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ORIGINAL RESEARCH

Analysis of Risk Factors and Risk Prediction for Cervical Lymph Node Metastasis in Thyroid Papillary Carcinoma

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Background: To analyze the risk factors of cervical lymph node metastasis (LNM) of thyroid papillary carcinoma (PTC) and construct the prediction model.

Methods: Clinical data of 1105 patients with pathologically confirmed PTC in our hospital from February 2019 to May 2024 were retrospectively analyzed, and randomly divided into a training set and validation set according to the proportion of 7:3. With cervical central LNM (CLNM) and lateral LNM (LLNM) as outcome variables respectively, ultrasound characteristics were analyzed and C-TIRADS scores were performed Combined with the general situation of the patient, preoperative serum thyroglobulin (Tg) level, BRAFV600E (hereinafter referred to as BRAF) gene mutation and other characteristics of the patient, analysis was conducted to determine the independent risk factors for cervical CLNM and LLNM of PTC, and establish Nomogram prediction models. The test data set is used to validate the model. The area under the ROC curve (AUC) and the decision curve analysis (DCA) were used to evaluate the prediction efficiency of the model.

Results: The analysis shows that male, age < 55 years old, tumor diameter ≥ 1 cm, capsular invasion, positive serum thyroglobulin (Tg), BRAF gene mutation type and C-TIRADS score are independent risk factors for cervical CLNM in PTC ($P < 0.05$). Tumor diameter ≥ 1 cm, capsular invasion, tumor located at the upper pole and presence of CLNM are independent risk factors for LLNM in PTC. Based on the above risk factors, Nomogram prediction models for CLNM and LLNM are constructed respectively. The AUC of the CLNM prediction model is 91.5%. LLNM model is 96.1%.

Conclusion: Ultrasound indicators, C-TIRADS score combined with BRAF gene status, Tg and clinical indicators of patients have important value in predicting cervical CLNM and LLNM in PTC. The Nomogram prediction models constructed based on the above indicators can effectively predict the risk of LNM in PTC.

Keywords: thyroid, cancer, lymph nodes, metastasis, prediction model

Background

The incidence of thyroid cancer has been steadily increasing and now ranks as the most common endocrine malignancy. Among them, papillary thyroid carcinoma (PTC) represents the most prevalent histological subtype of thyroid cancer.[1] Despite PTC's relatively favourable biology and prognosis, it can still early on manifest lymph node metastasis within the neck region. Reports indicate that lymph node metastasis (LNM) occurs in approximately 30% to 80% of PTC patients,[2,3] including cervical central LNM (CLNM) and lateral LNM (LLNM). Studies have indicated that cervical LNM is one of the adverse prognostic factors in PTC,[4] and it is closely related to distant metastasis and recurrence, which may lead to secondary surgery. Cervical lymph node dissection is an important means to treat lymph node metastasis of thyroid cancer, but its dissection scope and indications are still controversial.[5] The Thyroidology Branch of the Chinese Medical Association and Japanese guidelines recommend routine prophylactic central neck dissection, which can significantly reduce the risk of recurrence.[6] However, European and American guidelines recommend performing prophylactic central lymph node dissection (pCND) only for patients with T3, T4 stages and clinical N1b (cN1b), and do not recommend performing pCND for clinical N0(cN0) PTC in T1 and T2 stages.[7] For the indications of lateral

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cervical lymph node dissection, only therapeutic lateral lymph node dissection (LND) is recommended. Therefore, preoperative assessment of LNM is of great significance for surgeons to choose an appropriate surgical plan. Ultrasound examination remains the primary diagnostic tool for thyroid disorders, and in August 2020, the Chinese Society of Ultrasound in Medicine's Superficial Organs and Vascular Group introduced the Chinese Thyroid Imaging Reporting and Data System (C-TIRADS),[8] making the stratification of thyroid nodule malignancy more convenient and concise. However, the accuracy of ultrasound alone in detecting cervical LNM in PTC is suboptimal.[9] BRAF gene mutation is a common type of genetic mutation in PTC, and previous studies have shown that it is associated with poor prognosis in PTC.[10] Currently, there have been many studies on risk prediction models for PTC with LNM, but a prediction model for PTC with CLNM and LLNM combined with the above characteristics has not been reported yet.

Given this context, our study conducted a retrospective analysis, combining the clinical characteristics, pathological features, and BRAF gene status of PTC patients with ultrasound to analyze the risk factors associated with cervical CLNM and LLNM in PTC. Based on these findings, we constructed corresponding Nomogram prediction models.

Methods

Study Subjects

This study was conducted with the approval of our hospital's ethics committee [2021KY307-01]. Patients with papillary thyroid carcinoma who underwent total or subtotal thyroidectomy in our hospital from February 2019 to May 2024 were retrospectively collected. Among them, those who underwent prophylactic lymph node dissection surgery (all of them received prophylactic central cervical lymph node dissection, and therapeutic LND was added if preoperative ultrasound indicated suspected lateral cervical lymph node metastasis) were screened out. The clinical and imaging data of all these patients were collected. The identifiable information of all patients was deleted to ensure the confidentiality of the data source. There were 1105 eligible cases, which were randomly divided into a training set of 774 cases and a validation set of 331 cases at a ratio of 7:3. Inclusion criteria were as follows: (1) Age > 18 years; (2) Standard thyroid ultrasound examination performed preoperatively, along with C-TIRADS scoring; (3) Preoperative ultrasound-guided fine-needle aspiration biopsy with BRAF gene status detection; (4) Postoperative pathological confirmation of PTC; (5) Clinical and imaging data were complete. Exclusion criteria were: (1) Poor ultrasound image quality preventing C-TIRADS scoring; (2) Pre-existing benign thyroid conditions such as autoimmune thyroiditis and subacute thyroiditis that could lead to elevated serum Tg levels. (3) The patient had a history of head and neck radiotherapy. (4) The patient has another malignant tumor.

According to pathological results, all enrolled patients were categorised into two groups based on the presence or absence of cervical CLNM or LLNM: the cervical CLNM group and the non-cervical CLNM group, the cervical LLNM group and the non-LLNM group.

Ultrasound Instruments and Methods

We utilised GE LOGIQ E9, and GE Voluson E10 colour Doppler ultrasound diagnostic instruments, equipped with high-frequency linear array probes with frequencies ranging from 5 to 12 MHz. Fully expose the patient's anterior cervical region, and scan and store images according to thyroid and cervical lymph node scanning standards. General clinical data for enrolled patients were collected. Thyroid nodule ultrasound data were gathered at the image storage and transmission system workstation. This included recording general ultrasound characteristics of thyroid nodules such as size, echogenicity, morphology, margins, multiplicity, capsular invasion, nodule location and applying C-TIRADS scoring. Ultrasound images were interpreted by two experienced associate chief physicians in thyroid ultrasound. In case of disagreement between the two associate chief physicians, the final decision will be recorded after consultation and agreement with the chief physician who has 25 years of experience. If a patient had multiple nodules, the nodule with the most suspicious PTC features was included for statistical analysis.

