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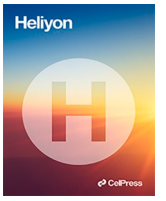

Research article

A model based on ultrasound and clinical factors to predict central lymph node metastasis in cN0 papillary thyroid microcarcinoma

Shaokun Sun, Qin Zhou, Tao Hu *

Department of Thyroid Surgery, The First People's Hospital of Kunshan, Suzhou, Jiangsu, China

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ABSTRACT

Objective: The prevalence of thyroid malignancies has sharply elevated in the past few years, and a large number of newly diagnosed thyroid malignancies was papillary thyroid microcarcinomas (PTMC). The efficacy of prophylactic central lymph node dissection (PCLND) in patients with clinical lymph node-negative (cN0) PTMC is still debatable. In this study, we aimed to create a predictive model to assess the likelihood of central lymph node metastasis (CLNM) in cN0 PTMC.
Methods: Two hundred and fifty three patients diagnosed with cN0 PTMC who received surgery in the First People's Hospital of Kunshan from October 2018 to June 2023 were enrolled. Multivariate logistic regression was employed to evaluate the patient's clinical and ultrasonographic information to determine independent factors. Two prediction models were generated and their ability to evaluate the likelihood of CLNM in cN0 PTMC was determined and compared.
Results: Multivariate analysis based on clinical characteristics revealed that, CLNM was markedly linked to age, tumor size, and extrathyroidal infiltration in cN0 PTMC. Multivariate analysis utilizing clinical and ultrasound features demonstrated that age, tumor size, extrathyroidal infiltration, shape, microcalcification were independent risk factors for CLNM. The analysis of the receiver operating characteristic curve demonstrated that the predictive nomogram utilizing clinical and ultrasound features was more beneficial for predicting CLNM. And decision curve demonstrates the same. The model's calibration curve exhibited strong consistency.
Conclusions: Age, tumor size, extrathyroidal infiltration, shape, microcalcification are significant independent factors of CLNM in cN0 PTMC. A predictive model derived from these independent clinical and ultrasound factors has a good value, but further validation is still required.

The prevalence of papillary thyroid carcinoma (PTC), which represents the predominant form of thyroid malignancy, is increasing annually [1]. Despite the majority of patients with PTC have a relatively favorable prognosis, they are at risk of developing early central lymph node metastases (CLNM), which leads to a higher rate of local recurrence after surgery [2]. Over half of recently identified thyroid cancers are classified as papillary thyroid microcarcinoma (PTMC) [3], of ones are PTCs with a maximal tumor size of one cm. PTMC patients ofen have a relatively favorable prognosis because PTMC lesions are modest in size and do not easily pierce the surrounding normal thyroid tissue. Nevertheless, the occurrence of CLNM in PTMC remains significant, reaching approximately 44%–51 % in some series [4,5]. In addition, once patients with PTMC develop CLNM, they typically face a markedly elevated risk of death, distant metastasis, and recurrence [6]. Therefore, in clinically positive central lymph nodes (cN1) patients, there always has a consensus on the national and international levels for therapeutic central lymph node dissection. Nevertheless, in patients with PTMC

* Corresponding author.
E-mail address: ht1801@Sina.com (T. Hu).

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who are clinical lymph node-negative (cN0), it is questionable if prophylactic cervical lymph node dissection (PCLND) is required [7, 8].

Currently, the primary method for preoperative identification of CLNM is ultrasonography; however, researches demonstrated that the sensitivity of CLNM prediction by a single ultrasound is only 18 %–38 % [9]. The diagnostic value of ultrasound evaluation is limited because of anatomic position of the central lymph nodes, occlusion of sternum, and interference of gas in the trachea. An earlier investigation revealed an association among CLNM and clinical features including tumor size and extrathyroidal infiltration [10].

