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Risk Factors for Lymph Node Metastasis in Papillary Thyroid Carcinoma: A Retrospective Study

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ABSTRACT

At present, the risk factors of cervical lymph node metastasis (LNM) in papillary thyroid carcinoma (PTC) are still controversial. This study was aimed to investigate the risk factors of various types of LNM in PTC with tumor diameter > 1 cm. The clinical data of 2216 PTC patients were retrospectively analyzed. Univariate and multivariate logistic regression models were used to analyze the risk factors of LNM. In addition, the receiver operator characteristic (ROC) curve was used to find the best cut-off value of CLNM for predicting LLNM. Finally, the independent risk factors of LLNM were used to construct the prediction of LLNM nomogram. Age ≤ 55 years old, male, bilateral lobe tumors, ETE, 2–3 cm tumor diameters, and fasting plasma glucose (FPG) were independent risk factors for CLNM. The ROC curve showed that the best cut-off value was 2.5. Age, male, bilateral lobe tumors, tumor diameters ≥ 2 cm and CLNM ≥ 3 were significantly associated with LLNM , while CLNM = 1 or 2 was a protective factor for LLNM. Only tumor diameters ≥ 3 cm was significantly associated with skip LLNM. The nomogram model (C-index = 0.745) can be used to predict LLNM in PTC patients and guide the clinical selection of appropriate treatment options. Patients with high risk factors should undergo prophylactic lymph node dissection. The nomogram we established has a good predictive ability for LLNM, and for high-risk groups, it is necessary to actively perform prophylactic lateral lymph node dissection.

Introduction

Thyroid cancer (TC) is a malignant endocrine tumor with a high prevalence rate. The most common type in the population is papillary thyroid cancer (PTC), and patients usually have a good prognosis [1, 2]. For patients with PTC, TC surgery is the main treatment. Unilateral lobe with or without isthmus resection and total thyroidectomy are the two most widely used surgical protocol [3]. However, among patients with PTC, lymph node metastasis (LNM) is very common, and some studies have shown that its comorbidity rate can reach 40 % to 90 % of which the incidence of central lymph node metastasis (CLNM) is about 30 % to 80 %, and the incidence of lateral lymph node metastasis (LLNM) is about 18.6 % to 64 % [2]. LNM often means an increase in the probability of cancer recurrence and a negative impact on the survival rate of patients [4]. Therefore, patients with CLNM and LLNM need neck lymph node dissection (LND), which means that patients have to face greater risks. In clinical practice, central lymph node dissection (CLND) is widely carried out. This is because previous studies have shown that CLND can effectively reduce the recurrence rate and contribute to accurate staging. Another reason is aggressive tumors require aggressive surgical treatment and that CLND causes few permanent postoperative complications, except for transient hypothyroidism [5]. But there is a dispute about the criteria for patients to carry out lateral lymph node dissection (LLND) [6]. Prophylactic LLND is different from CLND, which is widely carried out in clinical practice, and it is not considered as a standard treatment method (except for the patients who have performed biopsy) [3].

Faced with such a high risk of LNM, many experts have studied its risk factors [7, 8]. Sex, age, tumor size and micro calcification were considered to be related, and the risk factors of CLNM and LLNM were considered that there is no big difference [7, 8]. However, there is still room for discussion on the independent risk factors and links of the two types of transfer.

At present, according to the guidelines for thyroid cancer management in the United States, it is recommended that patients with PTC undergo preoperative ultrasound examination to evaluate the CLNM [3]. However, it should be recognized that due to the influence of the overlying thyroid, ultrasound examination still has some limitations [9]. Some studies have shown that the sensitivity of ultrasound examination to CLNM is not ideal [10]. At the same time, the diagnostic accuracy of ultrasound for LLNM is as low as 27.3 %, with low reference significance [8]. The contradiction is that potential LNM may be retained after TC surgery, becoming a hidden danger of cancer recurrence [8].