C-TIRADS scoring is primarily based on the tally of suspicious ultrasound features (vertical growth, solid nodules, markedly hypoechoic, punctate echogenic foci/microcalcifications, and indistinct/irregular margins as suspicious malignant features, while comet-tail artefact is a benign feature).[8] If nodules exhibit the benign feature of a comet-tail artefact,

one point is deducted from the total score. The scores are added to obtain a total score ranging from –1 to 5 points. If there is no thyroid tissue between the PTC nodule and the capsule, it is defined as a PTC capsule invasion.[11] If it is located at the upper pole, it is defined as the nodule being located at the upper pole.

Laboratory and Pathological Examinations

All enrolled patients underwent preoperative serum thyroid function testing using the chemiluminescence method to obtain serum thyroglobulin (Tg) values. Following a prior study,[12] a Tg level ≤10 ug/L was deemed negative, while a Tg level >10 ug/L was considered positive. Scoring assessments were conducted blindly in retrospect. Preoperatively, all enrolled patients underwent ultrasound-guided fine-needle aspiration biopsy, and the biopsy specimens were subjected to BRAF gene status testing, categorised as either mutated or wild-type.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0. Normally distributed measurement data were presented as mean ± standard deviation (χ±s). Differences between groups were analysed using independent sample *t*-tests or non-parametric Mann–Whitney *U*-tests for continuous data. Categorical data were presented as frequencies (percentages) and analysed for intergroup differences using the chi-square test. Multifactorial analysis employed binary logistic regression analysis to identify independent risk factors influencing cervical CLNM and LLNM. The Nomogram prediction models were constructed using R (R 4.4.1) and used the rms package to generate calibration curves and ROC curves. The clinical utility of the predictive model was assessed using decision curve analysis. Statistical significance was established at $P < 0.05$.

Results

Basic Characteristics

A total of 1105 PTC patients were included. Among them, there were 267 males (24.2%), aged 22 ~ 78 (42.26 ± 12.24) years old, and 838 females (75.8%), aged 20 ~ 88 (44.8 ± 11.25) years old. The enrolled patients were randomly divided into a training group of 774 cases and a validation group of 331 cases in a ratio of 7:3. The basic characteristics of the training group and the validation group are shown in Table 1. There were no significant differences in clinical characteristics, pathological characteristics, and ultrasonic characteristic indexes between the two groups ($P > 0.05$), indicating that the two sets of data were evenly matched.

Table 1 Basic Characteristics of the Training Group and the Validation Group

Parameter	Training Group (n=774, %)	Validation Group (n=331, %)	Total (n=1105)	χ^2/*U Value*	*P*-value
Gender					
Male	188 (24.3)	79 (23.9)	267	0.023	0.081
Female	586 (75.7)	252 (76.1)	838		
Age (years)					
<55	619 (80.0)	265 (80.1)	884	0.001	0.974
≥55	155 (20.0)	66 (19.9)	221		
Diameter (cm)					
<1	572 (73.9)	250 (75.5)	822	0.322	0.570
≥1	202 (26.1)	81 (24.5)	283		
Tg Level					
Negative	334 (43.2)	140 (42.3)	474	0.069	0.792
Positive	440 (56.8)	191 (57.7)	631		
Lesions					
Single	449 (58.0)	182 (55.0)	631	0.866	0.352
Multiple	325 (42.0)	149 (45.0)	474		

(*Continued*)

Table 1 (Continued).

Parameter	Training Group (n=774, %)	Validation Group (n=331, %)	Total (n=1105)	χ^2/*U Value*	*P*-value
$BRAF^{V600E}$					
Wild-type	176 (22.7)	82 (24.8)	258	0.536	0.464
Mutant type	598 (77.3)	249 (75.2)	847		
Capsule invasion					
NO	683 (88.2)	285 (86.1)	968	0.978	0.323
YES	91 (11.8)	46 (13.9)	137		
Tumor location (upper pole)					
NO	640 (82.7)	276 (83.4)	916	0.079	0.778
YES	134 (17.3)	55 (16.6)	189		
LNM					
NO	514 (66.4)	220 (66.5)	734	0.000	0.985
YES	260 (33.6)	111 (33.5)	371		
CLNM					
NO	536 (69.3)	231 (69.8)	767	0.032	0.859
YES	238 (30.7)	100 (30.2)	338		
LLNM					
NO	660 (85.3)	277 (83.7)	937	0.452	0.501
YES	114 (14.7)	54 (16.3)	168		
C-TIRADS Score					
1	14 (1.8)	6 (1.8)	20	0.399	0.985
2	274 (35.4)	117 (35.3)	391		
3	190 (24.5)	80 (24.2)	270		
4	196 (25.3)	81 (24.5)	277		
5	100 (12.9)	47 (14.2)	147		

Construction and Verification of a Prediction Model for Cervical CLNM in PTC

Univariate and Multivariate Analysis of CLNM in the Occurrence of PTC

The training set comprised 774 patients, with 238 cases in the cervical CLNM group, resulting in a metastasis rate of 30.7%, and 536 cases in the non-cervical CLNM group.

The results of univariate analysis showed that male ($\chi^2 = 30.074$, $P < 0.001$), age < 55 years old ($\chi^2 = 14.645$, $P < 0.001$), tumor diameter ≥ 1.0 cm ($\chi^2 = 72.137$, P < 0.001), C-TIRADS score ($\chi^2 = 258.823$, $P < 0.001$), capsular invasion ($\chi^2 = 108.223$, $P < 0.001$), positive serum Tg ($\chi^2 = 33.318$, $P < 0.001$), tumor location ($\chi^2 = 28.203$, $P < 0.001$) and BRAF gene status mutant type ($\chi^2 = 67.223$, $P < 0.001$) were related to PTC with cervical CLNM ($P < 0.05$). However, there was no statistically significant difference in the number of lesions between the CLNM group and the non-CLNM group ($P > 0.05$). The result of univariate logistic regression analysis of risk factors for CLNM in PTC patients is presented in Table 2.

Eight characteristics with statistically significant differences between the two groups were selected for multivariate logistic regression analysis. Male (OR = 2.206, $P = 0.002$, 95% CI = 1.329 ~ 3.663), age < 55 years old (OR = 2.988, P <0.001, 95% CI = 1.596 ~ 5.591), tumor diameter ≥ 1.0 cm (OR = 3.792, $P < 0.001$, 95% CI = 2.325 ~ 6.184), positive serum Tg (OR = 2.197, $P < 0.001$, 95% CI = 1.388 ~ 3.480), capsular invasion (OR = 9.321, P <0.001, 95% CI = 3.801~22.858), and BRAF gene mutation type (OR = 6.859, $P < 0.001$, 95% CI = 3.062 ~ 15.367) are independent risk factors for CLNM in PTC. The C-TIRADS score is positively correlated with the occurrence of CLNM in PTC (OR = 3.698, $P < 0.001$, 95% CI = 2.911 ~ 4.698). The results of multivariate logistic regression analysis of risk factors for CLNM in PTC patients are presented in Table 3.