In this investigation, our objective was to found out predictors linked to CLNM in cN0 PTMC, then create a prediction model to enhance the accuracy of diagnosis by integrating clinical information and ultrasonographic features, with the hope of providing some reference for clinical PCLND. To this end, we performed a retrospective analysis of data from 253 cN0 PTMC patients diagnosed after surgery and developed a predictive model to examine the value of ultrasound combined with clinical features to predict CLNM, with the aim to provide guidance for the medical management of patients with cN0 PTMC.

1. Materials and methods

1.1. Patients

We included 253 cN0 PTMC patients from the First People's Hospital of Kunshan from October 2018 to June 2023. The entire cohort of patients underwent evaluation and received medical care at the hospital mentioned above. Patients with cN0 PTMC were defined as those without LNM based on preoperative imaging evaluations. All operations were conducted by surgeons possessing over a decade of surgical experience in our hospital. The individuals were classified into the CLNM and non-CLNM groups according to whether the central lymph nodes had metastasized or not.

The inclusion criteria for this research were: (1) Patients who were undergoing initial thyroid surgery; (2) confirmed postoperative pathology; (3) absence of CLNM through preoperative ultrasound; and (4) complete clinical and ultrasound data.

Exclusion criteria were: (1) Patients with diverse pathological subtypes of thyroid cancer; (2) without central lymph node dissection; and (3) a history of neck radiation therapy or other surgical interventions.

1.2. Data collection

We collected data on the patients' clinical characteristics, including age, sex, maximum tumor diameter, focality (unifocal or multifocal), extrathyroidal infiltration, tumor location (left, right, isthmus, bilobed), history of Hashimoto's thyroiditis (HT), BRAF gene mutation (V600E), and presence of CLNM in pathology, and preoperative ultrasonographic characteristics, such as margin, shape, microcalcifications, and internal echogenicity.

1.3. Analysis of ultrasonic characteristics

All patients received ultrasonography of thyroid gland with central lymph nodes within 1 month prior to surgery. Patients were positioned supine with full exposure of the neck examination area. Ultrasound imaging of each nodule was performed using the Mindray Resona 7T ultrasound system with the L 12-5 probe, operating at a frequency in the range of 5–12 MHz. Ultrasound examination was performed by two experienced sonographers, blinded to the pathological results, and recorded the ultrasound imaging features, including margin, shape, microcalcifications, and internal echogenicity. If there was any objection, an additional sonographer was consulted to reach a final determination.

1.4. BRAF V600E mutation analysis

BRAFV600E mutation testing was conducted using a commercially available kit from BIO-RAD Company (California, USA). The target DNA was extracted, and digital PCR was conducted followed the kit instructions. The results were determined using the reading criteria provided in the mutation detection kit.

1.5. Statistical analysis

All data were analyzed utilizing SPSS 23.0 software. Categorical data are summarized as frequencies or percentages. Univariate analysis was conducted utilizing t-tests and χ^2 tests to compare variables between groups. Risk factors linked to CLNM were screened by univariate analysis, then statistically significant factors were incorporated into the multivariate logistic regression equation. A prediction nomogram was constructed based on the multivariate logistic regression analysis outcomes utilizing R software (version 4.1.0). The model's prognostic capability was assessed utilizing the calibration plot and receiver operating characteristic (ROC) curve. Decision curve analysis (DCA) was employed to ascertain the clinical value of the nomogram by measuring the net advantage at various thresholds. We generated calibration plots and validated them via 500 bootstrap repetitions to minimize bias. Statistical significance was define as P-values <0.05.

2. Results

253 cN0 PTMC patients were included in this cohort, including 49 % with CLNM. The mean age of the cohort was 44.7 ± 11.7 years (range: 24–76). The cohort comprised 67 males and 186 females, with a male/female ratio of 1:2.78. Tables 1 and 2 show the patients' clinical and ultrasonic faeatures.