To sum up, we collected the clinical data of 2166 patients with PTC. It is worth noting that we excluded the data of PTMC (tumor diameter ≤ 1 cm) patients, and previous studies have proved that PTMC patients have the characteristics of delayed onset of symptoms and should not be studied together [11]. We evaluated the metastasis, and systematically and accurately analyzed the risk factors of CLNM and LLNM, which may have certain guiding significance for the prophylactic CLND and LLND, especially for prophylactic LLND.

Patients and Methods

Data source

This is a single center retrospective study, which was approved by the Ethics Committee. We collected the clinical data of 10 765 patients with PTC admitted to the Second Affiliated Hospital of Nanchang University from 2011 to 2021. Our data included patients with histologically proven PTC and complete clinical baseline data and preoperative laboratory examination data, including thyroid hormones, thyroid stimulating hormone (TSH), and fasting plasma glucose (FPG). The exclusion criteria were as follows: (1) Previous or concurrent presence of other malignant tumors; (2) Other thyroid diseases or thyroid surgery history; (3) Drugs that affect thyroid hormone levels were being used; (4) Suffering from diseases that affect the level of FPG or using drugs that affect the level of FPG; (5) No CLND or the data related to the tumor [tumor location, tumor size, extrathyroidal extension (ETE), LNM] were incomplete; and (6) Patients with PTMC (tumor size ≤ 1 cm). All patients signed the informed consent form and 2166 PTC patients were finally included in the study (▶ **Fig. 1**).

All patients underwent preoperative ultrasound or fine needle aspiration (FNA), and frozen sections were retained for histological examination during the operation. We performed prophylactic CLND for all PTC patients, unilateral lobe and isthmus resection combined with ipsilateral CLND for unilateral lobe tumors (this type of operation can avoid serious complications such as hypocalcemia and damage of recurrent laryngeal nerve [3]), total thyroidectomy combined with bilateral CLND for isthmus or bilateral lobe tumors (this type of operation can reduce the risk of postoperative hypothyroidism and clear the malignant primary focus more thoroughly [3]). We do not recommend prophylactic LLND, but therapeutic LLND was performed on 1321 patients with PTC who were positive or suspected positive for LLNM as indicated by preoperative ultrasound or FNA.

Data collection

The clinical baseline data of patients were from outpatient data. FPG comes from blood chemical analysis on the morning after admission (6:00–8:00 AM), and the patient needs to fast for at least 8 hours; TSH, fT3, and fT4 were from the three examinations of thyroid function within half a month before surgery. Tumor related data were obtained from frozen biopsy and color Doppler ultrasound reports after LND.

Statistical analysis

All statistical analyses were conducted with R software (4.1.0). Classified variables were expressed in quantity and percentage, and continuous variables were expressed in mean ± standard deviation. Logistic regression was used to analyze the risk factors of CLNM and LLNM, and univariate logistic regression analysis was conducted for each variable. All variables with $p < 0.2$ in univariate logistic analysis were included in the multivariate logistic regression analysis model. The receiver operator characteristic (ROC) curve was used to determine the best cut-off value for predicting the CLNM number of LLNM, and the area under the curve (AUC) was used to reflect the prediction ability. Multivariate logistic regression analysis screened independent factors to establish a nomograph for predicting LLNM and used consistency index and calibration curve to test the consistency of the prediction model. In our study, $p < 0.05$ was statistically significant.