Table 2 Univariate Logistic Regression Analysis of Risk Factors for CLNM in PTC Patients

Parameter	CLNM Group (n=238, %)	Non-CLNM Group (n=536, %)	Total (n=774)	χ^2/*U Value*	*P*-value
Gender					
Male	88 (37.0)	100 (18.7)	188	30.074	<0.001
Female	150 (63.0)	436 (81.3)	586		
Age (years)					
<55	210 (88.2)	409 (76.3)	619	14.645	<0.001
≥55	28 (11.8)	127 (23.7)	155		
Diameter (cm)					
<1	128 (53.8)	444 (82.8)	572	72.137	<0.001
≥1	110 (46.2)	92 (17.2)	202		
Tg Level					
Negative	66 (27.7)	268 (50.0)	334	33.318	<0.001
Positive	172 (72.3)	268 (50.0)	440		
Lesions					
Single	150 (63.0)	299 (55.8)	449	3.548	0.060
Multiple	88 (37.0)	237 (44.2)	325		
$BRAF^{V600E}$					
Wild-type	10 (4.2)	166 (31.0)	176	67.223	<0.001
Mutant type	228 (95.8)	370 (69.0)	598		
Capsule invasion					
NO	167 (70.2)	516 (96.3)	683	108.223	<0.001
YES	71 (29.8)	20 (3.7)	91		
Tumor location (upper pole)					
NO	171 (71.8)	469 (87.5)	640	28.203	<0.001
YES	67 (28.2)	67 (12.5)	134		
C-TIRADS Score					
1	0 (0.0)	14 (2.6)	14	258.823	<0.001
2	6 (2.5)	268 (50.0)	274		
3	46 (19.3)	144 (26.9)	190		
4	120 (50.4)	76 (14.2)	196		
5	66 (27.7)	34 (6.3)	100		

Table 3 Multivariate Logistic Regression Analysis of Risk Factors for CLNM in PTC Patients

Factor	B	Standard Error	Wald	*P*-value	OR (95% CI)
Gender (Male)	0.791	0.259	9.362	0.002	2.206 (1.329~3.663)
C-TIRADS Score	1.308	0.122	114.649	<0.001	3.698 (2.911~4.698)
BRAF Mutated	1.926	0.412	21.893	<0.001	6.859 (3.062~15.367)
Age <55 Years	1.094	0.32	11.714	0.001	2.988 (1.596~5.591)
Tg Positive	0.787	0.235	11.268	0.001	2.197 (1.388~3.480)
Diameter ≥1.0 cm	1.333	0.250	28.516	<0.001	3.792 (2.325~6.184)
Location (upper pole)	−0.212	0.356	0.353	0.553	0.809 (0.403~1.627)
Capsule invasion	2.232	0.458	23.789	<0.001	9.321 (3.801~22.858)
Constant	−9.1	0.713	162.94	<0.001	

Construction of Nomogram Prediction Model for Cervical CLNM in PTC

Based on the seven independent risk factors obtained above, a Nomogram prediction model for cervical CLNM in thyroid PTC was constructed (Figure 1). The total score for each patient was calculated by adding up the scores corresponding to each risk factor in the Nomogram model. The point where the total score intersects with the risk axis, determined by drawing a vertical line, represents the risk of PTC developing cervical CLNM.

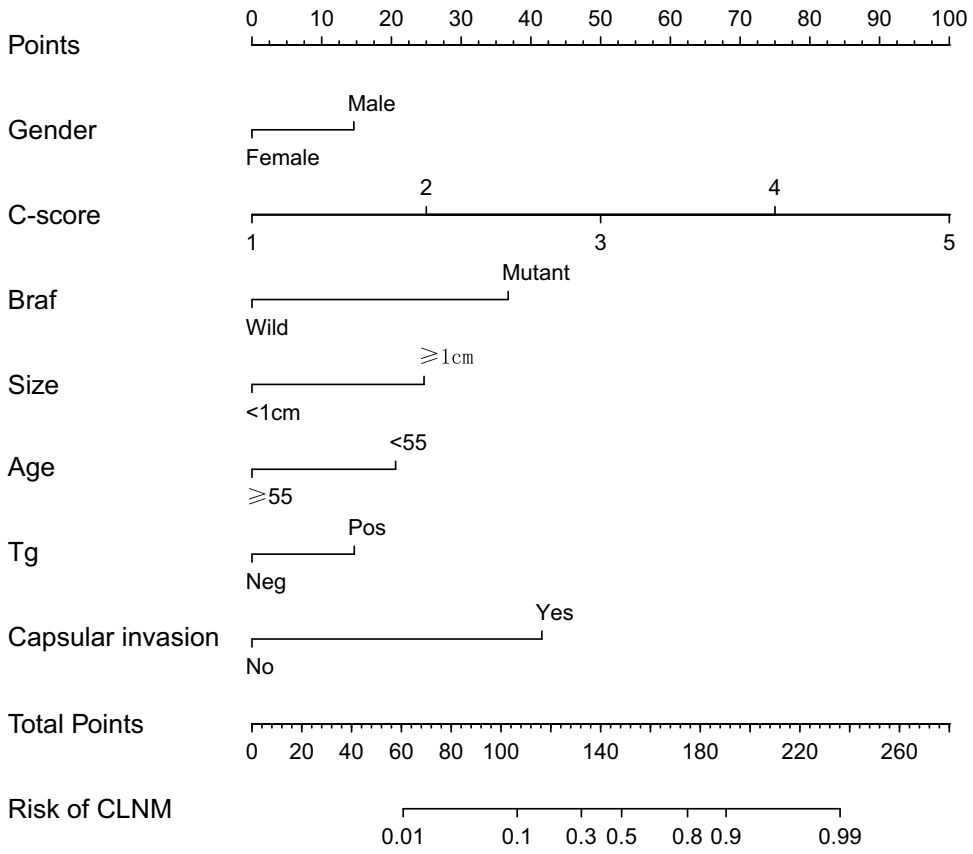

Figure 1 Nomogram for Predicting the Risk of Cervical CLNM in PTC.