2.1. Association of CLNM with clinical and ultrasonic characteristics of cN0 PTMC

Within the cohort, univariable analysis demonstrated that CLNM was markedly linked to age (P = 0.002), tumor size (P < 0.001), sex (P = 0.004), focality (P = 0.038), extrathyroidal infiltration (P < 0.001), and BRAF V600E mutation (P = 0.026) (Table 1). Nevertheless, the tumor location (P = 0.125) and incidence of HT (P = 0.951) did not exhibit statistically significant difference between the two cohorts.

Regarding the ultrasonic features of all cN0 PTMC (Table 2), internal echogenicity (P = 0.757) was not a significant feature linked to CLNM. However, margin (P = 0.018), shape (P < 0.001), and microcalcification (P = 0.001) were relative influencing factors of CLNM.

2.2. Multivariate logistic regression analysis

CLNM in cN0 PTMC patients was markedly linked to age <55 years (odds ratio [OR]: 2.746, P = 0.005, 95 % confidence interval [CI]: 1.349–5.690), tumor size ≥0.5 cm (OR: 2.697, P = 0.001, 95 % CI: 1.547–4.702), and extrathyroidal infiltration (OR: 10.386, P = 0.003, 95 % CI: 2.270–47.533) in the multivariate analysis based on clinical characteristics, as shown in Table 3.

In the multivariate analysis based on clinical and ultrasound characteristics, age <55 years (OR: 2.909, P = 0.006, 95 % CI: 1.361–6.216), tumor size ≥0.5 cm (OR: 2.896, P = 0.001, 95 % CI: 1.549–5.413), extrathyroidal infiltration (OR: 12.204, P = 0.002, 95 % CI: 2.594–57.415), shape (OR: 3.876, P = 0.001, 95 % CI: 1.980–7.588), and microcalcification (OR: 2.170, P = 0.012, 95 % CI: 1.183–3.978) were independent risk factors for CLNM (Table 4).

2.3. Development of the prediction nomogram

According to the outcomes of Table 3, the following model was derived to predict the likelihood of CLNM. To depict model 1, we constructed a nomogram utilizing independent clinical predictors (Fig. 1). Each prognostic factor was allocated a specific numerical value within this predictive nomogram, such as a positive extrathyroidal infiltration score of 100 points, or a negative extrathyroidal infiltration score of 0 points.

Table 1
Univariate analysis: Association between CLNM and the clinical features of cN0 PTMC.

Variables	CLNM(−) (n = 129)	CLNM(+) (n = 124)	X^2	P-value
Age(years)			10.015	0.002
<55	90 (69.8 %)	107 (86.3 %)		
≥55	39 (30.2 %)	17 (13.7 %)		
Tumor size(cm)			22.254	<0.001
≤0.5	83 (64.3 %)	43 (34.7 %)		
>0.5	46 (35.7 %)	81 (65.3 %)		
Sex			8.389	0.004
Male	24 (18.6 %)	43 (34.7 %)		
Female	105 (81.4 %)	81 (65.3 %)		
Focality			4.291	0.038
Unifocal	104 (80.6 %)	86 (69.4 %)		
multifocal	25 (19.4 %)	38 (30.6 %)		
Extrathyroidal infiltration			19.305	<0.001
−	127 (98.4 %)	102 (82.3 %)		
+	2 (1.6 %)	22 (17.7 %)		
Tumor location			5.736	0.125
left	49 (38.0 %)	42 (33.9 %)		
right	68 (52.7 %)	58 (46.8 %)		
isthmus	7 (5.4 %)	17 (13.7 %)		
bilobed	5 (3.9 %)	7 (5.6 %)		
Hashimoto's thyroiditis			0.004	0.951
−	92 (71.3 %)	88 (71.0 %)		
+	37 (28.7 %)	36 (29.0 %)		
$Braf^{V600E}$			4.985	0.026
−	32 (24.8 %)	17 (13.7 %)		
+	97 (75.2 %)	107 (86.3 %)		

CLNM, central lymph node metastasis.

