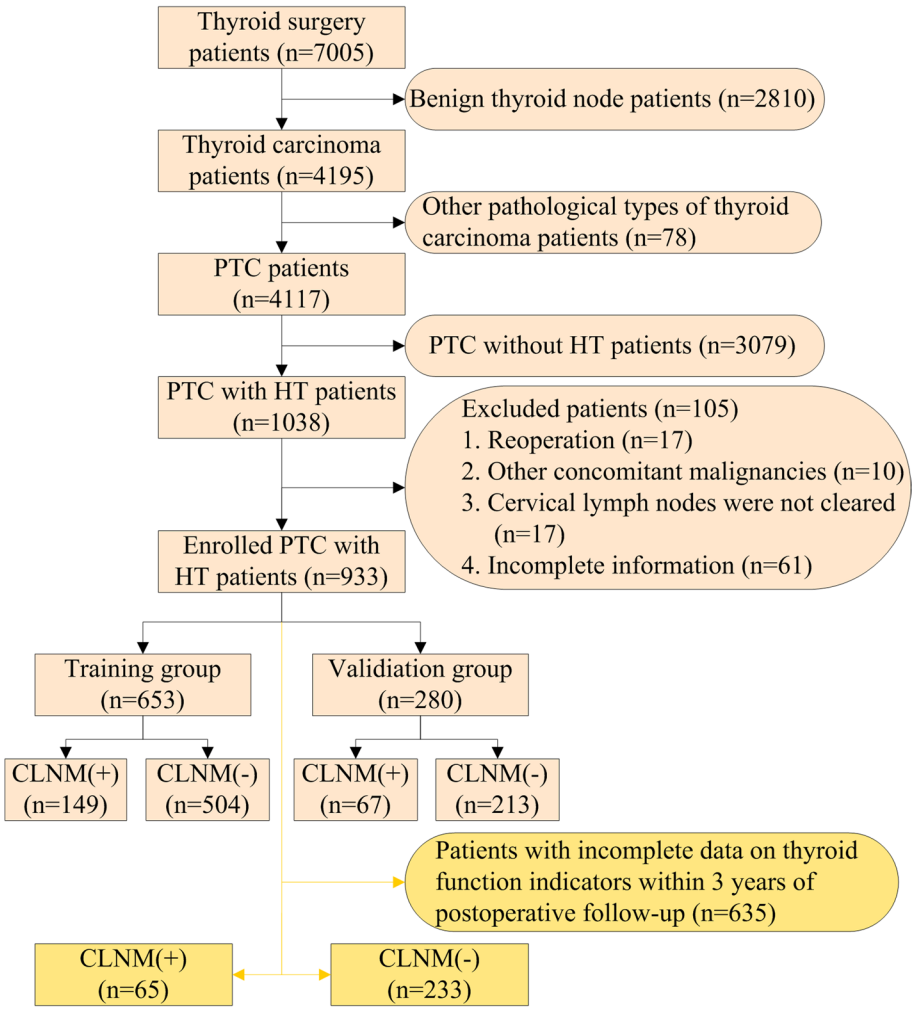

Fig. 1 Flowchart for data screening

USG parameters of the nodules were recorded: (1) echogenicity, (2) shape, (3) margin, (4) intranodular hyperechoic (IH), (5) colour Doppler flow imaging (CDFI), (6) calcification, (7) diffuse, (8) nodular position: location_UML, location_LRI, and (9) enlarged central lymph nodes (ECLNs).

Intraoperative frozen section pathology is performed on patients undergoing thyroid surgery, and the waiting time for results is approximately 0.5 h. The main purpose is to quickly clarify whether the nature of the tumour is benign or malignant to determine the surgical approach, extent of resection and extent of lymph node dissection. Paraffin section pathology is the final diagnosis of thyroid disease, and the waiting time is approximately 35 h. The main purpose is to further confirm the nature and differentiation of the tumour, which is the "gold standard" for the clinical diagnosis of benign or malignant lesions. The clinicopathological test results included the following: (1) HT, (2) nodular goitre, (3) diameter, (4) extrathyroidal extension (ETE), (5) multifocality, (6) bilateral, and (7) lateral lymph node metastasis (LLNM). Intraoperative and postoperative histopathological evaluations were performed by pathologists experienced in thyroid pathology.

Indicator explanation

This paragraph provides a detailed explanation of several indicators in the article. (1) When the malignant tumour was multifocal, we selected the largest diameter as the study sample. (2) On the basis of the patient's examination, experienced clinicians determined the surgical approach, extent of resection, clearance of the central (VI) or the lateral (II, III, IV) lymph nodes, and if the lateral lymph nodes were not cleared, LLNM was considered nonexistent. (3) The presence of HT was determined by pathologic testing. (4) For the interpretation of extrathyroidal gland invasion, this study was mainly based on the American Joint Committee on Cancer

(AJCC) 8th edition, and perithyroidal adipose tissue was no longer included in the scope of extrathyroidal gland invasion [32].

Basic information such as the age, gender and ethnicity of the patient during hospitalization were derived from the electronic ID card. Certain characteristics were obtained by questioning. "Marital status" was categorized as "Single", "Married" or "Divorced/Widowed". "Smoking" was classified into two categories on the basis of the number of cigarettes smoked per day: "No" indicates 0 cigarettes, and "Yes" indicates > 0 cigarettes. "Drinking" corresponds to alcohol drinking: "No" indicates drinking/time 0 g, "Yes" means drinking/time > 0 g. "Hypertension", "Diabetes", and "Heart disease" were all divided into two categories, with “No" indicating that the above diseases had not been clinically diagnosed prior to the procedure and "Yes" indicating that the disease had been diagnosed. "Family history of cancer" and "family history of thyroid disease" consider whether immediate family members have cancer or thyroid disease: "No" indicates that there is no family history, and "Yes" means that there is. Other variables needed to be obtained via ultrasound, blood and pathological examinations.

Surgical treatment

The surgical approach and extent were determined according to the intraoperative frozen section pathological examination results. For patients with an intraoperative diagnosis of benign thyroid lesions, unilateral or bilateral partial, major, or subtotal thyroidectomy was performed, as appropriate; for patients with an intraoperative diagnosis of malignancy, unilateral resection, unilateral plus major contralateral resection or bilateral thyroidectomy was performed. In this study, among 933 PTC patients with HT, 469 underwent total thyroidectomy, 365 underwent unilateral plus isthmus resection, and 99 underwent unilateral plus isthmus and contralateral partial resection. When central lymph node dissection was performed, 103 patients also underwent lateral cervical lymph node dissection. Unilateral or bilateral laryngeal recurrent nerve exploration was performed to avoid laryngeal nerve injury during thyroid surgery.

Thyroid function indicators follow-up

We retrospectively collected thyroid function indicators, mainly T3, T4, FT3, FT4, TSH, Tg, TGAb, and TPOAb, at 3 days, 1 month, 3 months, 6 months, 1 year, 2 years, and 3 years, respectively, after the implementation of surgical treatments in PTC patients with HT from 2015–2019. In accordance with the strict screening and inclusion criteria, follow-up patients had to be highly compliant, and complete follow-up records of thyroid function indicators for 3 consecutive years were obtained through outpatient or inpatient examinations. Patients whose data were incomplete were excluded from the follow-up study. Finally, 298 patients were included in the postoperative thyroid function follow-up analysis, including 65 patients in the CLNM (+) group and 233 patients in the CLNM (-) group, as shown in Fig. 1. Postoperative complications may occur after surgical treatment of thyroid cancer. Subclinical hypothyroidism is characterized by high TSH levels and normal FT4 levels; overt hypothyroidism is characterized by high TSH levels and low FT4 levels; subclinical hyperthyroidism is characterized by very low TSH levels and normal FT4 levels; and overt hyperthyroidism is characterized by low TSH levels and high FT4 levels. The detailed reference standards for the thyroid function indicators are shown in Table 1.

Construction of the nomogram

We screened risk factors in two steps. First, LASSO regression is a shrinkage method that actively selects from a large number of potentially multicollinear variables in a regression to obtain a set of more relevant and interpretable predictors [28]. LASSO minimizes the regression coefficients via a continuous shrinking operation to reduce the likelihood of overfitting, and the regression coefficients progressively converge to zero as the penalty coefficient log(λ) is gradually increased, thus allowing the selection of nonzero variables to remain in the model. In this study, tenfold cross-validation was used to select the penalty term λ. We calculated the mean-square error of the test data, where a smaller error was considered to indicate better model performance, and filtered out the variables corresponding to the log(λ) value with the smallest error.

After risk factors were selected via LASSO regression, nonzero variables were considered significant, and a multivariate logistic regression model for prediction was established. We also obtained coefficients, odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values for variables with statistical significance

Table 1 Reference standards for thyroid function indicators

Indicators	High	Normal	Low
T3 (nmol/L)	> 3.1	1.3—3.1	< 1.3
T4 (nmol/L)	> 181	66—181	< 66
FT3 (pmol/L)	> 6.8	3.1—6.8	< 3.1
FT4 (pmol/L)	> 22	12—22	< 12
TSH (uIU/ml)	> 4.2	0.27—4.2	< 0.27
Tg (ng/ml)	> 77	3.5—77	< 3.5
TGAb (IU/ml)	> 115	0—115	-
TPOAb (IU/ml)	> 34	0—34	-

($P < 0.05$) as influencing factors. A nomogram based on the risk factors identified by the multivariate logistic regression model was established to assess the risk of CLNM.

Evaluation of the nomogram

The performance of the nomogram was evaluated by receiver operating characteristic (ROC) curves, calibration curves, decision curve analysis (DCA) and recursive partitioning analysis (RPA) for the training and validation groups [4, 24, 29]. A ROC curve was used to assess the discrimination, and a reasonable range of the area under the curve (AUC) is from 0.5 to 1; the closer the value is to 1, the better the prediction performance of the nomogram [4]. The calibration curve is a very important criterion used to assess the matching effect between the model's predicted and real values. The Hosmer–Lemeshow goodness-of-fit test was used to evaluate the calibration, and when $P > 0.05$, the model has good calibration ability [24]. As a novel tool to evaluate the clinical application value of the nomogram, DCA was used to assess the ability of predictive models to visualize clinical outcomes and to compare the net benefits of predictive nomograms [24]. RPA provides a simple, straightforward and intuitive statistical method to classify patients, and to test the discrimination of the nomogram, all patients were redefined into low-, medium-, and high-risk subgroups on the basis of the final risk scores. Many medical care studies have used RPA to detect prognostic and risk factors [33].

