ORIGINAL RESEARCH

Predictive Value of Ultrasound Imaging Characteristics and a BRAF V600E Nomogram for Central Lymph Node Metastasis Risk in Papillary Thyroid Microcarcinoma

Decang Zhu, MD; Xinping Wu, PhD; Lijuan Zhang, PhD; Zuqian Chen, PhD

ABSTRACT

Objective • The objective of this study was to construct and validate a nomogram for preoperatively identifying central lymph node metastasis (CLNM) in patients with papillary thyroid microcarcinoma (PTMC) using ultrasound imaging characteristics and the BRAF V600E gene mutation.

Methods • A retrospective data analysis was conducted on 216 PTMC patients who underwent surgery at our facility between February 2016 and June 2022. Univariate and multivariate analyses examined the relationship between CLNM and clinicopathological traits, the BRAF V600E mutation, and ultrasound imaging characteristics. The area under the curve (AUC) was calculated, and receiver operating characteristic (ROC) curves were constructed to assess the predictive efficacy of the model in both the training and validation sets. Calibration curves were generated to evaluate the agreement between predicted and observed outcomes. Decision curve analysis (DCA) was performed to assess the clinical suitability of the model. A nomogram was developed to illustrate the predicted likelihood of CLNM.

Results • The incidence rate of CLNM was found to be 38.4% (83/216 patients). Logistic univariate and multivariate analyses revealed that the BRAF V600E mutation, patient age less than 45 years, tumor size greater than 5 mm, thyroid capsule invasion, and presence of microcalcification in the tumor were independent risk factors for CLNM. The model demonstrated high exclusionary performance with AUC values of 0.88 and 0.877 in the training and validation cohorts, respectively. The calibration curve and DCA confirmed the accuracy of the predicted outcomes and the clinical value of the nomogram.

Conclusions • A model incorporating ultrasound imaging characteristics and the BRAF V600E mutation can effectively predict the risk of central lymph node metastasis in patients with papillary thyroid microcarcinoma before surgery. The identified risk factors, including tumor size greater than 5 mm^3, BRAF V600E mutation, patient age less than 45 years, nodule capsule invasion, and presence of microcalcification, can aid in surgical decision-making. The nomogram provides a valuable tool for clinicians to assess the likelihood of CLNM in PTMC patients. (*Altern Ther Health Med.* 2023;29(8):139-143).

Decang Zhu, MD; Lijuan Zhang, PhD; Department of Ultrasound, Fourth Affiliated Hospital of Nanjing Medical University, Jiangsu, China. **Xinping Wu, PhD,** Department of Ultrasound, Jiangsu Integrated Hospital of Traditional Chinese and Western Medicine, Nanjing, Jiangsu, China. **Zuqian Chen, PhD**, Fourth Affiliated Hospital of Southern Medical University.

Corresponding author: Zuqian Chen , PhD
E-mail: ch0001@126.com

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common histological category of thyroid carcinoma, accounting for 80% to 90% of patients and showing an increasing incidence.[1] When PTC malignancies have a maximal diameter of 10 mm or less, they are classified as papillary thyroid microcarcinomas (PTMC) by the World Health Organization. The use of high-frequency ultrasound (US) and ultrasound-guided fine needle aspiration biopsy (FNAB) has improved the preoperative diagnosis rate of PTMC.[2] Despite the generally favorable prognosis of PTMC, recent studies have shown that 40-60% of patients present with central lymph node metastasis (CLNM)[3]; for patients with visible central lymph nodes, central lymph node dissection (CLND) is recommended. The American Thyroid Association (ATA) guidelines suggest prophylactic central lymph node dissection (pCLND) for high-risk individuals with clinically negative PTC, particularly those with extrathyroidal extension or tumor size >4 cm.[3,4]

However, on cervical ultrasound, pCLND is not recommended for individuals with tumors smaller than five millimeters and no preoperative indications of lymph node metastasis. Despite the low incidence of CLNM in PTMC patients, the decision to perform pCLND relies on clinician discretion due to the lack of reliable predictive factors for

CLNM. Accurate anticipation of CLNM probability is crucial for determining an appropriate treatment strategy for patients with clinically node-negative PTMC. Although preoperative ultrasonography is commonly used for the diagnosis of thyroid cancer and detection of CLNM, its sensitivity for CLNM is limited due to the hidden anatomical structures of the thyroid and the non-specific appearance of metastatic lymph nodes during ultrasound evaluation. The BRAF V600E mutation, which is more prevalent in PTC, is associated with invasive clinicopathological characteristics.[4]

In this study, we aimed to develop a predictive model for estimating the probability of CLNM in PTMC patients by integrating preoperative ultrasonographic features, clinical information, and the BRAF V600E gene mutation. The objective of this model is to assist in clinical management and decision-making regarding the management of PTMC patients.