Table 2
Univariate analysis: Association between CLNM and the ultrasonic features of cN0 PTMC.

Variables	CLNM(−) (n = 129)	CLNM(+) (n = 124)	X^2	P-value
Margin			5.574	0.018
Smooth	57 (44.2 %)	37 (29.8 %)		
Ill-defined	72 (55.8 %)	87 (70.2 %)		
Shape			13.427	<0.001
Oval	56 (43.4 %)	27 (21.8 %)		
Taller-than-wide	73 (56.6 %)	97 (78.2 %)		
Microcalcification			10.216	0.001
	80 (62.0 %)	52 (41.9 %)		
+	49 (38.0 %)	72 (58.1 %)		
Echogenicity			0.096	0.757
Hypo echogenicity	114(88.4 %)	108(87.1 %)		
Iso/Hyperechogenicity	15(11.6 %)	16(12.9 %)		

CLNM, central lymph node metastasis.

Table 3
Multivariate logistic regression analyses: Association between CLNM and the clinical features of cN0 PTMC.

Characteristics	*P-value*	*OR*	95%*CI OR*
Age<55 years	0.005	2.746	1.349–5.690
Tumor size≥ 0.5 cm	0.001	2.697	1.547–4.702
Sex	0.054	1.884	0.988–3.593
Focality	0.234	1.491	0.772–2.879
Extrathyroidal infiltration	0.003	10.386	2.270–47.533
$Braf^{V600E}$	0.238	1.537	0.753–3.134

Table 4
Multivariate logistic regression analyses: Association between CLNM and clinical and the ultrasound features of cN0 PTMC.

Characteristics	*P-value*	*OR*	95%*CI OR*
Age<55 years	0.006	2.909	1.361–6.216
Tumor size≥ 0.5 cm	0.001	2.896	1.549–5.413
Sex	0.266	1.475	0.743–2.929
Focality	0.281	1.475	0.727–2.992
Extrathyroidal infiltration	0.002	12.204	2.594–57.415
$Braf^{V600E}$	0.387	1.392	0.657–2.950
Margin	0.108	1.680	0.893–3.163
Shape	0.001	3.876	1.980–7.588
Microcalcification	0.012	2.170	1.183–3.978

Another prediction model, model 2, which involves independent clinical and ultrasound predictors, was established and a nomogram was plotted (Fig. 2). According to model 2, patients with positive extrathyroidal infiltration still received the highest scores.

2.4. Comparison and evaluation of the two prediction nomograms

This study generated the ROC curve for the two prediction nomograms to assess their discriminating ability. Examining the ROC curve and AUC comparison, we concluded that model 2, which is based on independent clinical and ultrasound predictors, has a stronger capacity to discriminate CLNM in cN0 PTMC (Fig. 3).

The results of DCA also showed that model 2 has better predictive power (Fig. 4).

During internal validation (500 bootstraps), the nomogram's prognostic precision reached 0.705. The calibration plot corroborated the forecasting accuracy, demonstrating a correspondence between the empirical observations and the prediction by the nomogram (Fig. 5).

3. Discussion

CLNM frequently occurs in patients with PTMC, and even cN0 PTMC are often found with CLNM after surgery. According to the earlier research, the incidence of postoperative CLNM in cN0 PTMC patients is 30 % [11].

Currently, central lymph node dissection is advised for cN1a, cN1b PTMC patients. However, lymph node dissection in cN0 PTMC patients is a subject of ongoing debate [7,8]. The reasons for advocating PCLND include prolonging the disease-free survival and