Statistical analysis

Open source R software version 4.3.3 (https://www.r-project.org) and the Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 (SPSS Inc., Chicago, IL, United States) were used for data analysis and modelling in this study. To compare the baseline information and clinical characteristics of the training and validation groups, categorical variables were expressed as actual cases and percentages (%) using the chi-square test or Fisher's exact test, and continuous variables were expressed as the mean ± standard deviation (SD) via Student's t test or the Wilcoxon rank-sum test. In the present study, the following R packages were downloaded to construct the nomogram, perform LASSO regression analysis, plot ROC curves, perform calibration, and construct the DCA curve: "Hmisc", "rms", "glmnet", "pROC" and "rmda". All of the statistical tests were two-sided, and P values < 0.05 were considered statistically significant.

Results

Baseline characteristics

Among the 933 PTC patients with HT, 98 (10.50%) were men and 835 (89.50%) were women; the average age was 46.78 ± 10.76 years. A total of 216 (23.15%) patients with CLNM and 717 (76.85%) patients without CLNM were included. The model was established on the basis of a training group of 653 PTC patients with HT. There were 73 (11.18%) men and 580 (88.82%) women; the mean age was 46.78 ± 10.76 years; 149 (22.82%) patients developed CLNM, and 504 (77.18%) patients did not. A total of 280 PTC patients with HT were included in the validation group. When the 43 influencing factors were compared between the training and validation groups, the differences were not statistically significant ($P > 0.05$), except for the variables Diffuse and Smoking. These findings indicate that the clinical data of the patients in the training and validation groups were well distributed and could be further analysed. The specific clinical characteristics are shown in Table 2.

Selection of characteristics

In this study, LASSO regression was used to screen for possible risk factors in the training cohort. To prevent model overfitting and multicollinearity among variables, tenfold cross-validation was used for variable screening. When λ.min = 0.0167 and log(λ) = 4.0923, the cross-validation error is minimized, and the model performs optimal prediction, as shown in Fig. 2A. As the penalty coefficient log(λ) increases, the regression coefficients converge to 0, and the variables included in the model are gradually reduced, as shown in Fig. 2B. Moreover, the model selected 19 variables with nonzero coefficients as possible risk factors, which were age, BMI, marriage status, drinking status, hypertension, diabetes status, diffuse, shape, IH, diameter, multifocality, ETE, LLNM, ECLN, TG, HDL, T4, FT4, and TGAb. The coefficients for all of the variables are shown in Table S1.

Finally, the 19 variables mentioned above were included in the multivariate logistic regression analysis, and the results revealed that drinking (OR = 3.351, 95% CI, 1.390–7.922, $P = 0.006$), IH (OR = 1.961, 95% CI, 1.277–3.035, $P = 0.002$), diameter ≥ 1 cm (OR = 1.636, 95% CI, 1.019–2.602, $P = 0.039$), multifocality (OR = 1.630, 95% CI, 1.036–2.548, $P = 0.033$), ETE (OR = 2.887, 95% CI, 1.026–8.557, $P = 0.047$), CLNE (OR = 1.799, 95% CI, 1.053–3.034, $P = 0.029$), and LLNM (OR = 4.878, 95% CI, 1.984–12.774, $P < 0.001$) were independent risk factors for CLNM in PTC patients with HT, whereas older age (OR = 0.977, 95% CI, 0.954–0.999, $P = 0.049$), and higher BMI (OR = 0.932, 95% CI, 0.871–0.996, $P = 0.039$) were

Table 2 Baseline clinical characteristics of PTC patients with HT ($N = 933$)

Characteristics	Total n (%)	Training Group n (%)	Validation Group n (%)	x^2 or *t*-test	*P* value
All patients	933 (100)	653 (100)	280 (100)		
Group				0.136	0.712
CLNM (+)	216 (23.15)	149 (22.82)	67 (23.93)		
CLNM (-)	717 (76.85)	504 (77.18)	213 (76.07)		
Age (years)	46.78 ± 10.76	46.68 ± 10.77	47.01 ± 10.76	0.424	0.672
BMI	24.63 ± 3.56	24.67 ± 3.49	24.51 ± 3.73	-0.656	0.512
Gender				1.056	0.304
Male	98 (10.50)	73 (11.18)	25 (8.93)		
Female	835 (89.50)	580 (88.82)	255 (91.07)		
Ethnicity				3.204	0.202
Han	692 (74.17)	492 (75.34)	200 (71.43)		
Uygur	98 (10.50)	61 (9.34)	37 (13.21)		
Other nationalities	143 (15.33)	100 (15.32)	43 (15.36)		
Marital status				2.325	0.313
Single	39 (4.18)	31 (4.75)	8 (2.86)		
Married	858 (91.96)	599 (91.73)	259 (92.50)		
Divorced/Windowed	36 (3.86)	23 (3.52)	13 (4.64)		
Smoking				5.895	0.015
Yes	44 (4.72)	38 (5.82)	6 (2.14)		
No	889 (95.28)	615 (94.18)	274 (97.86)		
Drinking				2.819	0.093
Yes	39 (4.18)	32 (4.90)	7 (2.50)		
No	894 (95.82)	621 (95.10)	273 (97.50)		
Hypertension				0.715	0.398
Yes	165 (17.68)	120 (18.38)	45 (16.07)		
No	768 (82.32)	533 (81.62)	235 (83.93)		
Diabetes				0.447	0.504
Yes	78 (8.36)	52 (7.96)	26 (9.29)		
No	855 (91.64)	601 (92.04)	254 (90.71)		
Heart disease				1.358	0.244
Yes	45 (4.82)	28 (4.29)	17 (6.07)		
No	888 (95.18)	625 (95.71)	263 (93.93)		
Family history of cancer				0.032	0.858
Yes	137 (14.68)	95 (14.55)	42 (15.00)		
No	796 (85.12)	558 (85.45)	238 (85.00)		
Family history of thyroid disease				0.669	0.414
Yes	21 (2.25)	13 (1.99)	8 (2.86)		
No	912 (97.75)	640 (98.01)	272 (97.14)		
Diameter (cm)				0.099	0.753
≥ 1	260 (27.87)	180 (27.57)	80 (28.57)		
< 1	673 (72.13)	473 (27.43)	200 (71.43)		
ETE				0.316	0.574
Yes	35 (3.75)	23 (3.52)	12 (4.29)		
No	898 (96.25)	630 (96.48)	268 (95.71)		
LLNM				0.027	0.869
Yes	45 (4.82)	31 (4.75)	14 (5.00)		
No	888 (95.18)	622 (95.25)	266 (95.00)		
ECLN				1.201	0.273
Yes	167 (17.90)	111 (17.00)	56 (20.00)		

Table 2 (continued)

Characteristics	Total n (%)	Training Group n (%)	Validation Group n (%)	x^2 or *t*-test	*P* value
No	766 (82.10)	542 (83.00)	224 (80.00)		
Location_UML				1.968	0.374
Upper pole	203 (21.76)	134 (20.52)	69 (24.64)		
Middle third	399 (42.77)	283 (43.34)	116 (41.43)		
Lower pole	331 (35.47)	236 (36.14)	95 (33.93)		
Location_LRI				0.371	0.831
Left lobe	420 (45.02)	298 (45.64)	122 (43.57)		
Right lobe	482 (51.66)	334 (51.15)	148 (52.86)		
Isthmus	31 (3.32)	21 (3.21)	10 (3.57)		
Bilateral				0.166	0.684
Yes	166 (17.79)	114 (17.46)	52 (18.57)		
No	767 (82.21)	539 (82.54)	228 (81.43)		
Multifocality				0.006	0.940
Yes	255 (27.33)	178 (27.26)	77 (27.50)		
No	678 (72.67)	475 (72.74)	203 (72.50)		
Diffuse				5.727	0.017
Yes	464 (49.73)	308 (47.17)	156 (55.71)		
No	469 (50.27)	345 (52.83)	124 (44.29)		
Echogenicity				2.335	0.300
Hypoechoic	932 (99.89)	653 (100)	279 (99.64)		
Isoechoic/Hyperechoic	1 (0.11)	0 (0)	1 (0.36)		
Margin				0.018	0.892
Clear	236 (25.29)	166 (25.42)	70 (25.00)		
Unclear	697 (74.71)	487 (74.58)	210 (75.00)		
Shape				0.002	0.966
Regular	144 (15.43)	101 (15.47)	43 (15.36)		
Irregular	789 (84.57)	552 (84.53)	237 (84.64)		
IH				0.216	0.642
Yes	484 (51.88)	342 (52.37)	142 (50.71)		
No	449 (48.12)	311 (47.63)	138 (49.29)		
CDFI				1.463	0.226
Yes	541 (57.98)	387 (59.26)	154 (55.00)		
No	392 (42.02)	266 (40.74)	126 (45.00)		
Calcification				0.291	0.590
Yes	342 (36.66)	243 (37.21)	99 (35.36)		
No	591 (63.34)	410 (62.79)	181 (64.64)		
TG (mmol/L)	1.43 ± 0.92	1.42 ± 0.85	1.46 ± 1.08	0.544	0.586
CHOL (mmol/L)	4.42 ± 0.90	4.43 ± 0.90	4.40 ± 0.91	-0.355	0.723
HDL (mmol/L)	1.29 ± 0.29	1.29 ± 0.29	1.29 ± 0.30	0.123	0.902
LDL (mmol/L)	2.51 ± 0.71	2.52 ± 0.71	2.47 ± 0.72	-1.021	0.308
T3 (nmol/L)	1.67 ± 0.44	1.68 ± 0.48	1.63 ± 0.32	-1.600	0.110
T4 (nmol/L)	94.54 ± 19.72	95.33 ± 20.42	92.70 ± 17.88	-1.867	0.062
FT3 (pmol/L)	4.64 ± 1.49	4.70 ± 1.69	4.51 ± 0.84	-1.872	0.062
FT4 (pmol/L)	15.69 ± 4.37	15.77 ± 4.84	15.49 ± 3.02	-0.903	0.367
TSH (uIU/ml)	3.17 ± 2.68	3.24 ± 2.91	3.02 ± 2.07	-1.159	0.247
Tg (ng/ml)	19.74 ± 49.23	21.19 ± 53.44	16.37 ± 37.49	-1.571	0.117
TRAb (mmol/L)	0.80 ± 2.16	0.72 ± 1.31	0.99 ± 3.40	1.316	0.189
TGAb (IU/ml)	368.45 ± 642.39	364.31 ± 623.59	378.10 ± 685.28	0.300	0.764
TPOAb (IU/ml)	127.19 ± 162.72	125.97 ± 163.51	130.05 ± 161.13	0.351	0.726