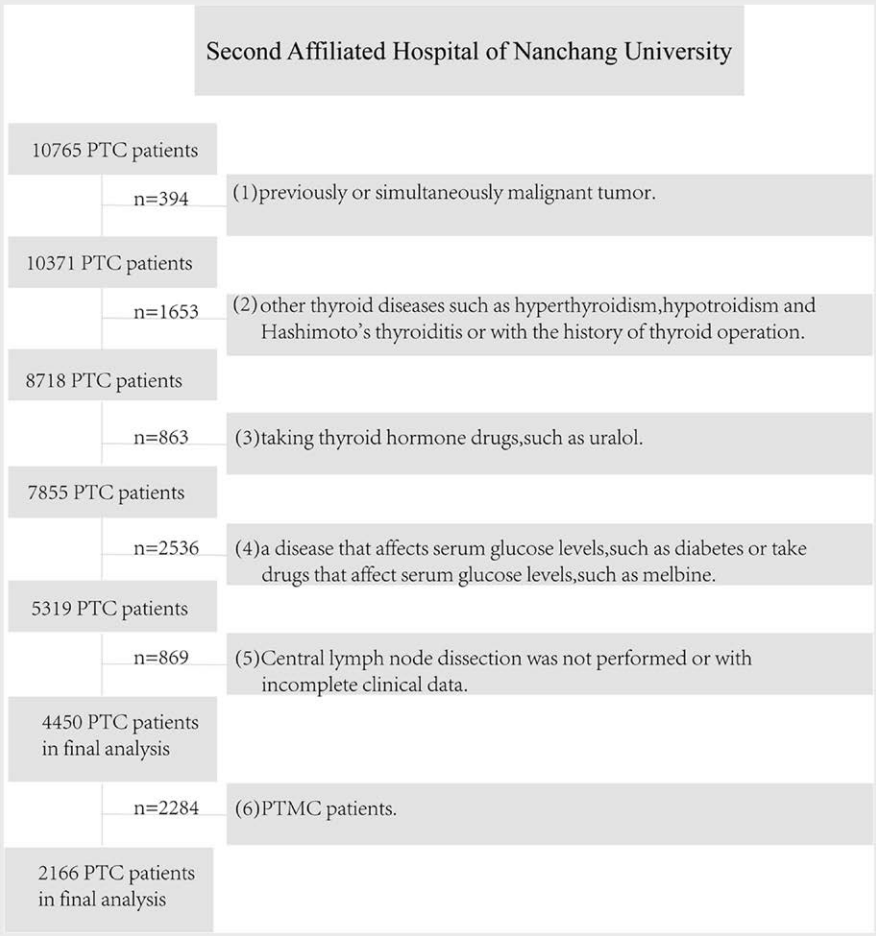
Results

Demographic and clinicopathological characteristics of the patients

Our study included 2166 patients with PTC (the largest tumor diameter > 1 cm), 598 males (27.61 %) and 1568 females (72.39 %), ranging in age from 10 to 83 years (average age 42.00 ± 12.80 years). All patients underwent CLND, 1321 patients underwent therapeutic LLND, 924 cases of CLNM and 438 cases of LLNM were found, including 98 cases of skip metastasis. The demographic and clinicopathological characteristics of 1321 patients who underwent LLND are detailed in ▶ **Table 1**.

Univariate and multivariate logistic regression analysis of risk factors for CLNM

The age, sex, lesion location, extrathyroidal extension, tumor size, FPG, TSH, and fT4 of the patients were included in the univariate regression analysis. Age, male, bilateral lobe tumors, and extrathyroidal extension were significantly related to CLNM, while FPG, TSH were not significantly associated with CLNM (▶ **Table 2**). We included all variables in the multivariate logistic regression model. The results showed that age, male, bilateral lobe tumors, ETE, 2–3 cm tumors, and FPG were significantly related to CLNM. With the decrease of age, the OR value was higher (45–55, OR = 1.76; 35–45,



▶ **Fig. 1** PTC patients exclusion flowchart.

OR = 2.79; ≤ 35, OR = 5.48). In addition, FPG was significantly related to CLNM in the multivariate regression, However, there was no significant correlation in the univariate regression (▶ **Table 2**). We found that the increase of FSG level was significantly related to the increase of age, male and ETE. When the age factor of PTC patients was controlled, the risk role of Glu on CLNM was reflected, which may explain that Glu was statistically significant in the multivariate logistic regression analysis, but not significantly related in the univariate logistic regression analysis.

The number of CLNM predicts LLNM

Previous studies using CLNM number predicted LLNM showed that CLNM was significantly correlated with LLNM [12]. In order to further determine the prediction ability of CLNM to LLNM, we studied 924 PTC patients with CLNM confirmed by pathology and determined the best cut-off value of CLNM to predict LLNM with ROC curve (▶ **Fig. 2**). ROC curve shows that the best truncation value of CLNM was 2.5 (Sensitivity = 0.665, Specificity = 0.659, AUC = 0.702, $p < 0.001$).