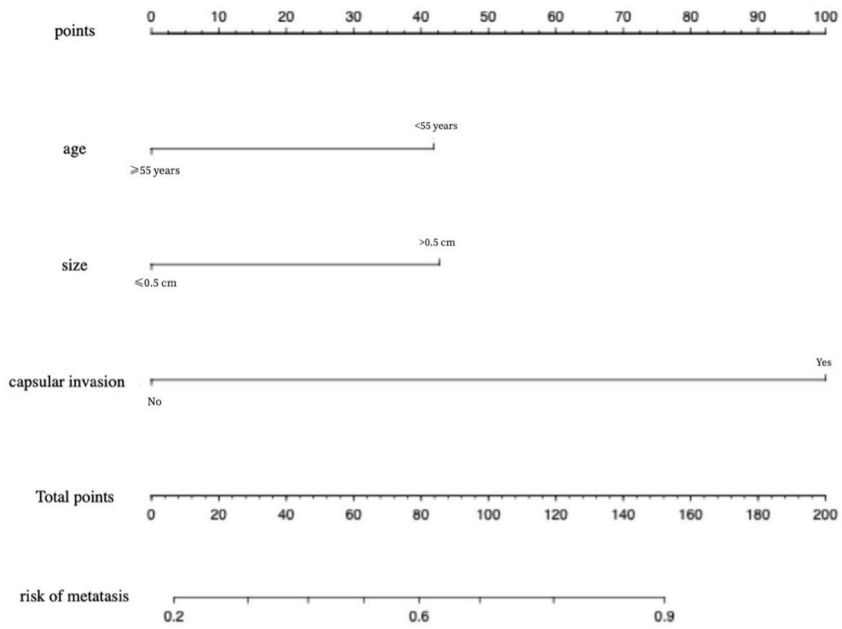

Fig. 1. Prediction nomogram. The predictive nomogram was constructed utilizing the following factors: age, tumor size, and extrathyroidal infiltration.

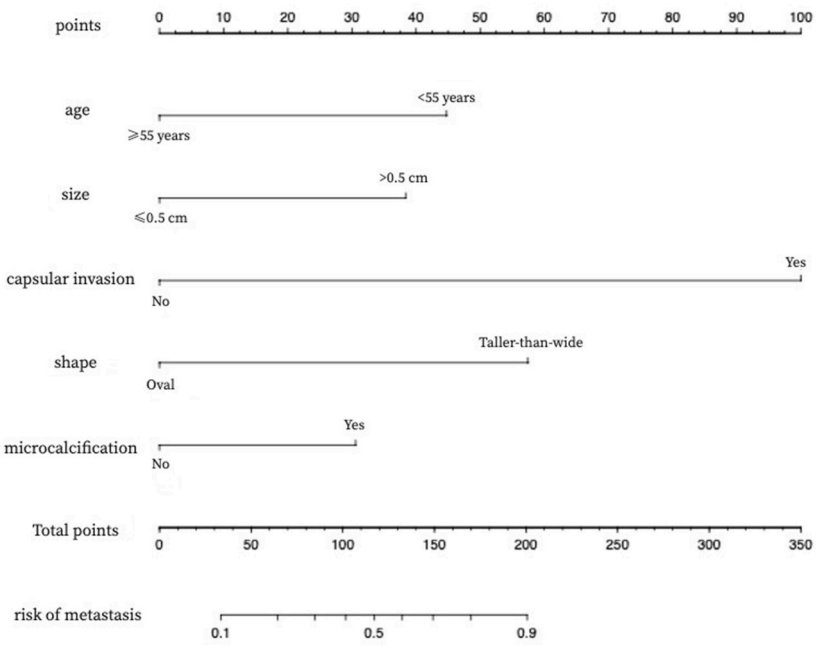

Fig. 2. Prediction nomogram. The predictive nomogram was constructed utilizing the following factors: age, tumor size, extrathyroidal infiltration, shape, and microcalcification.