Table 2 (continued)

Characteristics	Total n (%)	Training Group n (%)	Validation Group n (%)	x^2 or *t*-test	*P* value
AFP (ng/ml)	3.23 ± 1.95	3.25 ± 2.02	3.19 ± 1.79	-0.429	0.668
CEA (ng/ml)	1.45 ± 0.95	1.45 ± 0.97	1.46 ± 0.91	0.136	0.892
CT (pg/ml)	1.02 ± 1.14	1.06 ± 1.20	0.93 ± 0.97	-1.742	0.082

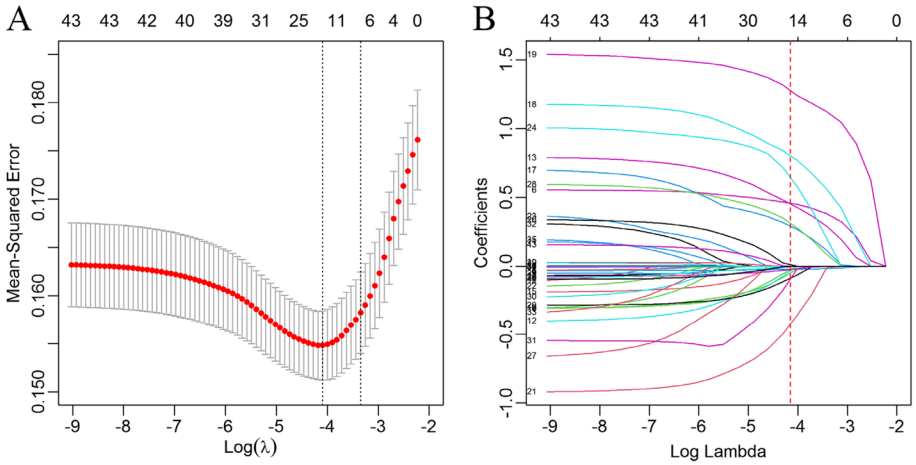

Fig. 2 Demographic and clinical characteristic selection via the LASSO binary logistic regression model. **A** Cross-validation curves. The X-axis shows the logarithm of the penalty coefficient log(λ), the Y-axis shows the mean squared error, and a smaller error value indicates a better model fit. The left dashed line (λ.min) indicates the λ with the smallest error and the best model fit; the right dashed line (λ.1SE) indicates the 1 standard error to the right of the λ.min. The optimal lambda in the LASSO model was selected as λ.min = 0.01672 for tenfold cross-validation. **B** LASSO coefficient path diagram for 43 risk factors. As log(λ) increases, the regression coefficients gradually converge to 0. The vertical line was drawn at the value chosen for tenfold cross-validation, and the optimal λ resulted in 19 variables with nonzero coefficients

regarded as protective factors. Using dependent variable transformation, we derived risk values for younger age (OR = 1.024, 95% CI, 1.000–1.049, $P = 0.049$) and lower BMI (OR = 1.073, 95% CI, 1.004–1.148, $P = 0.039$), as shown in Fig. 3. Table 3 presents the distribution of groups with and without CLNM, with statistically significant differences ($p < 0.05$). Age and BMI are continuous variables, and we plotted the probability density distributions separately, as presented in Fig. 4A and B.

Nomogram for predicting CLNM in PTC patients with HT

The 9 independent factors derived from multiple regression analysis based on the training group data were used to develop a nomogram to assess the risk of CLNM in PTC patients with HT (Fig. 5). According to the scale above the nomogram, the corresponding points (ranging from 0 to 100 points) for each risk factor can be calculated and summed to obtain the total points, which corresponds to the risk of CLNM in PTC patients with HT. A larger total number of points represents a greater risk of developing CLNM, corresponding to a risk range approximately of 0–100%.

Evaluating the effectiveness of the nomogram in predicting CLNM

The ROC curves of the nomogram for predicting the risk of CLNM in the training and validation groups are shown in Fig. 6A and B, respectively. The AUC value for the training group was 0.768 (95% CI, 0.723–0.812), with a diagnostic threshold of 0.292, sensitivity of 0.557 and specificity of 0.847. Validation was performed by using the validation group dataset. The AUC value for the validation group was 0.773 (95% CI, 0.705–0.841), with a diagnostic threshold of 0.270, sensitivity of 0.627 and specificity of 0.808. The difference in the AUC value between the training and validation groups was only 0.005. The above results indicate that the nomogram model has good discrimination ability. We grouped these 9 risk factors according to their data sources (basic clinical information, thyroid ultrasound, and pathological tests), plotted ROC curves, and calculated AUC values, as shown in Fig. 6C and D.

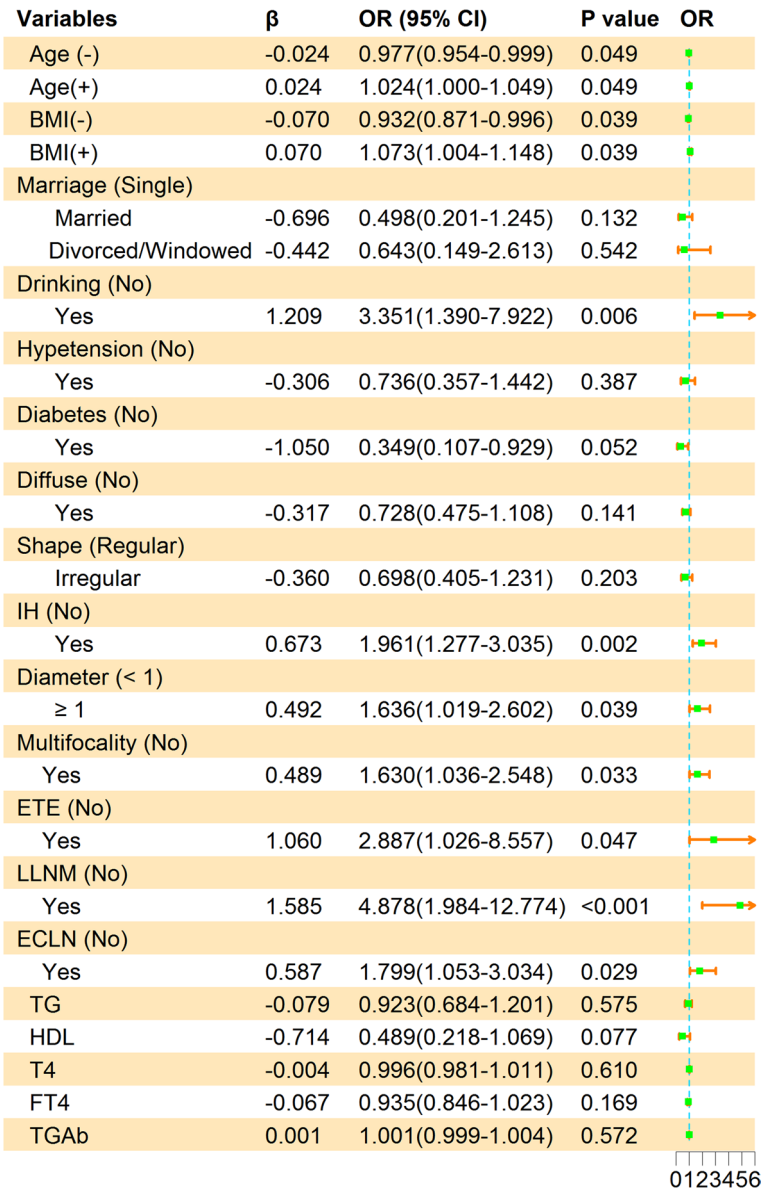

Fig. 3 Multivariate analysis of risk factors associated with CLNM in the training dataset

Calibration curve of the nomogram

The consistency of the match between the nomogram model-predicted and actual values was evaluated by the calibration curve, which was assessed by the Hosmer–Lemeshow goodness-of-fit test. When $P > 0.05$ (a larger P value indicates better calibration), the calibration ability of the model is good. The calibration curve values for the training and validation groups were 0.944 and 0.640, respectively (Fig. 7A and 7B), both of which were greater than 0.05, indicating that the nomogram model-predicted and actual values had good agreement and excellent calibration capability. Moreover, we also calculated the mean absolute errors of the calibration curves for the training and validation groups via 1000 bootstrap repetitions of sampling, which were 0.016 and 0.024, respectively (Figure S1), implying that the nomogram model has a good calibration effect.

DCA curve of the nomogram

Decision curve analysis (DCA) revealed that the use of the nomogram model to predict the risk of CLNM in PTC patients with HT provides a net benefit for implementing clinical interventions within a certain threshold probability range (Fig. 8A and B). The areas enclosed

Table 3 Distribution of groups with and without CLNM

Variables	Training Group n (%)			Validation Group n (%)			Total n (%)		
	CLNM (+)	CLNM (-)	*P* value	CLNM (+)	CLNM (-)	*P* value	CLNM (+)	CLNM (-)	*P* value
Total	149 (100)	504 (100)		67 (100)	213 (100)		216 (100)	717 (100)	
Age	43.25 ± 12.25	47.69 ± 10.08	< 0.001	42.06 ± 12.70	48.56 ± 9.59	< 0.001	42.88 ± 12.37	47.95 ± 9.94	< 0.001
BMI	24.10 ± 3.70	24.82 ± 3.41	0.018	24.18 ± 3.73	24.71 ± 3.73	0.164	24.13 ± 3.70	24.76 ± 3.51	0.034
Drinking			0.004			0.037			0.001
No	135 (90.60)	486 (96.43)		63 (94.03)	210 (98.59)		198 (91.67)	696 (97.07)	
Yes	14 (9.40)	18 (3.57)		4 (5.97)	3 (1.41)		18 (8.33)	21 (2.93)	
IH			< 0.001			0.002			< 0.001
No	38 (25.50)	264 (52.38)		22 (32.84)	116 (54.46)		60 (27.78)	380 (53.00)	
Yes	111 (74.50)	240 (47.62)		45 (67.16)	97 (45.54)		156 (72.22)	337 (47.00)	
Diameter			< 0.001			< 0.001			< 0.001
< 1	82 (55.03)	391 (77.58)		35 (52.24)	165 (77.64)		117 (54.17)	556 (77.55)	
≥ 1	67 (44.97)	113 (22.42)		32 (47.76)	48 (22.54)		99 (45.83)	161 (22.45)	
Multifocality			< 0.001			< 0.001			< 0.001
No	91 (61.07)	384 (76.19)		37 (55.22)	166 (77.93)		128 (59.26)	550 (76.71)	
Yes	58 (38.93)	120 (23.81)		30 (44.78)	47 (22.07)		88 (40.74)	167 (23.29)	
ETE			< 0.001			< 0.001			< 0.001
No	134 (89.93)	496 (98.41)		58 (86.57)	210 (98.59)		192 (88.89)	706 (98.47)	
Yes	15 (10.07)	8 (1.58)		9 (13.43)	3 (1.41)		24 (11.11)	11 (1.53)	
LLNM			< 0.001			< 0.001			< 0.001
No	127 (85.23)	495 (98.21)		55 (82.09)	211 (99.06)		182 (84.26)	706 (98.46)	
Yes	22 (14.77)	9 (1.79)		12 (17.91)	2 (0.94)		34 (15.74)	11 (1.54)	
ECLN			< 0.001			0.003			< 0.001
No	109 (73.15)	433 (85.91)		45 (67.16)	179 (84.04)		154 (71.30)	612 (85.36)	
Yes	40 (26.85)	71 (14.09)		22 (32.84)	34 (15.96)		62 (28.70)	105 (14.64)	