Univariate and multivariate logistic regression analysis of the risk factors of LLNM

The risk factors of LLNM and CLNM were considered to have little difference [1]. Therefore, all the variables included in the CLNM univariate logistic regression were included in the LLNM univariate logistic regression analysis. In addition, according to the best cut-off value predicted by CLNM for LLNM, we divided these 1321 cases into three groups: CLNM = 0, CLNM = 1 or 2, and CLNM = ≥ 3, and these three groups included in the LLNM univariate logistic regression analysis. The results showed that age, male, bilateral lobe tumors, tumor ≥ 2 cm, CLNM ≥ 3 were significantly related to LLNM. The variables of $p < 0.2$ in the univariate regression were included in the multivariate logistic regression analysis. Among them, age, male, bilateral lobe tumors, tumors ≥ 2 cm, CLNM and LLNM were significantly related. Unexpectedly, CLNM = 1 or 2 was the protective factor of LLNM [OR = 0.71 (0.51–0.99)] (▶ **Table 3**). These independent risk factors were used to construct nomogram (▶ **Fig. 3a**) to predict LLNM. For example, a 40-year-old male PTC patient with bilateral lobe tumors has a tumor size of 2 cm and CLNM = 3. The variable value corresponds to a point. The corresponding scores of age, male, tumor site, tumor size, and CLNM number were 40,

▶ **Table 1** Baseline characteristics of PTC patients.

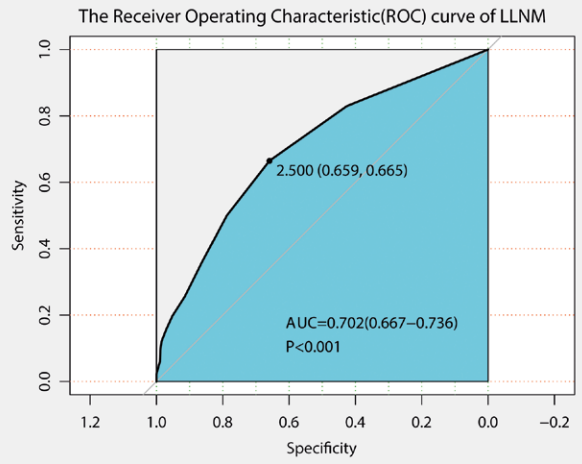
Characteristics	All PTC patients	PTC patients undergoing LLND
Number of patients (n)	2166	1321
Age	42.00 ± 12.80	39.96 ± 12.46
≤ 35	742 (34.26 %)	536 (40.58 %)
35–45	571 (26.36 %)	346 (26.19 %)
45–55	472 (21.79 %)	265 (20.06 %)
≥ 55	381 (17.59 %)	174 (13.17 %)
Gender		
Male	598 (27.61 %)	402 (30.43 %)
Female	1568 (72.39 %)	919 (69.57 %)
LNM		
Yes	1022 (47.18 %)	–
No	1144 (52.82 %)	–
CLNM		
0	1242 (57.34 %)	397 (30.05 %)
1–3	499 (23.04 %)	499 (37.78 %)
≥ 3	425 (19.62 %)	425 (32.17 %)
LLNM		
Yes	438 (20.22 %)	438 (33.16 %)
No	1728 (79.78 %)	883 (66.84 %)
Lesions		
Unilateral	1385 (63.94 %)	792 (59.95 %)
Unilateralisthmus	217 (10.02 %)	148 (11.21 %)
Bilateral	472 (21.79 %)	330 (24.98 %)
Bilateralisthmus	63 (2.91 %)	37 (2.80 %)
isthmus	29 (1.34 %)	14 (1.06 %)
Extrathyroidal Extension		
Yes	705 (32.55 %)	483 (36.56 %)
No	1461 (67.45 %)	838 (63.44 %)
Maximum tumor diameter (cm)	1.96 ± 1.03	2.01 ± 1.06
1.0–1.5	760 (35.09 %)	435 (32.93 %)
1.5–2.0	503 (23.22 %)	311 (23.54 %)
2.0–3.0	529 (24.42 %)	340 (25.74 %)
>4.0	374 (17.27 %)	235 (17.79 %)
Glucose	5.93 ± 1.58	5.98 ± 1.62
TSH	2.07 ± 1.73	2.08 ± 1.69
fT3	3.24 ± 0.51	3.25 ± 0.51
fT4	1.30 ± 0.46	1.31 ± 0.45

PTC: Papillary thyroid cancer; LNM: Lymph node metastasis; CLNM: Central lymph node metastasis; LLNM: Lateral cervical lymph node metastasis; TSH: Thyrotrophin; fT3: Free triiodothyronine; fT4: Free thyroxine; LLND: Lateral lymph node dissection.