reducing postoperative local recurrence and metastasis [12,13], and obtaining a detailed pathology report of the patient, which can provide a more accurate and scientific tumor-node-metastasis (TNM) staging and risk of recurrence, thus providing a reference value for further treatment. In the research by Ma et al. [14], among 456 cN0 PTC patients, the postoperative pathology showed that 184 cases were positive for CLNM, with a metastasis rate as high as 40.3 %. According to the expert agreement in China, PCLND can be performed without damaging the surrounding organs and nerves, such as parathyroid glands and the recurrent laryngeal nerve [15]. However, the 2022 National Comprehensive Cancer Network (NCCN) recommends PCLND for those with cN0 with tumors more than 4 cm or extrathyroidal infiltration. Conversely, for those presenting with cN0 and T1 or T2 stage tumors lacking elevated risk features

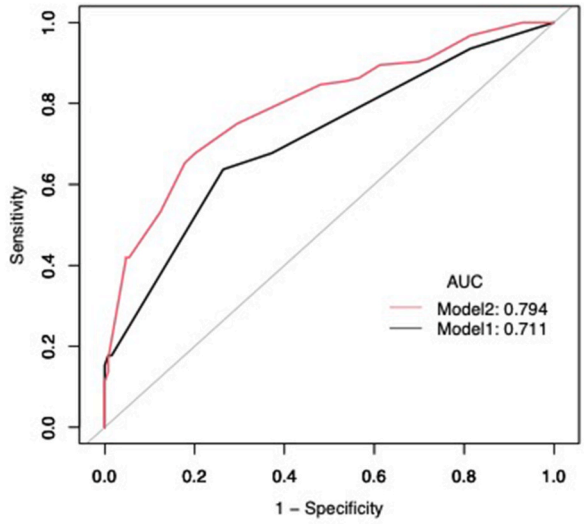

Fig. 3. Receiver operating characteristics (ROC) curve and area under the curve (AUC) of models 1 and 2.

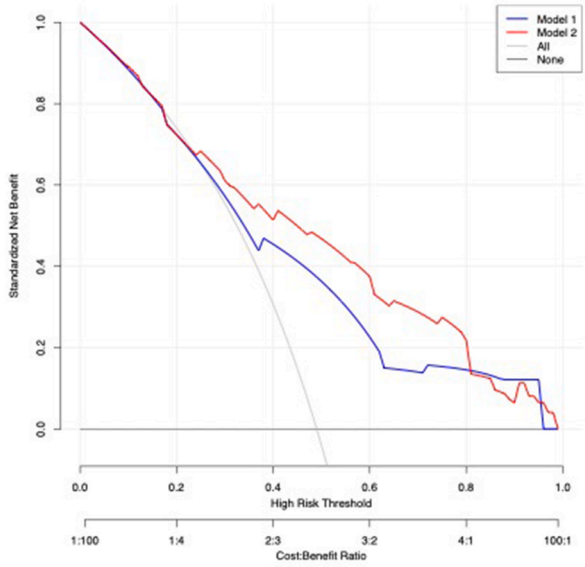

Fig. 4. Decision curve analysis (DCA) of the two predictive nomograms.

for lymph node metastasis, CLND is not advised [16].

The efficacy of preoperative detection, exemplified by ultrasound, is currently unsatisfactory. Indeed, studies have revealed the sensitivity of CLNM prediction by ultrasound in cN0 PTMC patients is $\leq$ 38 % [9,17]. Therefore, significant likelihood of hidden CLNM should not be disregarded, even in cases of cN0 PTMCs. It is unwise to execute PCLND solely based on preoperative US. Because preoperative CLNM determines the extent of surgery, identifying risk factors for CLNM in cN0 PTMC and detecting patients who are at a high risk for PCLND is crucial.

This research includes clinical and ultrasound information of PTMC. Multivariate logistic analysis utilizing the clinical and ultrasound information of PTMC patients showed that age <55 years, tumor size $\geq$0.5 cm, extrathyroidal infiltration, shape, microcalcification were independent risk factors for CLNM in PTMC patients.

The cutoff point for thyroid cancer in the TNM staging method was 55 years. Age is a significant risk factor of CLNM,as a sign of a poor prognosis in patients with PTMC [18]. Our study also revealed that those under 55 years of age exhibited an elevated incidence of CLNM compared to their older counterparts, and revealed age was an independent predictor of CLNM. Therefore, a thorough evaluation of the central lymph nodes prior to surgery is essential for younger ones with PTMC.