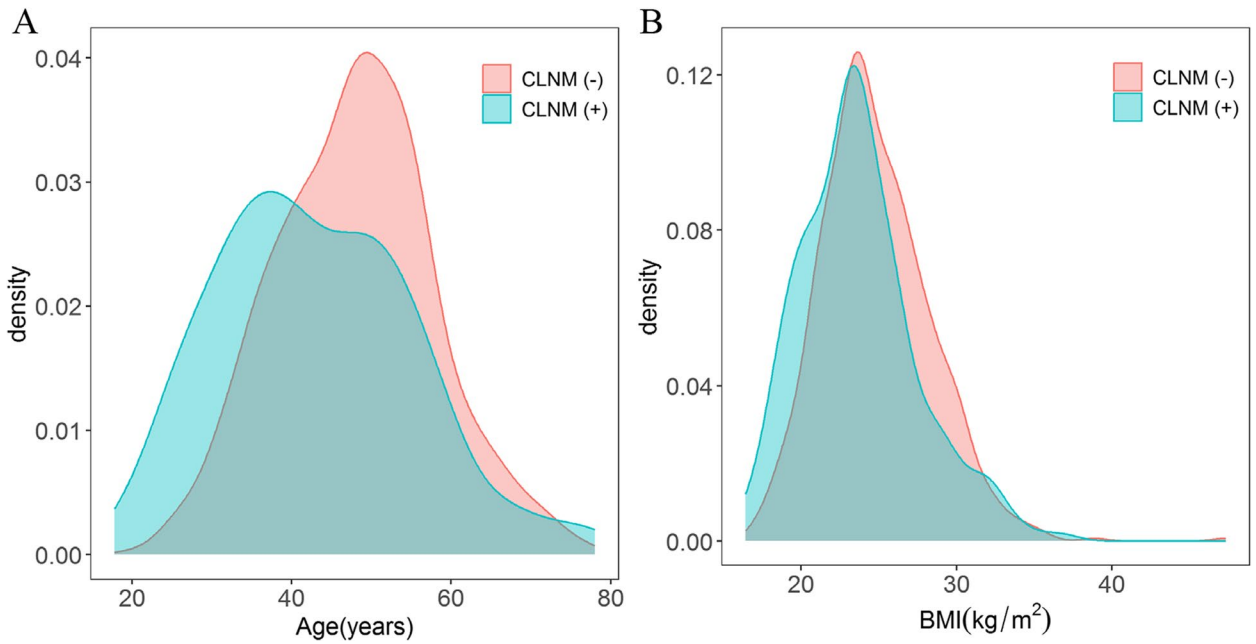

Fig. 4 Probability density distributions of the risk factors age and BMI

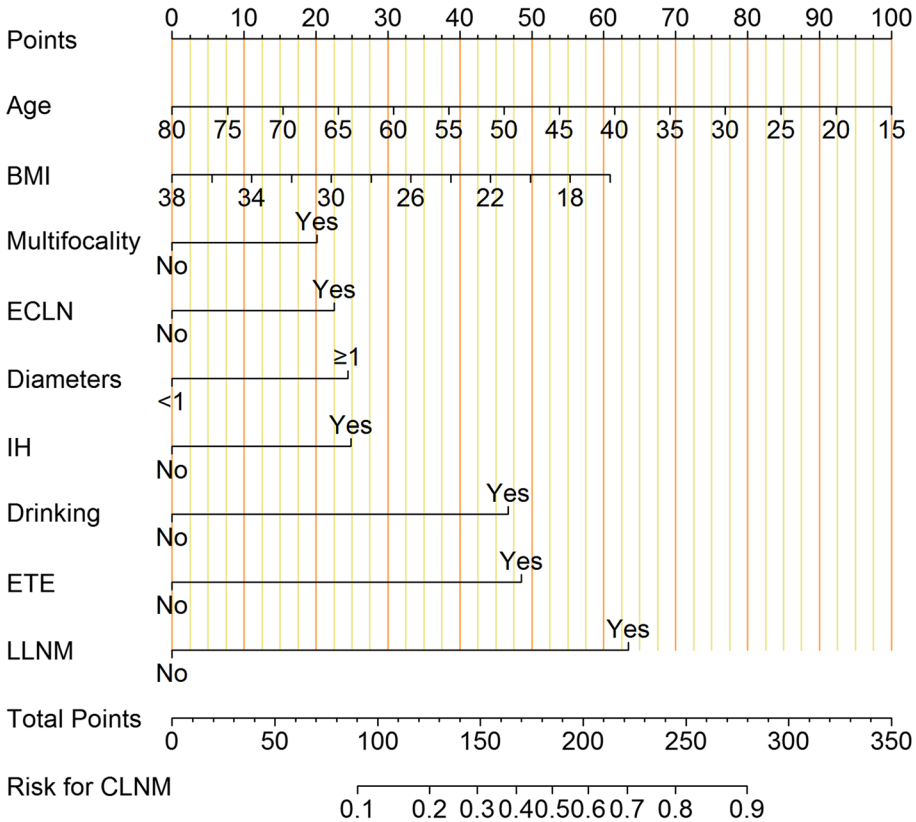

Fig. 5 Nomogram to estimate the risk of CLNM in PTC patients with HT. Risk factors were assigned corresponding points. Age: points range from 0 to 100, decreasing by 1.54 points for each additional year; BMI: points range from 0 to 61, with a decrease of 2.77 points for each additional unit; Multifocality: "Yes" receives 20 points; ECLN: "Yes" receives 22.50 points; Diameters: "≥ 1" receives 24 points; IH: "Yes" receives 25 points; Drinking: "Yes" receives 47 points; ETE: "Yes" receives 48.50 points; LLNM: "Yes" receives 63.50 points

by the upper black horizontal line (nonpatients), the right side of the solid plywood line (all patients) and the dashed blue line (model predictions) were considered to effectively benefit from clinical interventions. The nomogram-estimated threshold probability ranges for the training and validation groups to benefit from clinical interventions were 0.07–0.92 and 0.09–1, respectively.

Novel risk stratification based on the predictive nomogram

Each risk factor in the nomogram has its corresponding points, and the total points of PTC patients with HT can be used to quantitatively estimate the risk of CLNM; therefore, we determined two critical total points (130, 190) via recursive partition analysis (Fig. 9). We divided the total points into three subgroups: (1) the low-risk group (total points < 130, risk 0–23%), (2) the moderate-risk group (130 ≤ total points ≤ 190, risk 24–55%), and (3) the high-risk group (total points > 190, risk 56–100%). In the training group, the percentages of CLNM occurring in the low-, moderate-, and high-risk groups were 11.92%, 31.16%, and 69.23%, respectively ($P < 0.001$). Similarly, in the validation group, the percentages of CLNM were 11.38%, 32.58%, and 79.17% in the low-, moderate-, and high-risk groups, respectively ($P < 0.001$). The results revealed that the higher the risk level was, the greater the proportion of people in the CLNM (+) group. We further investigated whether there were significant differences in the relative risk of CLNM among the risk categories identified by the nomogram. When the distributions of the numbers in different risk groups were compared, we detected significant differences among all of the groups ($p < 0.001$), but no statistically significant differences were detected when the same risk groups were compared ($p > 0.05$). The above specific results are shown in Table 4.

Postoperative thyroid function follow-up

According to the strict screening criteria, 298 PTC patients with HT after surgery had complete thyroid function follow-up records, of which 65 (21.81%) developed CLNM and 233 (78.19%) did not, and the quantitative distributions were not statistically significant compared with those of the overall CLNM (+) and CLNM (-) groups ($x^2 = 0.230$, $P = 0.632$).