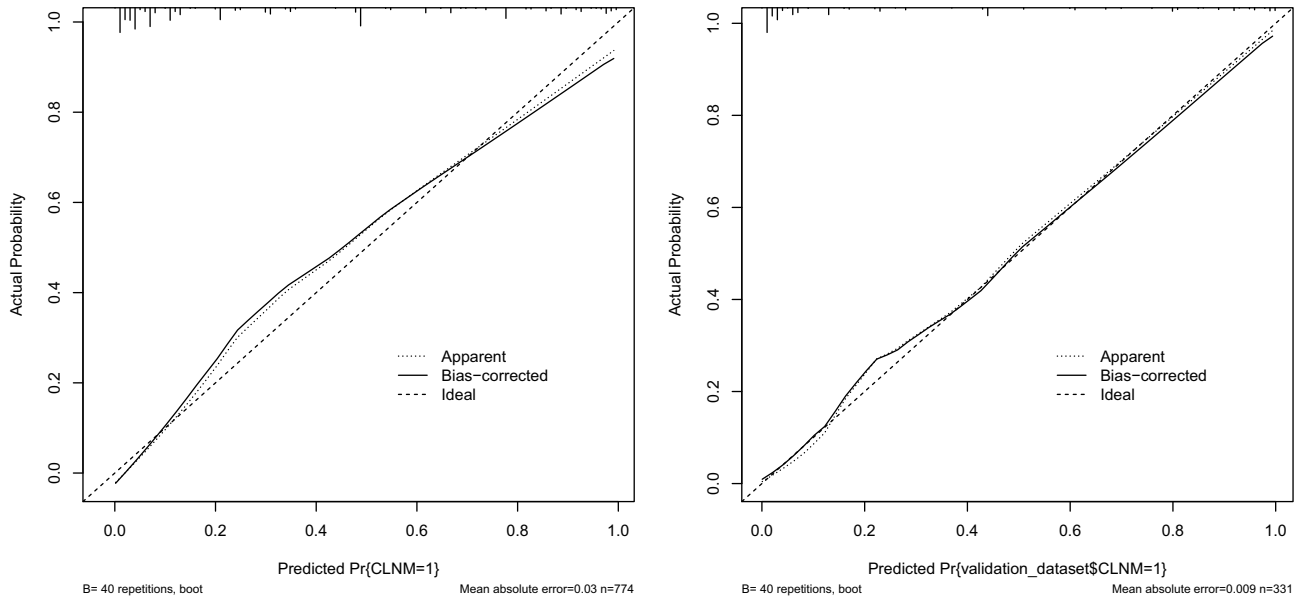

Figure 2 Calibration Curve Analysis of the Relationship Between Predicted Probability and Actual Incidence of Cervical CLNM in PTC for the Training (**A**) and Validation (**B**) Sets.

Validation of the Nomogram Prediction Model for Cervical CLNM in PTC

The Nomogram model was internally validated by using modeling set self-sampling (Bootstrap method), and the model was externally validated by using 331 cases of data in the validation set. Calibration curves (Figure 2) and ROC curves (Figure 3) were used to evaluate the predictive performance of the model after resampling. Both calibration curves for the

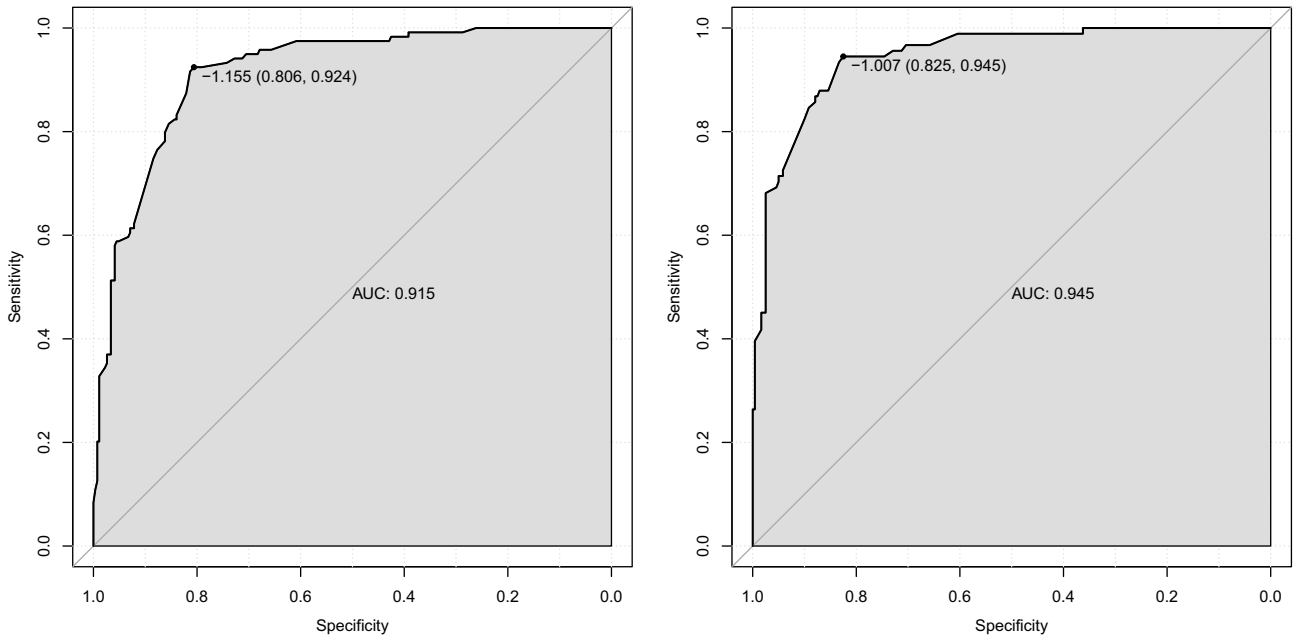

Figure 3 ROC Curves for the Nomogram Prediction Model of Cervical CLNM in PTC for the Training (**A**) and Validation (**B**) Sets.

two datasets showed that the predicted values were close to the actual values, indicating good model calibration. The ROC curve showed an AUC of 91.5% for the model, with a sensitivity of 74.8% and specificity of 75.0%. In the validation dataset, the AUC was 94.5%, suggesting high diagnostic efficiency for this model.

Figure 4 displays the decision curve for the Nomogram prediction model. The results indicate that when the high-risk threshold ranges from 0.0 to 1.0, the net benefit is greater than zero. This suggests that the predictive model has clinical value in predicting the occurrence of cervical CLNM in PTC. Furthermore, as the high-risk threshold decreases, the net benefit increases.