Many earlier researches revealed that males are a risk factor for cervical CLNM in cN0 PTMC [5,14]. However, many studies

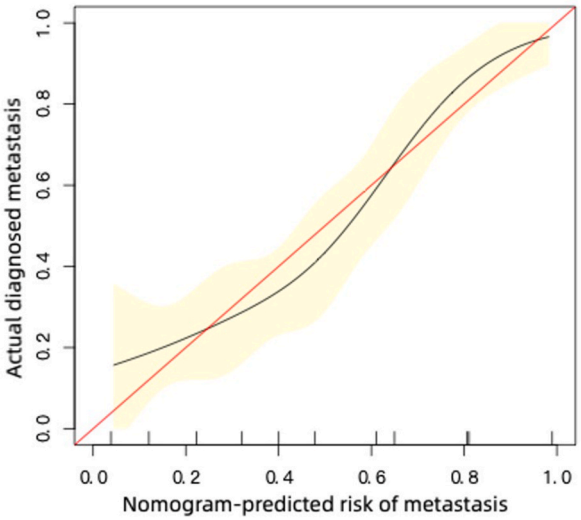

Fig. 5. Calibration curves of the predictive nomogram derived from independent clinical and ultrasound predictors. The red line denotes the reference, and the black line denotes the fit. The yellow area denotes the 95 % CI. Following 500 repetitions of bootstrap, the calibration plots exhibited strong concordance the predicted probability and actual probability.

reached the opposite conclusion [19]. In our investigation, the proportion of males in the CLNM cohort exceeded that of the non-CLNM cohort, yet gender did not emerge as a significant determinant for CLNM. This observation might be attributed to the limited sample size, low representation of male subjects, specific inclusion criteria for the research, and variations in surgical approaches employed.

The stage and prognosis of patients with PTMC can be indicated by the size of the tumor [16]. Even if there is no standard measure for PTMC tumor size that can be used to forecast CLNM, many studies use a cutoff of 0.5 cm. Indeed, Xie et al. [20] retrospectively studied 462 cases, revealing that tumor size (>0.5 cm) can independently predicted central CLNM occurrence, aligning with the current study's findings. Moreover, our study revealed a notable correlation between CLNM and PTMC lesions exceeding 0.5 cm in size.

One well-known predictior for central CLNM in PTMC is extrathyroidal infiltration. According to earlier studies [21], patients with PTMC who present characteristics such as extrathyroidal infiltration face an elevated likelihood of CLNM development compared to those without such characteristic. This aligns with our findings, which indicated that extrathyroidal infiltration was associated with a significant tendency for CLNM.

Prior research has demonstrated a connection between thyroid microcalcifications and CLNM in PTC [22], which was confirmed in our study. Microcalcifications reflect the accelerated growth of cancer cells and the buildup of calcium salt accumulation resulting from vascular and fibrous expansion. Microcalcifications are prevalent in PTC and are a characteristic indicator of thyroid malignancy. Consequently, when preoperative ultrasonography detects microcalcifications within thyroid lesions, heightened scrutiny of the central lymphatic nodes is warranted during the surgical intervention.

Research indicates that multifocal PTMC patients tend to have higher TNM stages, recurrence, and death [23].In our study, those with CLNM had a higher incidence of multifocal tumors relative to patients without CLNM. Although multifocal tumors showed a correlation with CLNM incidence, this characteristic was not established as an independent risk factor. The disparities could be explained by the variations in the research' selection criteria [24]. In our article, the margin was not established as a notable risk predictor for CLNM, aligning with the conclusions drawn from earlier researches [5,19].