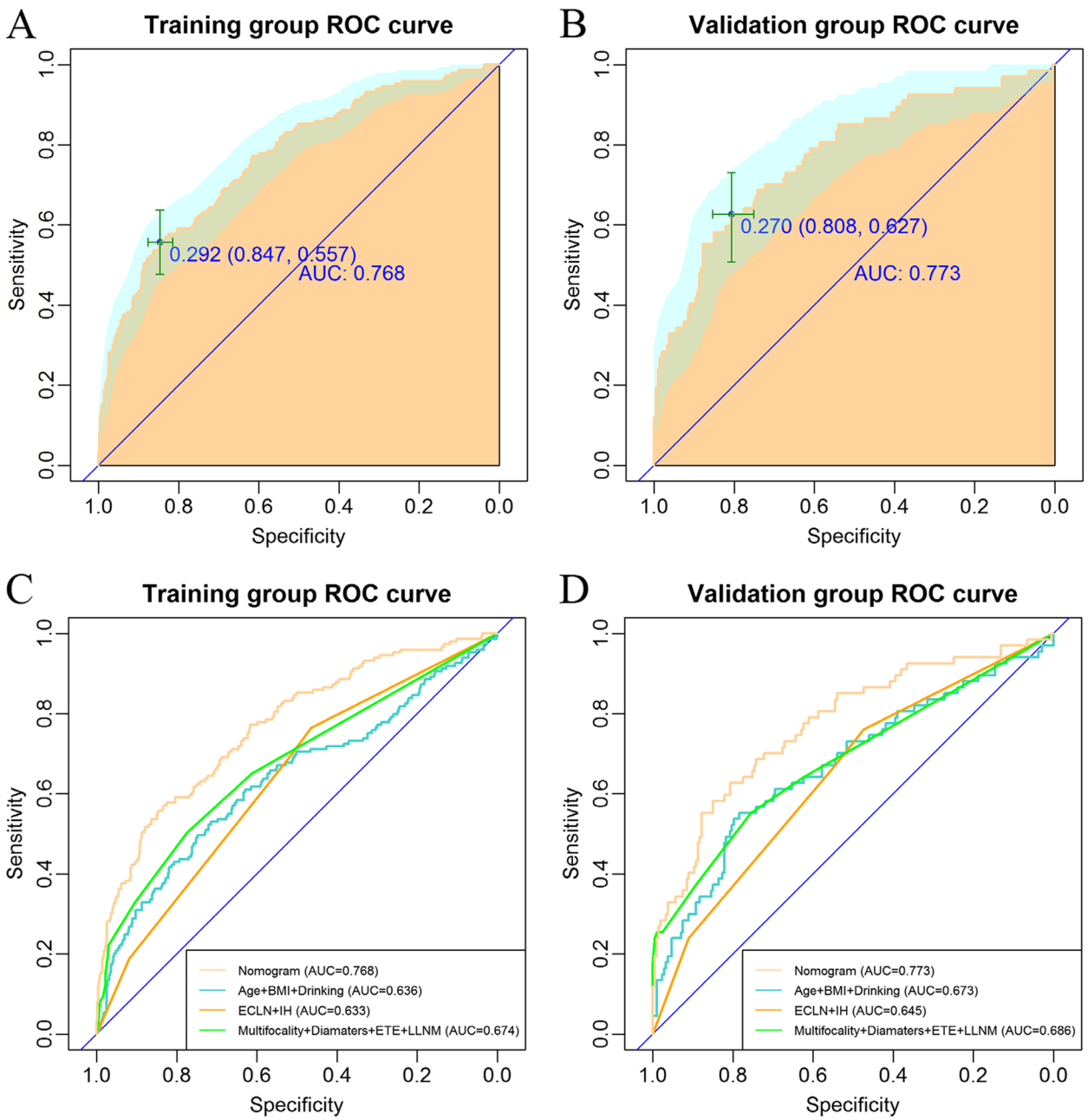

Fig. 6 The ROC curves of the nomogram for CLNM risk. **A** ROC curve for the training group, the light blue area represents the 95% confidence interval of the ROC curve, and the red-brown area represents the area under the ROC curve (AUC). **B** ROC curve for the training group. **C** ROC curves for different risk factors in the training group. **D** ROC curves for different risk factors in the validation group. Basic clinical information included: age, BMI, and drinking. Thyroid ultrasound included: ECLN and IH. Pathological findings included: diameter, multifocality, ETE and LLNM

The trends in postoperative thyroid function indicators and the differences between the CLNM (+) and CLNM (-) groups are shown in Table 5 and Fig. 9. Both the T3 and FT3 levels decreased to a trough at 3 days postsurgery, then gradually increased and peaked at 3 months postsurgery, with values approximating the preoperative levels. The T4 and FT4 levels gradually increased and reached a maximum at 3 months postoperatively, which was significantly greater than the preoperative levels. The TSH levels increased to the highest values at 1 month postsurgery and then decreased dramatically to below the preoperative levels. The Tg level increased to a maximum 3 days after surgery and then decreased rapidly to below the preoperative level. Both the TGAb and TPOAb

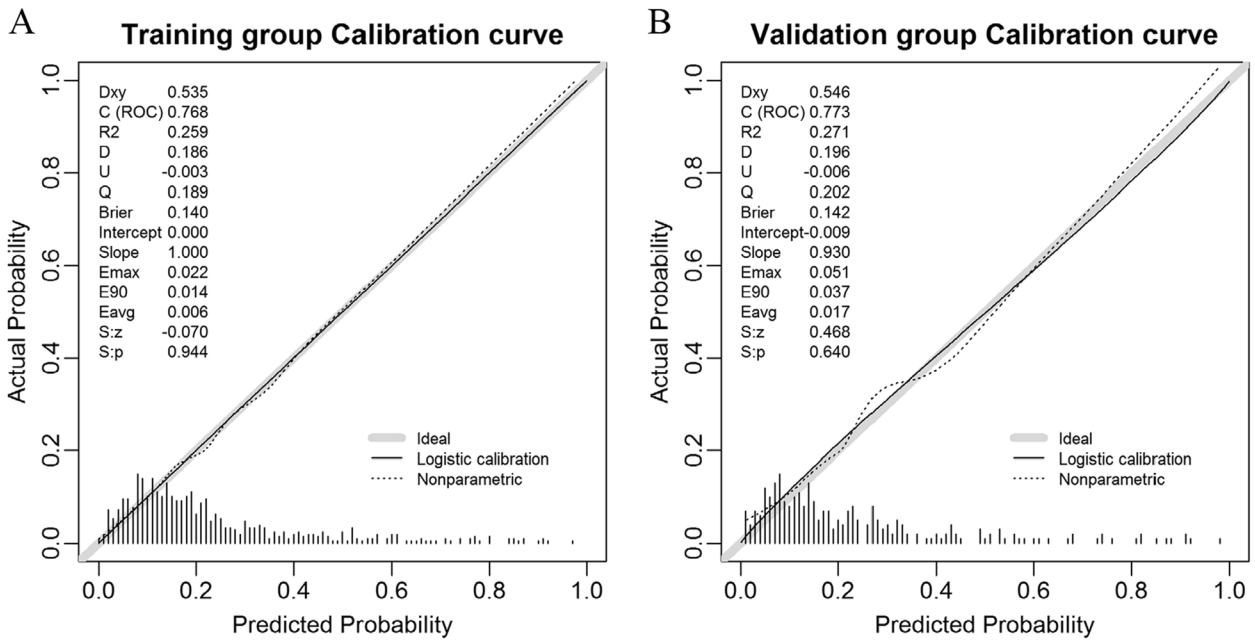

Fig. 7 Calibration curves for the training and validation groups. **A** training group, **B** validation group. The X-axis indicates the probability of nomogram prediction, the Y-axis represents the actual probability, and the grey area on the diagonal represents the perfect prediction of the ideal model. The solid black line represents the performance of the nomogram, which overlaps with the diagonal grey area, indicating that the model performs well

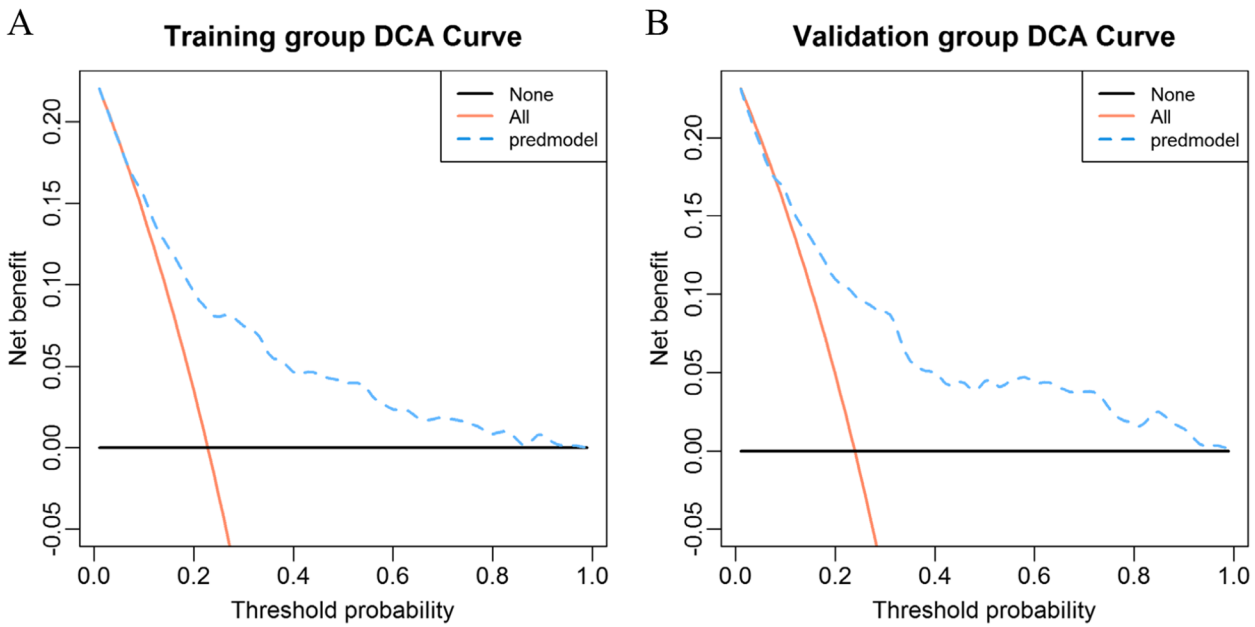

Fig. 8 DCA curve of the nomogram for CLNM risk. **A** training group, **B** validation group. The black horizontal line parallel to the x-axis indicates the patients who do not require additional clinical treatment interventions, with a benefit of 0. The red-brown diagonal line indicates the net benefit at different thresholds for additional clinical treatment interventions for patients identified as possibly requiring additional clinical treatment interventions