▶ **Table 2** Un-adjusted and adjusted association between the clinicopathologic features and CLNM.

Variables	Unadjusted Odds Ratio (95 % CI)	p-Value	Adjusted Odds Ratio (95 % CI)	p-Value
Age				
≤ 35	**4.38 (3.33–5.81)**	**<0.001**	**5.48 (4.08–7.42)**	**<0.001**
35–45	**2.48 (1.87–3.32)**	**<0.001**	**2.79 (2.07–3.79)**	**<0.001**
45–55	**1.64 (1.21–2.23)**	**0.001**	**1.76 (1.29–2.42)**	**0.001**
≥ 55	1		**1**	
Gender				
Female	**1**	**–**	**1**	**–**
Male	**1.48 (1.23–1.79)**	**<0.001**	**1.47 (1.20–1.81)**	**<0.001**
Lesions				
Unilateral	**1**	**–**	**1**	**–**
Unilateralisthmus	0.95 (0.71–1.28)	0.751	0.95 (0.69–1.29)	0.723
Bilateral	**2.06 (1.70–2.55)**	**<0.001**	**2.11 (1.68–2.64)**	**<0.001**
Bilateralisthmus	1.10 (0.65–1.83)	0.708	1.00 (0.57–1.72)	0.999
Isthmus	0.71 (0.30–1.52)	0.391	0.64 (0.27–1.40)	0.275
Extrathyroidal Extension				
Yes	**1.60 (1.34–1.92)**	**<0.001**	**1.76 (1.44–2.14)**	**<0.001**
No	**1**		**1**	
Maximum tumor diameter				
1.0–1.5	**1**		**1**	
1.5–2.0	**1.27 (1.01–1.6)**	**0.038**	1.24 (0.98–1.59)	0.080
2.0–3.0	**1.45 (1.16–1.81)**	**0.001**	**1.42 (1.12–1.81)**	**0.004**
≥ 3.0	**1.34 (1.03–1.72)**	**0.023**	1.20 (0.92–1.58)	0.178
Glu	1.00 (0.95–1.06)	0.91	**1.07 (1.01–1.14)**	**0.022**
TSH	1.04 (0.99–1.09)	0.12	1.04 (0.98–1.10)	0.193
FT4	0.87 (0.67–1.05)	0.18	0.81 (0.61–1.01)	0.091

27.5, 100, 43.5, and 75, respectively. The total score was 286, and the corresponding LLNM probability was about 80 %. The C-index of nomogram was 0.745 (95 % CI, 0.717–0.773), which shows that the prediction of LLNM in PTC patients by the model was consistent with the actual situation. In addition, we have built the calibration curve of nomogram (▶ **Fig. 3b**), the black curve represents the ideal line, the blue curve was calculated by bootstrapping (B = 1000 repetitions boot), the red dashed line represents the entire cohort, the closer it was to the ideal line, the more accurate the nomogram prediction will be. We analyzed 98 PTC patients with skip metastasis



▶ **Fig. 2** The Receiver Operating Characteristics (ROC) curve for predicting lateral lymph node metastasis from the number of central lymph node metastases.

and found that only tumor ≥ 3 cm was significantly correlated with skip metastasis ($p < 0.001$).