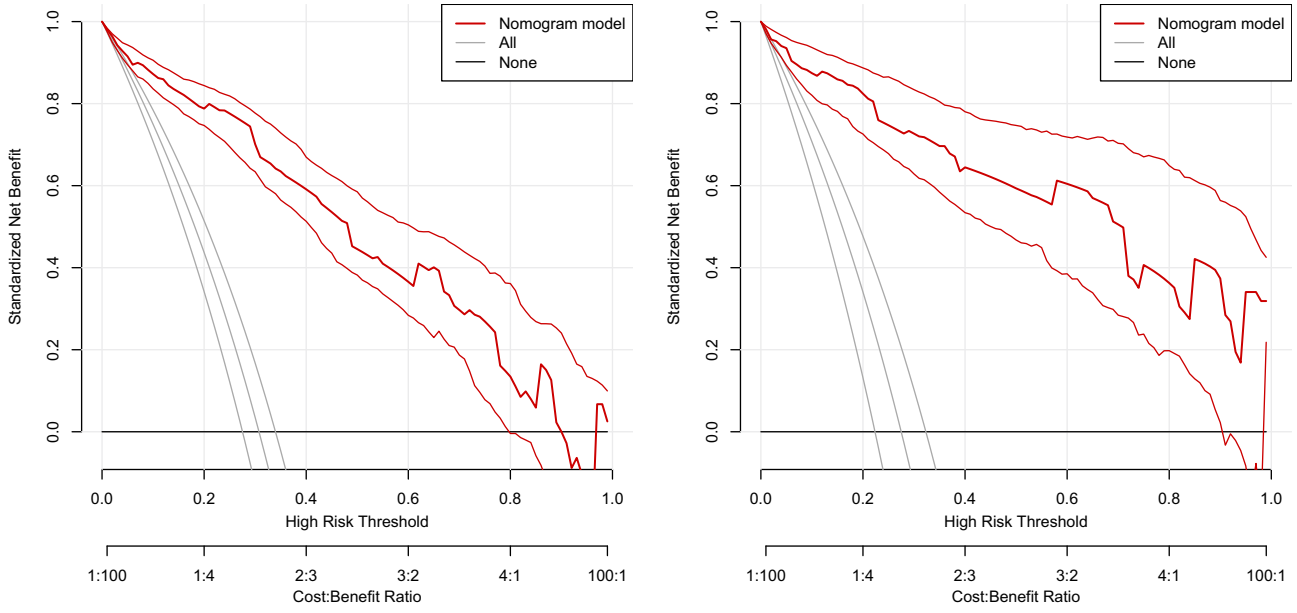

Figure 4 Decision Curve Analysis (DCA) for the Nomogram Prediction Model of Cervical CLNM in PTC for the Training (**A**) and Validation (**B**) Sets.

Construction and Verification of a Prediction Model for Cervical LLNM in PTC

Univariate and Multivariate Analysis of LLNM in the Occurrence of PTC

The training set comprised 774 patients, with 114 cases in the cervical LLNM group, resulting in a metastasis rate of 14.7%, and 660 cases in the non-cervical LLNM group. Among them, 92 cases were accompanied by CLNM metastasis at the same time, and only 22 cases had only LLNM.

Univariate analysis showed that male ($\chi^2 = 25.403$, $P < 0.001$), tumor diameter ≥ 1.0 cm ($\chi^2 = 124.161$, $P < 0.001$), positive serum Tg ($\chi^2 = 13.881$, $P < 0.001$), capsular invasion ($\chi^2 = 306.488$, $P < 0.001$), BRAF gene mutation type ($\chi^2 = 13.039$, $P < 0.001$), nodule located in the upper pole ($\chi^2 = 153.804$, $P < 0.001$), C-TIRADS score ($\chi^2 = 90.044$, $P < 0.001$), and the presence of CLNM ($\chi^2 = 162.209$, $P < 0.001$) were associated with the occurrence of LLNM in PTC ($P < 0.05$). However, there was no statistically significant difference in age and the number of lesions between the LLNM group and the non-LLNM group ($P > 0.05$). The result of univariate logistic regression analysis of risk factors for LLNM in PTC patients is presented in Table 4.

Eight characteristics with statistically significant differences between the two groups in the training set were selected for multivariate logistic regression analysis: tumor diameter ≥ 1.0 cm (OR = 5.122, $P < 0.001$, 95% CI = 2.567 ~ 10.221),

Table 4 Univariate Logistic Regression Analysis of Risk Factors for LLNM in PTC Patients

Parameter	LLNM Group (n=114, %)	Non-LLNM Group (n=660, %)	Total (n=774)	χ^2/*U Value*	*P*-value
Gender					
Male	49 (43.0)	139 (21.1)	188	25.403	<0.001
Female	65 (57.0)	521 (78.9)	586		
Age (years)					
<55	93 (81.6)	526 (79.7)	619	0.215	0.643
≥55	21 (18.4)	134 (20.3)	155		
Diameter (cm)					
<1	36 (31.6)	536 (81.2)	572	124.161	<0.001
≥1	78 (68.4)	124 (18.8)	202		
Tg Level					
Negative	31 (27.2)	303 (45.9)	334	13.881	<0.001
Positive	83 (72.8)	357 (54.1)	440		
Lesions					
Single	57 (50.0)	392 (59.4)	449	3.522	0.061
Multiple	57 (50.0)	268 (40.6)	325		
$BRAF^{V600E}$					
Wild-type	11 (9.6)	165 (25.0)	176	13.039	<0.001
Mutant type	103 (90.4)	495 (75.0)	598		
Capsule invasion					
NO	45 (39.5)	638 (96.7)	683	306.488	<0.001
YES	69 (60.5)	22 (3.3)	91		
Tumor location (upper pole)					
NO	48 (42.1)	592 (89.7)	640	153.804	<0.001
YES	66 (57.9)	68 (10.3)	134		
Presence of CLNM					
NO	21 (18.4)	515 (78.0)	536	162.209	<0.001
YES	93 (81.6)	145 (22.0)	238		
C-TIRADS Score					
1	0 (0.0)	14 (2.1)	14	90.044	<0.001
2	8 (7.0)	266 (40.3)	274		
3	25 (21.9)	165 (25.0)	190		
4	41 (36.0)	155 (23.5)	196		
5	40 (35.1)	60 (9.1)	100		

Table 5 Multivariate Logistic Regression Analysis of Risk Factors for LLNM in PTC

Factor	B	Standard Error	Wald	*P*-value	OR (95% CI)
Gender (Male)	0.553	0.362	2.332	0.127	1.739 (0.855~3.539)
C-TIRADS Score	0.356	0.19	3.505	0.061	1.427 (0.983~2.670)
BRAF Mutated	−0.07	0.606	0.013	0.908	0.932 (0.284~3.059)
Presence of CLNM	1.978	0.45	19.302	<0.001	7.229 (2.991~17.471)
Tg Positive	0.398	0.362	1.206	0.272	1.488 (0.732~3.026)
Diameter ≥1.0 cm	1.634	0.352	21.479	<0.001	5.122 (2.567~10.221)
Location (upper pole)	2.124	0.346	37.698	<0.001	8.367 (4.247~16.483)
Capsule invasion	2.862	0.344	69.318	<0.001	17.496 (8.919~34.318)
Constant	−6.695	0.849	62.238	<0.001	

capsular invasion (OR =17.496, $P < 0.001$, 95% CI = (8.919 ~ 34.318), nodule located in the upper pole of the thyroid (OR = 8.367, P < 0.001, 95% CI = 4.247 ~ 16.483), and the presence of CLNM in PTC (OR = 7.229, $P < 0.001$, 95% CI = 2.991 ~ 17.471) are independent risk factors for the occurrence of LLNM in PTC. The results of multivariate logistic regression analysis of risk factors for LLNM in PTC patients is presented in Table 5.

Construction of Nomogram Prediction Model for Cervical LLNM in PTC

Based on the above-obtained four independent risk factors, a Nomogram prediction model for the occurrence of LLNM in thyroid PTC was constructed (Figure 5).