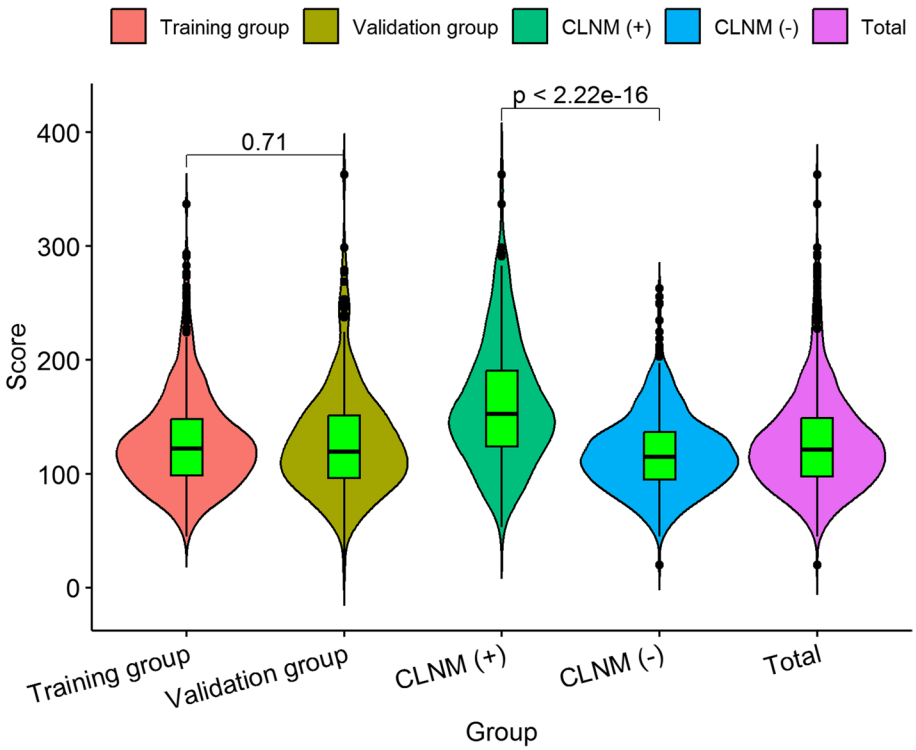

Fig. 9 Nomogram estimates of the distribution of points in each group violin plot. The length of the violin indicates the range of points, the width indicates the frequency of points, the violin contains a box diagram, and the black horizontal line in the box diagram indicates the average value of points. The average points of the training and validation groups were 128.08 ± 42.40 and 127.82 ± 46.63, respectively, with no statistically significant difference between the two groups ($p = 0.710$). The average score of 161.14 ± 54.42 points in the CLNM (+) group was significantly greater than that of 118.03 ± 34.12 points in the CLNM (-) group ($P < 0.001$). The overall average number of points was 128.01 ± 43.69. The distribution of points in the training group revealed that when points were < 130, the number of patients gradually increased, especially those in the CLNM (-) group, and the risk range was 0–23%, which was set as low risk. When points were 130 ≤ 190, the number of patients gradually decreased, with a risk range of 24–55%, which was designated as moderate risk. When points > 190, patients were predominantly in the CLNM (+) group, with a risk range of 56–100%, which was classified as high risk

Table 4 Metastasis risk stratification of PTC with HT patients on the basis of risk points of the nomogram model

Nomogram	LR <130	MR 130–190	HR >190	Total	*P* value	LR-MR *P* value	LR-HR *P* value	MR-HR *P* value
Training group								
CLNM (-)	340 (88.08)	148 (68.84)	16 (30.77)	504	< 0.001	< 0.001	< 0.001	< 0.001
CLNM (+)	46 (11.92)	67 (31.16)	36 (69.23)	149				
Total	386	215	52	653				
Validation group								
CLNM (-)	148 (88.62)	60 (67.42)	5 (20.83)	213	< 0.001	< 0.001	< 0.001	< 0.001
CLNM (+)	19 (11.38)	29 (32.58)	19 (79.17)	67				
Total	167	89	24	280				
P value	0.856	0.808	0.368					

levels gradually decreased. Thyroid function indicators T3, T4, FT3, FT4, TSH, Tg, and TPOAb levels within 3 years postoperatively were not significantly different between the CLNM (+) and CLNM (-) groups ($P > 0.05$). TGAb levels were higher in the CLNM (+) group than in the CLNM (-) group ($P < 0.1$) within 2 years after surgery, especially at 3 days, 1 month, and 1 year postoperatively ($P < 0.05$).

Table 5 Comparison of thyroid function between the CLNM (+) and CLNM (-) groups of PTC patients with HT 3 years after surgery

Variables	Time	Total n = 298	CLNM (+) n = 65	CLNM (-) n = 233	t	P
T3						
	Preoperative	1.65 ± 0.33	1.66 ± 0.29	1.64 ± 0.34	0.403	0.687
	3 days	1.13 ± 0.31	1.07 ± 0.23	1.14 ± 0.32	-1.285	0.200
	1 month	1.56 ± 0.37	1.58 ± 0.31	1.56 ± 0.38	0.468	0.640
	3 months	1.71 ± 0.42	1.73 ± 0.37	1.70 ± 0.44	0.504	0.615
	6 months	1.62 ± 0.36	1.68 ± 0.36	1.60 ± 0.35	1.615	0.107
	1 year	1.63 ± 0.36	1.68 ± 0.43	1.62 ± 0.34	1.066	0.287
	2 years	1.55 ± 0.27	1.59 ± 0.29	1.54 ± 0.26	1.079	0.282
	3 years	1.53 ± 0.28	1.52 ± 0.24	1.55 ± 0.29	-0.500	0.618
T4						
	Preoperative	93.43 ± 19.05	90.70 ± 17.04	94.18 ± 19.54	-1.311	0.191
	3 days	92.03 ± 23.25	85.31 ± 20.99	93.63 ± 23.53	-2.023	0.044
	1 month	104.27 ± 24.87	101.47 ± 20.50	105.05 ± 25.94	-1.025	0.306
	3 months	115.00 ± 26.43	111.87 ± 22.27	115.87 ± 27.46	-1.079	0.282
	6 months	114.72 ± 25.26	113.23 ± 22.70	115.13 ± 25.45	-0.536	0.593
	1 year	116.53 ± 23.41	118.33 ± 28.67	115.77 ± 21.04	0.787	0.434
	2 years	116.27 ± 23.91	117.30 ± 25.21	115.95 ± 23.59	0.311	0.756
	3 years	117.67 ± 23.37	113.83 ± 21.37	118.69 ± 23.89	-0.868	0.388
FT3						
	Preoperative	4.59 ± 0.89	4.72 ± 0.74	4.55 ± 0.93	1.325	0.186
	3 days	3.15 ± 0.73	3.05 ± 0.67	3.17 ± 0.74	-0.904	0.367
	1 month	4.37 ± 0.91	4.45 ± 0.90	4.35 ± 0.91	0.801	0.424
	3 months	4.99 ± 1.04	5.10 ± 1.25	4.96 ± 0.98	0.973	0.331
	6 months	4.74 ± 0.84	4.94 ± 0.78	4.68 ± 0.84	2.270	0.024
	1 year	4.74 ± 0.87	4.91 ± 0.98	4.69 ± 0.84	1.630	0.104
	2 years	4.63 ± 1.05	4.68 ± 0.77	4.61 ± 1.13	0.387	0.699
	3 years	4.46 ± 0.72	4.54 ± 0.58	4.44 ± 0.76	0.543	0.588
FT4						
	Preoperative	15.47 ± 2.77	14.95 ± 2.12	15.61 ± 2.92	-2.042	0.043
	3 days	15.99 ± 4.01	15.20 ± 4.19	16.18 ± 3.96	-1.379	0.169
	1 month	17.50 ± 4.33	17.56 ± 4.33	17.48 ± 4.34	0.136	0.892
	3 months	20.48 ± 4.77	20.52 ± 5.16	20.47 ± 4.66	0.065	0.948
	6 months	20.19 ± 4.43	20.31 ± 4.61	20.16 ± 4.39	0.244	0.808
	1 year	20.21 ± 4.15	20.89 ± 4.98	20.02 ± 3.89	1.159	0.250
	2 years	19.63 ± 3.74	19.64 ± 3.76	19.61 ± 3.72	0.047	0.962
	3 years	19.36 ± 3.69	19.37 ± 3.77	19.36 ± 3.69	0.03	0.997
TSH						
	Preoperative	3.03 ± 2.19	2.87 ± 2.11	3.07 ± 2.21	-0.664	0.507
	3 days	3.08 ± 3.82	3.74 ± 4.52	2.92 ± 3.62	1.211	0.227
	1 month	7.13 ± 13.36	7.78 ± 16.75	6.95 ± 12.29	0.441	0.660
	3 months	2.01 ± 5.64	2.64 ± 4.87	1.83 ± 5.83	1.032	0.303
	6 months	1.52 ± 4.88	1.65 ± 6.11	1.48 ± 4.50	0.254	0.800
	1 year	1.26 ± 5.63	0.67 ± 1.22	1.42 ± 6.31	-0.860	0.391
	2 years	1.21 ± 4.13	0.69 ± 1.12	1.38 ± 4.67	-0.927	0.355
	3 years	1.18 ± 3.39	0.96 ± 1.39	1.62 ± 3.74	-0.803	0.424
Tg						
	Preoperative	20.81 ± 51.65	17.16 ± 24.96	21.83 ± 56.91	-0.644	0.520
	3 days	55.80 ± 96.65	35.94 ± 73.92	60.55 ± 100.95	-1.433	0.154
	1 month	4.81 ± 15.94	4.91 ± 23.96	4.78 ± 12.92	0.058	0.954

Table 5 (continued)

Variables	Time	Total n = 298	CLNM (+) n = 65	CLNM (-) n = 233	t	P
	3 months	5.13 ± 16.35	4.34 ± 20.14	5.35 ± 15.17	-0.438	0.662
	6 months	3.13 ± 10.58	1.36 ± 2.98	3.62 ± 11.82	-2.634	0.009
	1 year	2.89 ± 10.21	1.21 ± 3.18	3.35 ± 11.78	-2.237	0.026
	2 years	2.26 ± 8.13	2.00 ± 5.64	2.34 ± 8.78	-0.234	0.816
	3 years	1.61 ± 4.59	1.45 ± 3.73	2.22 ± 7.05	-0.694	0.489
TGAb						
	Preoperative	369.34 ± 641.52	597.63 ± 948.09	305.65 ± 510.10	2.388	0.019
	3 days	284.76 ± 527.97	534.22 ± 874.29	222.40 ± 376.86	2.149	0.038
	1 month	333.86 ± 564.22	552.24 ± 878.38	279.26 ± 439.80	2.089	0.042
	3 months	277.25 ± 553.77	481.43 ± 936.32	222.94 ± 380.55	1.911	0.061
	6 months	236.00 ± 507.40	444.63 ± 913.45	179.74 ± 301.20	1.980	0.053
	1 year	251.77 ± 462.08	477.01 ± 966.40	168.87 ± 332.22	2.361	0.023
	2 years	199.10 ± 501.97	432.12 ± 878.19	133.86 ± 305.37	1.767	0.088
	3 years	299.77 ± 490.53	431.14 ± 952.99	154.85 ± 369.33	1.099	0.285
TPOAb						
	Preoperative	133.43 ± 163.47	114.87 ± 139.03	138.61 ± 169.57	-1.035	0.301
	3 days	123.94 ± 161.73	106.07 ± 138.18	128.41 ± 167.21	-0.761	0.448
	1 month	98.33 ± 123.58	81.56 ± 107.76	102.52 ± 127.13	-1.051	0.294
	3 months	91.52 ± 125.52	72.63 ± 114.54	96.54 ± 128.10	-1.198	0.232
	6 months	83.11 ± 122.36	57.54 ± 101.23	90.00 ± 126.84	-1.637	0.103
	1 year	76.26 ± 104.91	54.60 ± 76.68	81.78 ± 115.41	-1.264	0.208
	2 years	68.56 ± 116.39	54.10 ± 71.26	72.62 ± 104.51	-0.743	0.459
	3 years	59.14 ± 97.85	51.83 ± 59.14	65.12 ± 98.16	-0.692	0.473

Prevalence of postoperative complications

The prevalence of both subclinical hypothyroidism and hypothyroidism tended to increase and then decrease, occurring mainly within 6 months postoperatively and reaching the highest value at 1 month postoperatively, where the prevalence of overt hypothyroidism was significantly greater in the CLNM (+) group than in the CLNM (-) group, at 15.38% and 7.29%, respectively. The prevalence of subclinical hyperthyroidism progressively increased, with no significant difference between the CLNM (+) and CLNM (-) groups. Overt hyperthyroidism also demonstrated an increasing and then decreasing trend, reaching a maximum at 3 months postoperatively, which was greater in the CLNM (+) group than in the CLNM (-) group (32.31% and 25.32%, respectively). The percentage of patients whose TGAb or TPOAb levels exceeded the normal range decreased from 81.54% and 85.41%, respectively, preoperatively to 44.62% and 44.78%, respectively, at 3 years postoperatively in the CLNM (+) and CLNM (-) groups, suggesting that their Hashimoto's thyroiditis was gradually cured. The specific results are displayed in Fig. 10.