Discussion

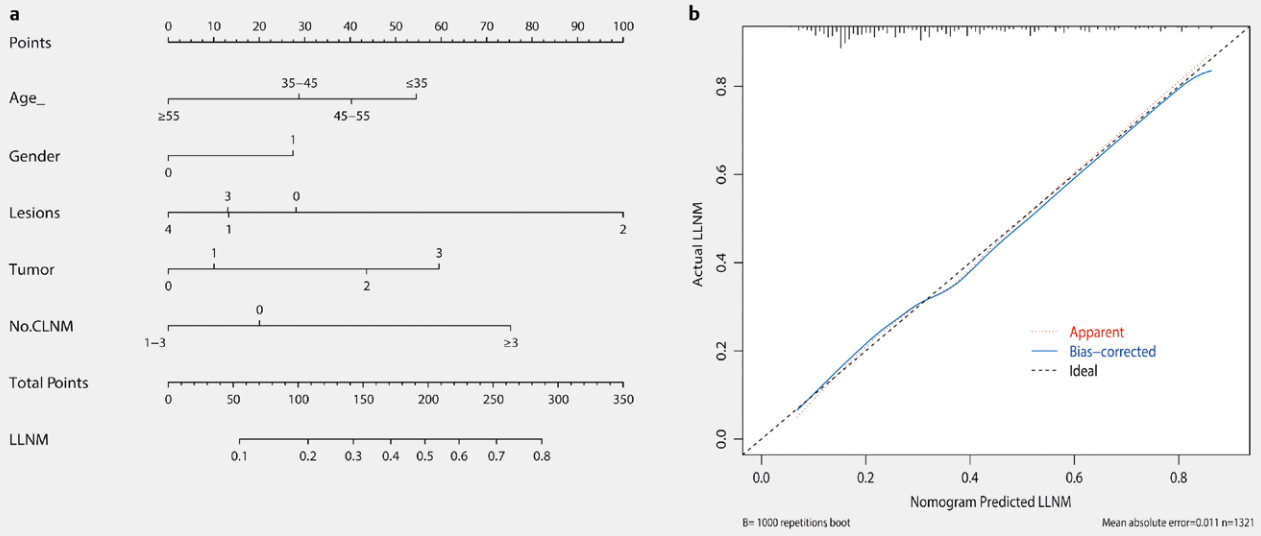
Although the postoperative survival rate of PTC patients was optimistic, the existing consensus was that PTC patients with LNM will have a higher risk of cancer recurrence after surgery [7, 13]. Once recurrence occurs, reoperation may increase the risk of permanent hypoparathyroidism, recurrent laryngeal nerve injury and other postoperative injuries [10, 14], This will cause great physical, psychological, and economic pressure to patients [13]. The current research shows that the recurrence rate of cancer in PTC patients after thyroid surgery and CLND will be reduced [15] , At the same time, it was recommended that all PTC patients observe cervical metastasis before and during operation [13]. However, prophylactic LND may increase the risk of complications [10, 14]. In addition, it may also affect the postoperative immune level of cancer patients, thus affecting the prognosis of patients [16]. Therefore, it was currently advocated to carry out therapeutic LLND according to preoperative ultrasound or CT reports, but the accuracy of conventional ultrasound was limited, and it was easy to miss diagnosis [17]. Therefore, it was important to find reliable risk factors for LNM in PTC patients.

CLNM

We studied 2166 patients with PTC in our hospital and preset the factors that may have differences. Our study found that age ≤ 55 years old was an independent risk factor for CLNM, while most studies now believe that < 45 years old was an independent risk factor for CLNM. Our study also found that the risk of CLNM was higher with the decrease of age, which was consistent with Liu's research results [7]. Male and ETE were also considered as independent risk factors of CLNM, which was consistent with previous research [1]. Bilateral lobe tumors were a risk factor for CLNM, while tumors at

▶ **Table 3** Un-adjusted and adjusted association between the clinicopathologic features and LLNM.