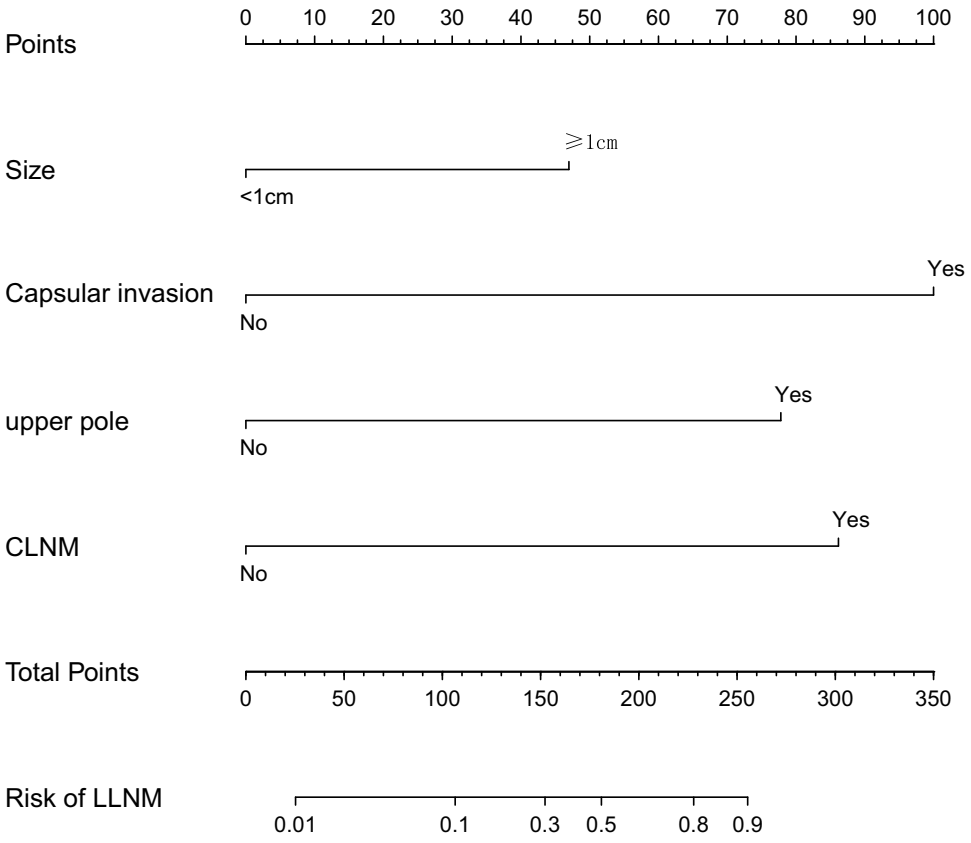

Figure 5 Nomogram for Predicting the Risk of Cervical LLNM in PTC.

Validation of the Nomogram Prediction Model for Cervical LLNM

The modeling set self-sampling (Bootstrap method) was used to internally validate the Nomogram model, and 331 cases of data in the validation set were used to externally validate the model. The calibration curve (Figure 6) and the ROC curve (Figure 7) were used to test the prediction effect of the model. The results of the calibration curves of both datasets showed that the predicted values were close to the actual values, suggesting that the model had good calibration. The ROC showed that the AUC of this model was 96.1%, the sensitivity was 61.3%, and the specificity was 68.7%. In the validation set, the AUC was 96.6%, suggesting that the model had acceptable diagnostic efficiency. Figure 8 displays the decision curve for the Nomogram prediction model of cervical LLNM in PTC. This suggests that the predictive model has clinical value in predicting the occurrence of cervical LLNM in PTC.

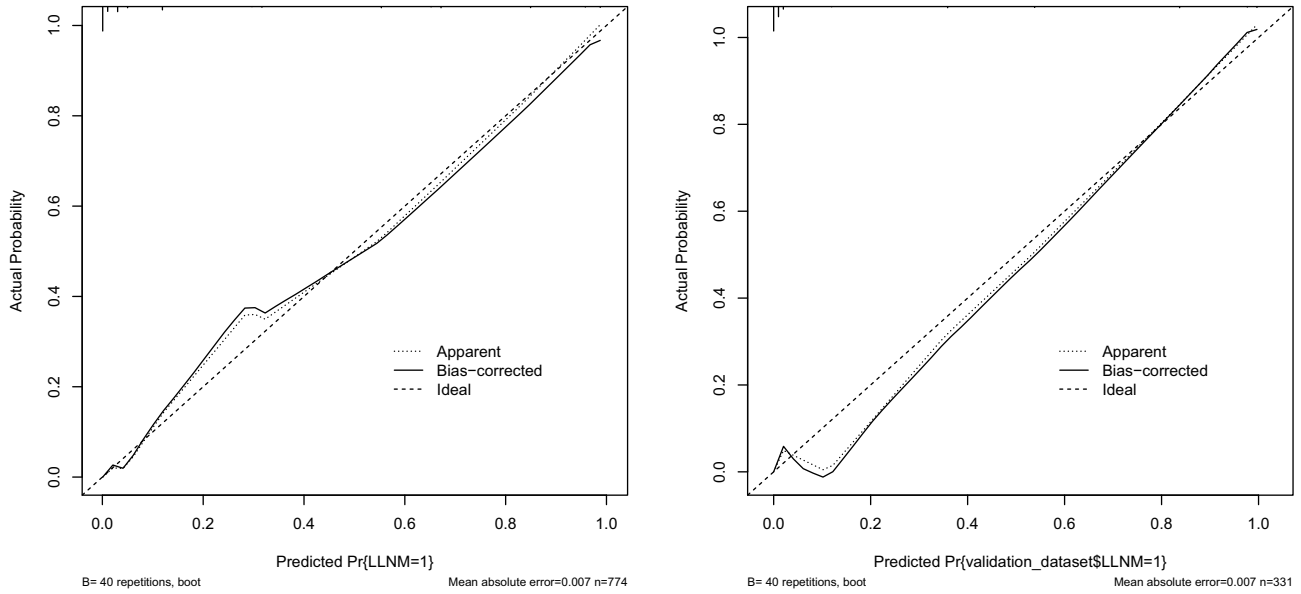

Figure 6 Calibration Curve Analysis of the Relationship Between Predicted Probability and Actual Incidence of Cervical LLNM in PTC for the Training (**A**) and Validation (**B**) Sets.