Incidence of postoperative complications

The Incidence of postoperative complications among PTC patients with HT in the CLNM (+) and CLNM (-) groups at different time within 3 years after surgery are shown in Figure S3. The overall incidences of subclinical hypothyroidism and subclinical hyperthyroidism were 45.97% and 69.13%, respectively, with no statistically significant difference between the CLNM (+) and CLNM (-) groups ($P > 0.05$). The overall incidence of overt hypothyroidism was 19.13%, which was significantly greater in the CLNM (+) group than in the CLNM (-) group ($P < 0.05$) (27.69% and 16.74%, respectively); the incidence of overt hyperthyroidism was 55.03%, which was slightly greater in the CLNM (+) group than in the CLNM (-) group (61.54% and 53.22%, respectively), but the difference was not statistically significant ($P > 0.05$). The above detailed results are shown in Table 6.

Discussion

Papillary thyroid carcinoma (PTC) is the most common differentiated thyroid malignancy, accounting for approximately 90% of all thyroid cancers [34, 35]. The incidence

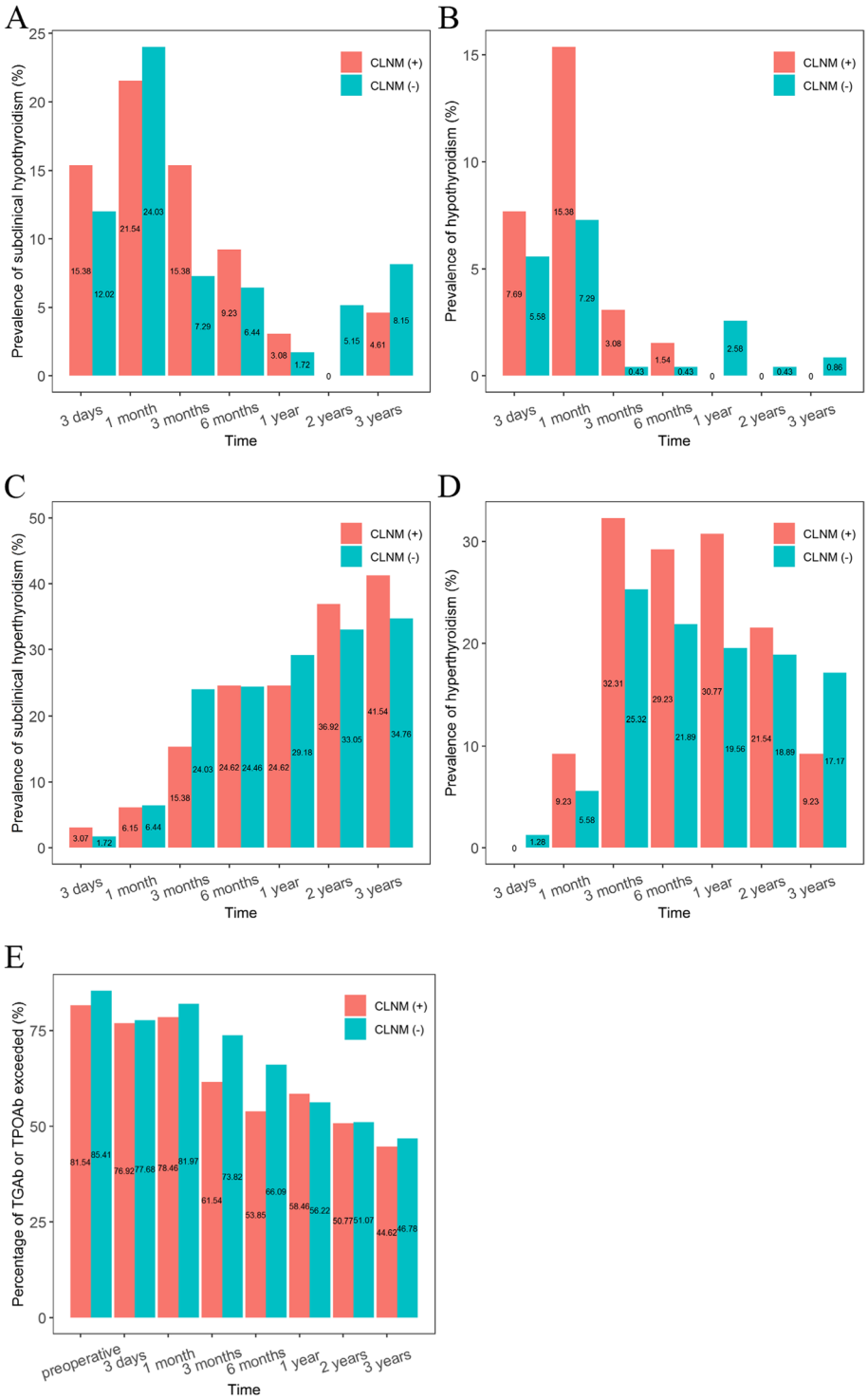

Fig. 10 Prevalence of postoperative complications in the CLNM (+) and CLNM (-) groups of PTC patients with HT at different time points within 3 years after surgery. **A** Subclinical hypothyroidism, **B** hypothyroidism, **C** subclinical hyperthyroidism, **D** hyperthyroidism, **E** percentages of TGAb or TPOAb levels exceeding the normal range

Table 6 Incidence of postoperative complications in the CLNM (+) and CLNM (-) groups of PTC patients with HT

Postoperative complication	Total n (%)	CLNM (+) n (%)	CLNM (-) n (%)	x^2	*P* value
All patients	298 (100)	65 (100)	233 (100)		
Subclinical hypothyroidism				0.001	0.974
Yes	137 (45.97)	30 (46.15)	107 (45.92)		
No	161 (54.03)	35(53.85)	126 (54.08)		
Hypothyroidism				3.942	0.047
Yes	57 (19.13)	18 (27.69)	39 (16.74)		
No	241 (80.87)	47 (72.31)	194 (83.26)		
Subclinical hyperthyroidism				0.344	0.557
Yes	206 (69.13)	43 (66.15)	163 (69.96)		
No	92 (30.87)	22 (33.85)	70 (30.04)		
Hyperthyroidism				1.421	0.233
Yes	164 (55.03)	40 (61.54)	124 (53.22)		
No	134 (44.97)	25 (38.46)	109 (46.78)		

of coexisting PTC and HT has increased significantly in the last 20 years, and the effect of HT on PTC has been a research hotspot [36, 37]. Several studies have shown that patients with coexisting PTC and HT are diagnosed at a younger age, and lymphovascular and perineural invasion negatively affect the prognosis of PTC patients with HT [38]. A study by Jin et al. [11] revealed that 17% (20/118) of PTC patients with HT had more than ten central compartment lymph nodes, but none of them developed lymph node metastasis. Similar findings have also been reported in previous studies [36, 39]. PTC patients with HT are more likely to have enlarged lymph nodes, prompting surgeons to perform more extensive central neck dissection. However, overly aggressive stripping may impair the normal function of the laryngeal return nerve [40]. Therefore, accurate identification of risk factors for CLNM can help assess the status of CLNM and determine the need for lymph node dissection, especially in PTC patients with HT [11].

Nomograms are statistical tools suitable for personalized risk assessment of oncology patients and are superior even to recognized experts in the field of oncology [41, 42]. In this study, we retrospectively collected clinical baseline information, blood test data, ultrasound data and pathologic features from 933 PTC patients with HT, and the patients were randomly divided into a training group ($n=653$) and a validation group ($n=280$) for model construction and internal validation, respectively. First, LASSO was applied to initially screen out 19 variables with nonzero regression coefficients. Subsequently, 9 independent risk factors for CLNM in PTC patients with HT were extracted via multivariate logistic regression and used to construct a nomogram model. We subsequently validated the performance of the nomogram model. ROC curve analysis indicated that the nomogram has good risk prediction and discrimination ability in both the training and validation groups. The calibration curve revealed that the nomogram exhibited good calibration ability in predicting CLNM risk. Moreover, DCA confirmed the clinical usefulness of the nomogram. Finally, we followed up the patients' thyroid function at 3 days, 1 month, 3 months, 6 months, 1 year, 2 years, and 3 years postoperatively and analysed the prevalence and incidence of postoperative complications in the CLNM (+) and CLNM (-) groups.

The nomogram model was used to plot the ROC curves, with AUC values of 0.768 (sensitivity of 0.557 and specificity of 0.847) and 0.773 (sensitivity of 0.627 and specificity of 0.808) for the training and validation groups, respectively. Zhao et al. [4] applied a nomogram to predict risk factors for CLNM in PTC patients with HT, and the estimated AUC values in the training and validation cases were 0.723 (sensitivity of 0.601 and specificity of 0.771) and 0.717, respectively. Wang et al. [43] confirmed the logistic regression model to predict the ROC curve of CLNM in PTC patients with HT and calculated an AUC value of 0.70 (sensitivity of 0.64 and specificity of 0.68). The AUC values estimated in this study are significantly greater than those of the above scholars, indicating that the developed nomogram model has good predictive and discriminative abilities. After observing the calibration curves (Fig. 7A and B), it is important to note that the constructed nomogram model provides excellent predictions for low-risk populations, average predictions for intermediate-risk populations, and somewhat overestimated predictions for high-risk populations. Combined with the results of the DCA curves (Fig. 8A and B) in clinical applications, this

nomogram model can accurately differentiate between CLNM patients and non-CLNM patients, providing a reference for clinicians to identify patients.