Variables	Unadjusted Odds Ratio (95% CI)	p-Value	Adjusted Odds Ratio (95% CI)	p-Value
Age				
≤ 35	**2.63 (1.77–3.98)**	**< 0.001**	**2.44 (1.58–3.85)**	**< 0.001**
35–45	**1.65 (1.08–2.56)**	**0.023**	**1.60 (1.01–2.59)**	**0.048**
45–55	**1.66 (1.06–2.62)**	**0.028**	**1.90 (1.17–3.10)**	**0.010**
≥ 55	1		**1**	
Gender				
Female	**1**	**–**	**1**	**–**
Male	**1.45 (1.14–1.86)**	**0.003**	**1.53 (1.16–2.00)**	**0.002**
Lesions				
Unilateral	**1**	**–**	**1**	**–**
Unilateralisthmus	0.78 (0.50–1.16)	0.232	0.80 (0.51–1.24)	0.337
Bilateral	**3.16 (2.42–4.14)**	**< 0.001**	**2.95 (2.21–3.96)**	**< 0.001**
Bilateralisthmus	1.00 (0.45–2.04)	0.999	0.75 (0.33–1.60)	0.471
Isthmus	0.74 (0.17–2.39)	0.641	0.66 (0.14–2.28)	0.545
Extrathyroidal Extension				
Yes	**1.28 (1.01–1.62)**	**0.041**	1.29 (0.99–1.68)	0.063
No	**1**		**1**	
Maximum tumor diameter				
1.0–1.5	**1**		**1**	
1.5–2.0	1.27 (0.91–1.77)	0.155	1.15 (0.80–1.65)	0.42
2.0–3.0	**2.12 (1.56–2.90)**	**< 0.001**	**1.94 (1.39–2.72)**	**< 0.001**
> 4.0	**2.94 (2.10–4.12)**	**< 0.001**	**2.50 (1.73–3.62)**	**< 0.001**
CLNM				
0	**1**		**1**	
1–2	0.90 (0.66–1.23)	0.52	**0.71 (0.51–0.99)**	**0.047**
≥ 3	**3.46 (2.58–4.68)**	**< 0.001**	**2.30 (1.66–3.19)**	**< 0.001**
Glu	1.03 (0.96–1.10)	0.47	**–**	**–**
TSH	1.05 (0.98–1.12)	0.18	**–**	**–**
FT4	1.09 (0.84–1.40)	0.495	**–**	**–**



▶ **Fig. 3** **a** This is a nomogram for evaluating lateral lymph node metastasis in papillary thyroid carcinoma. The significance of these features is as follows. Gender: 0, Female; 1, Male; Lesions: 0, Unilateral; 1, Unilateralisthmus; 2, Bilateral; 3, Bilateralisthmus; 4, isthmus; Tumor: 0, 1–1.5 cm; 1, 1.5–2 cm; 2, 2–3 cm; 3, ≥ 3 cm. According to the clinical characteristics of each patient, a vertical line was drawn to the points line to obtain the score of each characteristic, and then the total score was added and corresponding to the total points (line 7). Finally, LLNM was predicted based on the total score (line 8). **b**: The calibration curve of the nomogram for predicting possible lateral lymph node metastasis. The Y-axis shows the actual lateral lymph node metastasis, and the X-axis shows the lateral lymph node metastasis predicted by nomogram.

other locations (unilateral, unilateral with isthmus, bilateral with isthmus, isthmus) do not show significant correlation with CLNM in univariate and multivariate logistic regression analysis results. The possible reason was that bilateral lobe tumors were more likely to have lateral Extrathyroidal Extension (ETE), which means that such patients have a greater probability of multifocal PTC, it will be more aggressive, so bilateral lobe tumors were considered to have a high risk of CLNM [18].

The idea of our study was similar to that of many previous studies, but the results were somewhat different [6, 11, 19, 20]. Yang's study confirmed that some relative factors like tumor size were risk factors of CLNM [20]. However, in the analysis of tumor size, the classification criteria were PTC ≥ 1 cm and PTC ≤ 1 cm. It was believed that PTC ≥ 1 cm was a risk factor for tumors. However, some studies have shown that the pathological characteristics of PTMC (tumor ≤ 1 cm) and PTC (tumor size > 1 cm) were different [11]. Therefore, our study directly excluded the patients with PTMC, only studied the patients with PTC, and divided the tumor size into four groups (1–1.5 cm, 1.5–2 cm, 2–3 cm, ≥ 3 cm). Finally, we found that only the tumor size of 2–3 cm was an independent risk factor for CLNM in patients with PTC. In terms of patient selection, although Yang et al. has more patients, our more important advantage was that we exclude all patients with other malignant tumors in the past, which was different from Yang's exclusion of patients with head and neck cancer in the past. As the first-line immune organ in the human body, lymph node exists in the metastasis path of various cancers, and it was more rigorous to eliminate effects from other cancers [21]. Considering that thyroid gland was an important endocrine organ in the human body and PTC was an endocrine tumor, various hormone levels may be involved in the pathogenesis of PTC and LNM [14, 22, 23], We included fT4 and TSH in the study, but they were not found to be significantly correlated with CLNM. Different from previous studies, we included FPG into the risk factor study of CLNM and confirmed that FPG was an independent risk factor of CLNM. The mechanism may be that insulin-like growth factor binding protein-3 (IGHBP3) related to FPG may play a key role in LNM [24].