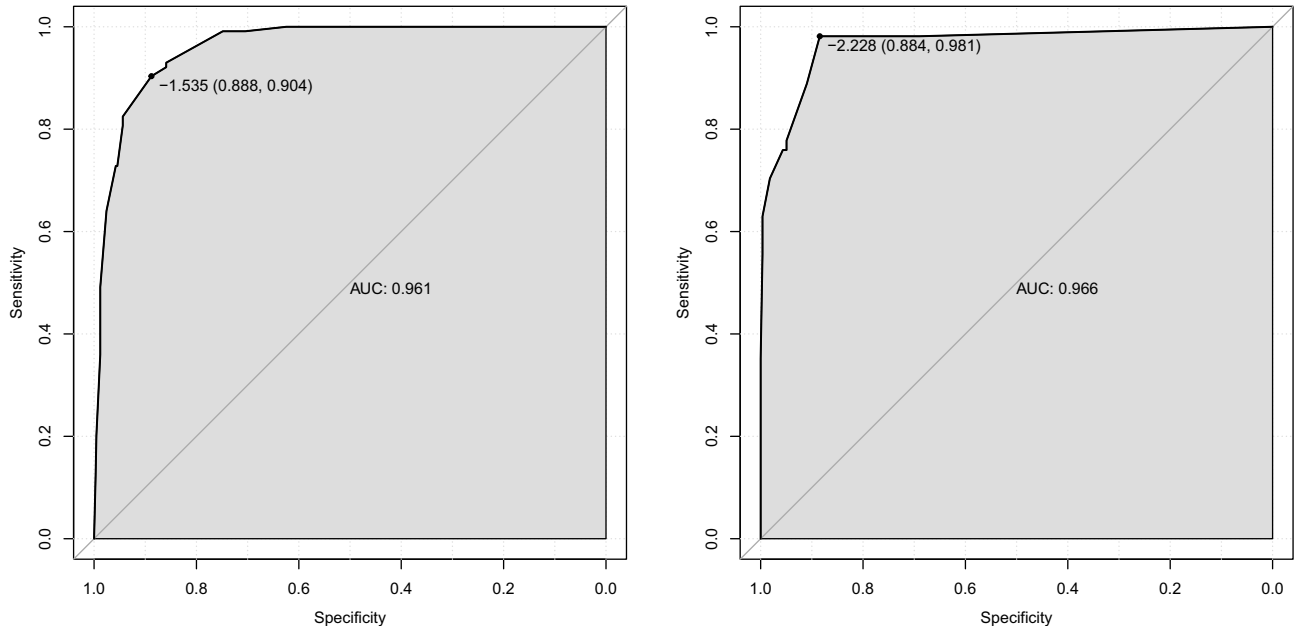

Figure 7 ROC Curves for the Nomogram Prediction Model of Cervical LLNM in PTC for the Training (**A**) and Validation (**B**) Sets.

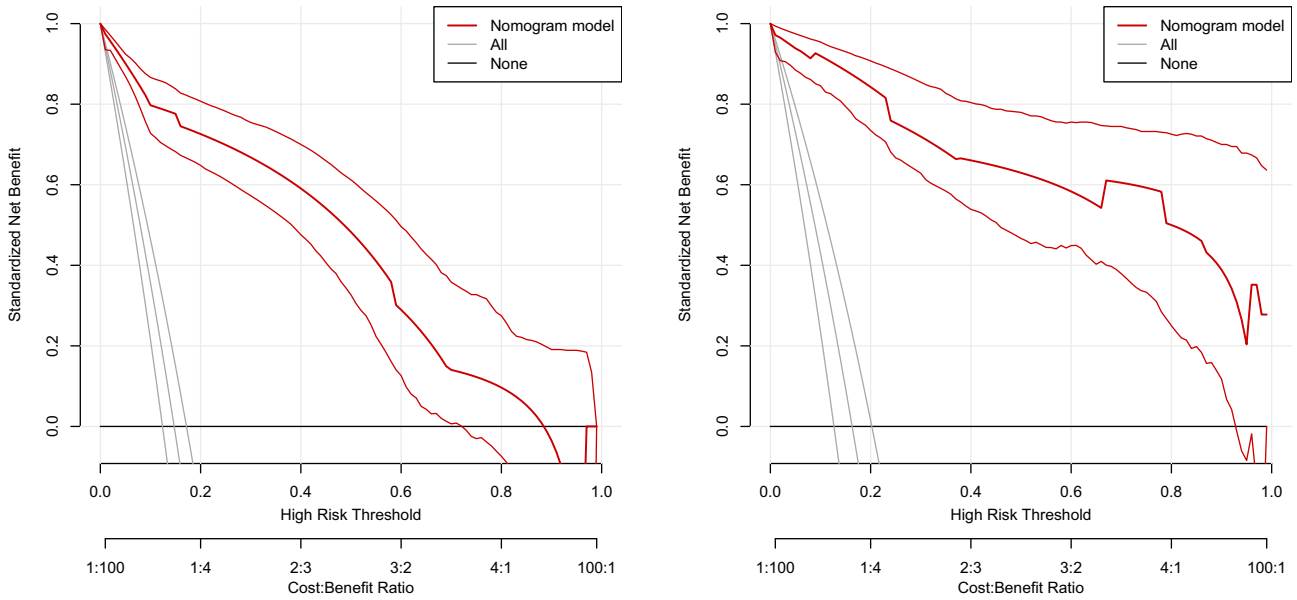

Figure 8 Decision Curve Analysis (DCA) for the Nomogram Prediction Model of Cervical LLNM in PTC for the Training (**A**) and Validation (**B**) Sets.

Discussion

PTC is a prevalent endocrine malignancy characterised by favourable biological behaviour, slow growth, and a positive prognosis. However, it tends to exhibit early-onset cervical LNM.[13] LNM is considered an independent risk factor for the recurrence of PTC.[14] Total thyroidectomy (TT) and subtotal thyroidectomy (STT) are still the two main surgical procedures[15] and remain the primary treatment modality for PTC, However, there is great controversy over preventive lymph node dissection. Some studies suggest that prophylactic lymph node dissection can lead to hypoparathyroidism and should not be used as a routine treatment option for PTC patients.[16] From the perspective of precision medicine, avoiding overtreatment of low-risk patients, accurately identifying patients at high risk of LNM, removing occult metastases, and reducing postoperative recurrence and distant metastasis are major challenges that clinicians currently need to face. Presently, ultrasound, CT, and MRI exhibit insufficient diagnostic precision for lymph node metastasis.[17,18] Consequently, predicting the occurrence of cervical CLNM and LLNM in PTC holds significant importance for formulating the best surgical approach before surgery, which is also the ultimate significance of this study.

In this study, we evaluated the risk of cervical CLNM and LLNM in PTC patients using a multifaceted approach, encompassing patient clinical data, ultrasound characteristics, serum Tg levels, ultrasound C-TIRADS scores, and BRAF gene status. The analysis results showed that Male, Age<55 years old, tumor diameter ≥ 1.0 cm, positive serum Tg, BRAF gene mutation type, capsular invasion and C-TIRADS score were related to the occurrence of cervical CLNM in PTC, Tumor diameter≥ 1.0 cm, capsular invasion, nodules located in the upper pole of the thyroid, and the presence of CLNM are related to the occurrence of cervical LLNM in PTC.