The results of this study suggested that age, BMI, drinking, IH, ECLN, diameter, multifocality, ETE and LLNM were the 9 independent risk factors for CLNM in PTC patients with HT. Age and BMI were negatively correlated with CLNM, and other indicators were positively correlated with CLNM. Our nomogram revealed that LLNM was the highest weighted risk factor for predicting CLNM (OR = 4.878), which is within the range of 0.202–5.135 reported by other scholars [44, 45], indicating that our results are reasonable. Lymph node metastasis in PTC patients usually occurs first in the ipsilateral CLNM, followed by the LLNM, and rarely by jump metastasis. Notably, numerous studies have shown that CLNM is also a risk factor for predicting LLNM [46, 47].

Several retrospective cohort studies have investigated the relationship between ETE and lymph node metastasis but remain controversial [48–50]. We predicted that ETE is a risk factor for the development of CLNM in PTC patients with HT (OR = 2.887), which is similar to the results of most studies [4, 51]. However, the findings of Liang et al. [13] and Wang et al. [43] indicated that ETE was not a risk factor for CLNM in PTC patients with HT, possibly due to the small sample size of the included studies. We also confirmed that multifocality (OR = 1.630) and a diameter ≥ 1 cm (OR = 1.636) are risk factors for developing CLNM. This has previously been reported in many studies [4, 13, 52, 53].

Mohamed et al. [54] reported that the presence of ECLN increased the predictive value in diagnosing PTC. The presence of ECLN on preoperative neck ultrasound can provide valuable information to help surgeons determine the optimal surgical treatment option for patients with PTC [55]. Our study confirmed that ECLN is an independent risk factor for CLNM (OR = 1.799), and the results provide us with a reminder to be vigilant for CLNM when ECLN is examined in PTC patients with HT. In this study, IH was also a risk factor for CLNM (OR = 1.961). IH may be a calcification or glially crystalline; the former is a malignant sign, whereas the latter is more common in benign nodules. Calcification is the deposition of calcium salts caused by vascular and fibrotic proliferation, reflecting the rapid growth of cancer cells [56, 57]. Therefore, if IH is detected on thyroid ultrasound, the status of the CLNM should be evaluated more carefully.

The relationship between alcohol drinking and thyroid cancer is controversial: some studies [58–60] have suggested that alcohol drinking reduces the risk of thyroid cancer, whereas others [61–63] have suggested that the potential carcinogenic effects of alcohol drinking increase the risk of thyroid cancer. The present study suggests that drinking (OR = 3.351) is also a risk factor for CLNM in PTC patients with HT. However, no studies have examined the association between alcohol drinking and the development of CLNM in PTC patients with HT, so these results need to be validated with an expanded sample. This study also revealed that younger age (OR = 1.024) and lower BMI (OR = 1.073) were risk factors for CLNM. These results are consistent with the findings of Zhao et al. [4].

Our study revealed that although TGAb was not a risk factor for CLNM, TGAb levels were significantly higher in the CLNM (+) group than in the CLNM (-) group, as were those in the regular postoperative follow-up test. Gao et al. [64] and Vasileiadis et al. [65] suggested that TGAb was an independent predictor for CLNM; a positive TGAb indicates that the tumour is active, and the incidence of CLNM was significantly greater in PTC patients with positive TGAb (20.3%-25.9%) than in patients with negative TGAb (10.0%-15.22%). This result also confirms the higher TGAb levels in PTC patients who developed CLNM, which is consistent with the present study.

Thyroid function indicators of PTC patients with HT followed up within 3 years after surgery showed the same trends in the CLNM (+) and CLNM (-) groups. Moreover, T3, FT3, T4 and FT4 also demonstrated approximately regular fluctuation trends. Bae et al. [66] analysed the trends of FT4 and TSH in PTC patients within 2 years after surgery. Serum TSH concentrations gradually increased up to 3 ~ 6 months and then decreased to a level higher than the preoperative level, whereas FT4 concentrations had the opposite trend as TSH in serial measurements. Our findings also confirmed the trend of increasing and then decreasing TSH levels in PTC patients with HT, whereas FT4 levels showed the opposite trend. Elevated serum TGAb or TPOAb levels are among the main diagnostic criteria for HT. In contrast, in the present study, the decrease in postoperative TGAb or TPOAb levels indicated that patients with HT gradually recovered.

Several studies have reported that the incidence of postthyroidectomy hypothyroidism ranges from 5.6% to 64.2%, depending on the duration of follow-up evaluation and the definition of hypothyroidism among patients who undergo lobectomy [67, 68]. In our study, postoperative hypothyroidism occurred in 194 (65.10%) patients, including 57 (19.13%) with overt hypothyroidism and 137 (45.97%) with subclinical hypothyroidism. The overall incidence of hypothyroidism was greater than that reported in previous studies, especially for overt hypothyroidism. This finding may be explained by the following: (1) Hashimoto's thyroiditis has been demonstrated

to be a risk factor for postoperative hypothyroidism and can increase the incidence of hypothyroidism [68]; (2) even patients without any signs or symptoms of hypothyroidism should be prospectively tested for biochemical hypothyroidism after surgery using a standardized follow-up protocol; and (3) the mean follow-up in our study was longer (3 years), which may also contribute to the high incidence. In this study, the incidence of postoperative overt hypothyroidism was significantly greater in the CLNM (+) group than in the CLNM (-) group. The probable reason for this result was that the thyroid hormone level secreted by the patient's body decreased significantly after thyroidectomy, and the proportion of patients with total thyroidectomy in the CLNM (+) group (65.74%) was greater than that in the CLNM (-) group (45.61%), with a relatively high risk of hypothyroidism. Although the TSH level was maintained within the normal range by thyroid hormone supplementation, the drug dosage should be regularly reviewed and appropriately adjusted according to the current thyroid function level, since it may promote the occurrence of hypothyroidism [69]. Another possible reason is that HT increases the incidence of postoperative complications of hypothyroidism, and some studies have confirmed that TGAb is a risk factor for CLNM, whereas elevated TGAb is an important marker for HT. In the present study, the TGAb levels were significantly greater in the CLNM (+) group than in the CLNM (-) group, which may promote the development of hypothyroidism.

The following shortcomings remain in this study: (1) The internal validation of the nomogram was from the same hospital, and there may be case selection bias. Therefore, it should be combined with multicentre large sample clinical data should be obtained for further analysis and evaluation. (2) A larger sample size of clinical data is still needed to improve the validity and reliability of the model. (3) Finally, this study has several potential limitations. This is a retrospective analysis, and further prospective studies are needed to clarify the potential causal relationship between HT and PTC. More patient samples are needed for prospective studies to identify and validate this risk prediction model to improve clinical management.

Conclusion

In conclusion, we found that CLNM in PTC patients with HT was associated with younger age, lower BMI, drinking, intranodular hyperechoic, ECLN, diameter ≥ 1 cm, multifocality, ETE and LLNM. We constructed a nomogram model by combining nine risk factors for the development of CLNM in PTC patients with HT, and the model exhibited high predictive accuracy. On the basis of the quantitative risk stratification provided by our nomogram, clinicians are able to identify PTC patients with HT who are at increased risk for CLNM. Prophylactic CLND and rigorous preoperative evaluation may improve the prognosis when PTC patients with HT have high scores according to the nomogram. The follow-up monitoring of patients during the 3-year postoperative period clearly demonstrated trends in thyroid function indicators in the CLNM (+) and CLNM (-) groups, and the incidence of the postoperative complications of hypothyroidism, subclinical hypothyroidism, hyperthyroidism, and subclinical hyperthyroidism were accurately predicted.

Abbreviations

PTC	Papillary thyroid cancer
HT	Hashimoto's thyroiditis
CLNM	Central lymph node metastasis
LASSO	Least absolute shrinkage and selection operator
BMI	Body mass index
IH	Intranodular hyperechoic
ETE	Extrathyroidal extension
ECLN	Enlarged central lymph nodes
LLNM	Lateral lymph node metastasis
ATA	American Thyroid Association
CLND	Central lymph node dissection
TG	Triglyceride
CHOL	Cholesterol
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
T3	Triiodothyronine
T4	Thyroxine
FT3	Free triiodothyronine
FT4	Free thyroxine
TSH	Thyroid stimulating hormone
TRAb	Thyrotropin receptor antibody
TGAb	Anti-thyroglobulin antibodies
TPOAb	Thyroid peroxidase antibodies
Tg	Thyroglobulin
AFP	Alpha fetoprotein
CEA	Carcinoembryonic antigen
CT	Calcitonin
CDFI	Colour Doppler flow imaging
AJCC	American Joint Committee on Cancer
ROC	Receiver operating characteristic
AUC	Area under the curve
DCA	Decision curve analysis
LR	Low risk
MR	Moderate risk
HR	High risk
CI	Confidence interval
OR	Odds ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13805-w.

Supplementary Material 1.

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Authors' contributions
Conceptualization: Pengwei Lou and Yuting Huang. Methodology: Pengwei Lou and Kai Wang. Software: Pengwei Lou, Feng Zhao and Kai Wang. Validation: Feng Zhao and Jiabo Xu. Formal analysis: Pengwei Lou, Yuting Huang, Jiabo Xu and Kai Wang. Investigation: Yuting Huang, Jiabo Xu and Hui Li. Resources: Yuting Huang, Jiabo Xu and Hui Li. Data curation: Pengwei Lou and Hui Li. Writing-Original draft: Pengwei Lou and Yuting Huang. Writing-Review and editing: Jiabo Xu and Kai Wang. Visualization: Pengwei Lou and Kai Wang. Supervision: Kai Wang and Jiabo Xu. Project administration: Kai Wang. All authors critically read the manuscript and gave final approval for publication.

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Data availability
The data that support the findings of this study are available from the Traditional Chinese Medicine Hospital Affiliated with Xinjiang Medical University, but restrictions apply to the availability of these data, which were used under license for the current research, and so are not publicly available. However, the data and materials of this study are available from the corresponding author for reasonable requests.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Studies involving human participants were reviewed and approved by the Ethics Committee and the Institutional Review Committee of Traditional Chinese Medicine Hospital Affiliated with Xinjiang Medical University (IRB No: 2022XE0171). Informed consent was obtained from all individual participants included in the study.

Consent for publication
Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Competing interests
The authors declare no competing interests.

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