LLNM

LLNM was also common in PTC patients [25]. There have been many studies on LLNM risk factors in the past, but the results were inconsistent [20, 26]. Heng's research believes that age ≤ 40 years old and tumor diameter ≥ 1 cm were significantly related to LLNM [26], In our study, age ≤ 55 years old was an independent risk factor for LLNM, but no significant negative correlation between LLNM and age was found. Tumor size ≥ 2 cm was an independent risk factor for LLNM, and the risk of LLNM was higher with tumor growth, which was different from their research [26]. In addition, bilateral lobe tumors were also significantly associated with LLNM. In the study on PTMC [27, 28], ETE was significantly correlated with LLNM. However, no significant correlation was found in our study, which may be due to the difference in pathological characteristics between PTMC and PCT [11].

Both Zeng and Liu have found that CLNM was an independent risk factor for LLNM. According to the ROC curve, the best critical value for CLNM to predict LLNM was calculated, which was 1.5 and 2.5, respectively [7, 28], Liu's study did not make a clear division between PTC and PTMC, which may be one of the reasons for the difference. To better confirm this, we also conducted the same study on PTC patients. The optimal critical value was 2.5. The re-

sults of logistic regression suggest that only CLNM ≥ 3 was an independent risk factor for LLNM, which suggests that the critical value of CLNM predicting LLNM was not the same in PTMC and PTC patients. In PTC patients, when LLNM ≥ 3, CLND should be actively performed in combination with other diagnoses. We tried to use the independent risk factors of LLNM in PTC patients to build a nomogram to predict the possibility of LLNM. As our nomogram shows, the number of CLNM plays a very important role in predicting LLNM. For the PTC patients we studied, this model has high sensitivity and specificity in predicting PTC. It was worth noting that when the number of CLNM was 1 or 2, LLNM was considered as a protective factor, which was different from previous studies, and its potential mechanism still needs to be further studied.

Existing studies believe that LLNM mainly occurs after CLNM, and a few PTC patients have skip metastasis [29]. There were 98 cases of skip metastasis, accounting for 22.3 % of LLNM. For patients with skip metastasis, many previous team studies believed that age, primary tumor in the upper part, and tumor size ≤ 1 cm were risk factors [30, 31]. In our study, only tumors ≥ 3 cm were found to be significantly associated with skip metastasis.

Our research has still some limitations. First, this was a retrospective study. There may be objective factors such as a single source of cases and a single medical institution (convergence of medical standards). In addition, some factors, such as multifocal, were not included in our study, which may limit the application of nomogram. However, we have made more achievements in summarizing and verifying the mentioned risk factors of CLNM, LLNM, and including new factors to expand the scope of research, which can guide and suggest the clinical development of LND.

Conclusion

Our study found that age, male, bilateral lobe tumors, ETE, 2–3 cm tumors, and FPG were independent risk factors of CLNM. The risk factors of LLNM were found to be little different from those of the above CLNM. What needs to be added was that CLNM ≥ 3 were significantly related to LLNM, while CLNM = 1 or 2 was the protective factor of LLNM, and no significant correlation was found between ETE and LLNM. For skip metastasis, we only found that tumor ≥ 3 cm was significantly associated with it. In addition, we also established a nomogram model according to the independent risk factors of LLNM, which has certain clinical significance in guiding prophylactic LLND.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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