PTC predominantly affects females, with a male-to-female ratio in this study of 1:3.1. This aligns with previous reports indicating male-to-female ratios of approximately 1:2 to 1:5.2 in PTC patients.[19] Although the incidence of PTC in males is lower than that in females, according to previous studies, that males are an independent risk factor for cervical LNM,[20] especially CLNM.[21] The analysis of this study shows that men are an independent risk factor for cervical CLNM, but not an independent risk factor for LLNM, which is consistent with previous studies. In this study, according to the thyroid cancer TNM staging system (eighth edition) released by the American Joint Committee on Cancer, 55 years old was selected as the cut-off value for patient age.[22] The results showed that the risk of cervical CLNM in those younger than 55 years was higher than that in those aged 55 or older ($P < 0.05$), consistent with findings by W et al.[23] Previous research has indicated an association between the size of PTC tumors and cervical LNM.[24] Studies have shown that tumor size is an important factor for cervical lymph node metastasis, with a higher risk of cervical LNM observed in

cases where PTC tumor diameter exceeded 1.0 cm.[15,25] The results of this study show that PTC tumor diameter exceeding 1.0 cm is an independent risk factor for CLNM and LLNM in PTC. Our study corroborates these findings. It is generally believed that thyroid microcarcinomas with a tumor diameter of less than 1 cm are relatively indolent. However, some scholars have found that microcarcinomas also have a certain metastasis rate.[26] To avoid overtreatment of low-risk populations, in our study, a cutoff value of 1 cm in diameter for papillary thyroid carcinoma (PTC) is used. In the future, a larger sample size will be used for further discussion. Previous studies have shown that capsular invasion is an independent risk factor for cervical LNM.[27] Wang et al's[28] study showed that tumor capsular invasion increases the possibility of invading lymphatic vessels. In this study, capsular invasion is an independent risk factor for CLNM and LLNM. In this study, only 33/1105 cases (3%) had LLNM without CLNM directly, indicating that the chance of capsular invasion breaking through the capsule is increased, with higher invasiveness and promoting the risk of LLNM. This also explains that PTC may metastasize to lateral cervical lymph nodes without directly passing through central lymph nodes. In this study, CLNM is an independent risk factor for LLNM. According to the metastasis pattern of PTC, this is predictable This suggests that except for very few skip metastases, almost all patients with LLNM are accompanied by the occurrence of CLNM.

Ultrasound is currently one of the primary methods for evaluating thyroid nodules, exhibiting excellent sensitivity and specificity in distinguishing between benign and malignant nodules. The Chinese Thyroid Imaging Reporting and Data System (C-TIRADS) guidelines, introduced by the Chinese Medical Association in 2020,[8] serve as ultrasound guidelines for differentiating between benign and malignant thyroid nodules in China. However, clinical research on whether C-TIRADS can predict CLNM in PTC remains limited. In this study, multivariate analysis revealed that C-TIRADS scores are an independent risk factor for cervical CLNM in PTC ($P<0.05$). For each one-point increase in C-TIRADS score, the risk of cervical LNM increased by 3.698 times (OR=3.698, 95% CI=2.911~4.698). This finding aligns with previous research results.[29] However, in the LLNM group, the C-TIRADS score had no statistical significance. When the tumor is located in the upper pole, the risk of lateral cervical lymph node metastasis is greatly increased. H et al[30] believe that there may also be lymphatic vessels between the upper lobe and the lateral lobe of the thyroid gland, and the tumor can metastasize directly to the lateral cervical region without passing through the central region, which is consistent with the results of this study. However, in this study, the location of nodules in the upper pole had no statistical significance in CLNM.

Serum Tg plays a crucial role in distinguishing thyroid nodular lesions. Its role in assessing prognosis and monitoring treatment efficacy is particularly pronounced in differentiated thyroid carcinoma.[31] Elevated Tg levels have been linked to the potential disruption of normal thyroid tissue by cancer cells, suggesting a relatively active and invasive tumour growth pattern in PTC patients.[32] The results of this study are consistent with it. There is a statistically significant difference in the positive rate of Tg between the cervical CLNM group and the non-cervical CLNM group ($P<0.05$).[29]

BRAF gene mutations are the most common genetic mutations in PTC,[33] closely associated with its onset. These mutations have been widely utilized in the diagnosis, treatment, and prognostic evaluation of thyroid cancer, and they are considered an independent risk factor for adverse PTC outcomes. Our study revealed that the probability of PTC with cervical CLNM occurring in individuals with the BRAF gene mutation is 6.859 times higher than in those with the wild-type gene (OR=6.859, $P<0.001$). Thus, BRAF gene mutations are an independent risk factor for PTC with cervical CLNM, consistent with the findings of Xu et al.[34]

The Nomogram prediction model obtained in this study reflects the importance of using certain parameters to predict the occurrence of cervical LNM in PTC. Through indicators such as patient age, tumor diameter, presence or absence of capsular invasion, whether the PTC tumor is located in the upper pole, serum Tg, C-TIRADS score, and BRAF gene status, relatively accurate judgments can be made. By establishing a Nomogram prediction model with independent risk factors, high-risk groups of PTC with cervical LNM can be effectively screened, helping clinicians make more reasonable surgical decisions and bringing great convenience to clinical work. The CLNM and LLNM prediction models constructed in this study have good predictive effects and strong operability and can objectively predict the risk of cervical LNM in PTC.

This study has several limitations: 1) It is retrospective in nature, which may introduce selection bias into the results; 2) The sample size included is limited as this is a single centre study; 3) Data collection was restricted,

and various factors may be associated with the occurrence of cervical lymph node metastasis (LNM) in papillary thyroid carcinoma (PTC), but this study did not analyze the relationships between other indicators and the occurrence of cervical CLNM and LLNM in PTC patients. 4) This article only explored the risk of LNM in PTC. However, studies have shown that some occult thyroid cancers, such as thyroid malignant nodules classified as Bethesda II or III,[35,36] are more difficult to detect and have a worse prognosis. In later research, the scope of the study can be expanded to explore the malignant risk analysis including such nodules. Therefore, in further research in the future, the sample size should be increased, more risk parameters should be added, and a prospective multicenter study should be conducted to verify the reliability of the research results and provide more value for clinical diagnosis and treatment. In addition, detailed partitioning should be carried out, and a prospective multicenter study should be conducted to verify the reliability of the research results.

Conclusion

Although PTC is considered a tumor with slow growth and favorable prognosis, it has a relatively high lymph node metastasis rate. For PTC patients, LNM is a significant concern. In this study, we explored the risk prediction of tumor location, capsule invasion, serum TG level, C-TIRADS score, and BRAF and other indicators for the occurrence of LNM in PTC. By constructing two risk prediction models based on the clinical and general ultrasound characteristics of PTC patients, we significantly improved the accuracy of preoperative prediction of CLNM and LLNM, providing great convenience for the selection of clinical treatment plans.

Abbreviations

PTC, Papillary thyroid carcinoma; LNM, Lymph node metastasis; C-TIRADS, Chinese Thyroid Imaging Reporting and Data System; CLNM, Central lymph node metastasis; LLNM, Lateral lymph node metastasis.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was approved by the Ethics Committee of Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University ([2021] KY307-01). The requirement for individual Informed consent was waived by the Ethics Committee of Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University because of the retrospective nature of the study. The study was carried out in accordance with the applicable guidelines and regulations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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