BRAF V600E is documented as the most prevalent mutation in PTC [25], and serves as a crucial component in the mitogen-activated protein kinase (MAPK) pathway [26]. Numerous researches have concluded that the BRAF V600E mutation is independently linked to prognostic variables, such as CLNM [27], although other investigations have reached a different conclusion [10,11]. So, the predictive value of BRAF V600E for CLNM in PTMC is still controversial. Among this investigation, the mutation frequency in the CLNM cohort (86.3 %) exceeded that of the non-CLNM cohort (75.2 %); nevertheless, the BRAF V600E mutation did not independently predict CLNM.

In this investigation, the incidence of CLNM was elevated among those with tumors that were taller than wider compared to those with other tumor shapes, indicating a potential correlation between CLNM and tumor shape, which aligns with the results reported in earlier research [28].

There are many prediction models for evaluating the likelihood of CLNM in cN0 PTMC. Ma et al. [14] analyzed all clinical characteristics to develop a predictive model for CLNM, which presented good performance. However, no ultrasound features were added. Zhu et al. [19] sought to construct a nomogram model utilizing ultrasound information and the BRAF V600E mutation of the primary tumor to anticipate LNM in PTMC patients, but clinical features were out of the consideration. Zhao et al. [18] analyzed both clinical and ultrasound characteristics, but just only one model incorporates tumor characteristics and ultrasound examination features were established. Rarely will two models based on clinical and ultrasound characteristics be built and compared. In our study, we not

only included the clinical and ultrasound characteristics but also the BRAF mutation status. We then developed and validated two prediction nomograms, one of which incorporated the three clinically independent risk predictors mentioed above, while the other incorporated independent clinical and ultrasound predictors to make it easier to predict CLNM in cN0 PTMC on an individual basis. Using the ROC and DCA curves, we concluded that a prediction nomogram incorporating clinical and ultrasound features would be more beneficial for predicting CLNM. The creation of this prognostic model will assist surgeons in performing precise CLND to optimize patient outcomes. The practical implementation of the nomogram offers a straightforward method to predict CLNM and requires only a simple addition calculation.

Our investigation also presents certain constraints that warrant discussion. Firstly, given its retrospective nature, selection bias is unavoidable, and the distribution of histological subtypes and clinical characteristics might vary in different geographical areas. Secondly, this research is confined to a single institution, which restricts the broader applicability of our observations. Additional external validation and extensive evaluations using multicenter, large-scale datasets are necessary to confirm the dependability of the predictive nomogram. Thirdly, the relatively modest sample size may diminish the statistical power to detect particular correlations and impair the accuracy of our estimates. More extensive cohort researches are necessary to improve the dependability of our results. Fourth, ultrasound features are highly relied on the sonographer's experience. More sonographer with extensive clinical experience could join the study. In the future, a multicenter prospective investigation encompassing a broader and more heterogeneous cohort will be valuable to confirm the robustness of our statistical method.

4. Conclusion

In summary, the results of this investigation revealed that a prediction nomogram based on independent clinical and ultrasound predictors has a better value than the nomogram based only on clinical predictors. Age $<$55 years, size $\geq$0.5 cm, extrathyroidal infiltration, margin, shape, and microcalcification are significant independent predictors of CLNM in cN0 PTMC patients. This prediction model will help the surgeon evaluate the status of the patients' central lymph nodes considering the necessity of central lymph node dissection surgery.

Ethics statement

All medical records are legal and reasonable. The research was reviewed and approved by the Ethics Committee of The First People's Hospital of Kunshan[number: 2024-03-004-K01].

Every patient gave their informed agreement to take part in the research and to have images of them and case details published in anonymous form.

Consent for publication

Written informed consent was provided by each participant for publishing.

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Data availability statement

The data related to this research has not been stored in a publicly accessible database, but it can be obtained from the corresponding author upon request.

CRediT authorship contribution statement

Shaokun Sun: Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Qin Zhou:** Writing – review & editing, Funding acquisition. **Tao Hu:** Writing – review & editing, Investigation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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