METHODS

Study Design

This study employed a retrospective analysis design, which involved examining previously collected data from medical records, pathology reports, and imaging results of patients. The aim was to analyze the relationship between various clinical factors, ultrasound findings, and the presence of CLNM in PTMC patients. The study included 216 individuals diagnosed with PTMC based on ultrasound and histopathology findings at our hospital between February 2021 and June 2022. Thyroidectomies and pCLND were performed on all individuals.

Inclusion and Exclusion Criteria

The inclusion criteria for the study were: (1) availability of complete clinical and preoperative ultrasound data; and (2) confirmation of PTMC diagnosis by postoperative pathology or biopsy. Exclusion criteria were: (1) history of previous thyroid surgery; (2) tumor size exceeding 10 mm; (3) absence of BRAF V600E mutation data; and (4) missing or incomplete ultrasound images.

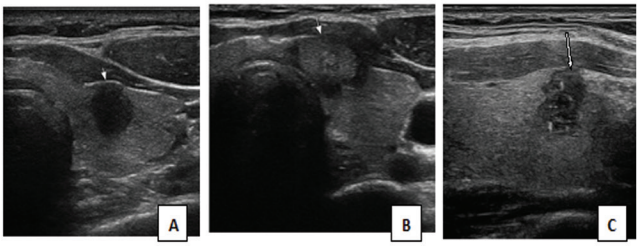
Data Collection

The retrospective analysis encompassed gathering basic clinical information, ultrasound findings, and pathological information of the PTMC patients who underwent thyroidectomies and prophylactic central lymph node dissection. The collected clinical and pathological data included age, sex, presence of the BRAF V600E mutation, and occurrence of central lymph node metastasis.

BRAF V600E Mutation Analysis

For the analysis of the BRAF V600E mutation, a commercially available kit from BIO-RAD Company (California, USA) was utilized. Genomic DNA was extracted, and the detection of the mutation was performed using digital PCR (ddPCR) analysis. The DNA sequencing was carried out through PCR amplification of exons using the Big Dye Terminator cycle.

Figure 1. Ultrasonography images of the thyroid gland of PTC patients. (A) A female patient aged 41 years: Small papillary carcinoma of the left lobe of the thyroid gland with obvious hypoechoic tumor; (B) a Female patient aged 52 years: Small papillary carcinoma near isthmus in the left lobe of the thyroid gland' (C) Male patient aged 35 years: Small papillary carcinoma of the right lobe of the thyroid.



Ultrasound Imaging

Ultrasound imaging of each nodule was performed using the Mindray Resona 7T ultrasound system with the L 12-5 probe, operating at a frequency range of 5 to 12 MHz. Two independent sonographers, blinded to the pathological and BRAF V600E mutation results, analyzed the ultrasound images of each nodule. Various parameters, including diameter (mm), texture, echo, boundary rule, presence of microcalcification, large calcification (microcalcification with a diameter ≤ 1 mm, coarse calcification with a diameter > 1 mm), capsule invasion, and halo sign were recorded (Figure 1). In cases of disagreement between the results, an additional sonographer was consulted to reach a final determination.

Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 software (IBM, Armonk, NY, USA). The quantitative evaluations involved the application of relevant statistical tests, including the *t* test, U test, Pearson Chi-square test, and Fisher exact test, to compare different categories. Logistic regression analysis was employed to identify variables strongly associated with the probability of CLNM, and an independent predictor model was developed. The performance of the model in the training and validation sets was assessed by constructing receiver operator characteristic (ROC) curves and calibration curves. Additionally, a nomogram was constructed, and its clinical applicability was evaluated using decision curve analysis (DCA) curves. Statistical significance was defined as a $P < .05$.

RESULTS

Exploration of the Risk Factors of CLNM in PTMC Patients

The study cohort consisted of 137 females and 79 males, with an average age of 42.45 ± 7.56 years. Among the PTMC individuals, 83 patients (38.4%) were found to have CLNM. The participants were randomly divided into training and validation groups in a 7:3 ratio. In the training cohort, significant associations were observed between CLNM and the following factors: BRAF V600E mutation, age younger than 45 years, tumor size larger than 5 mm[3], thyroid capsule invasion, presence of microcalcification, and presence of multifocal nodules ($P < .05$; Refer to Table 1).

Table 1. Investigation of Single Variables That Affect CLNM In PTMC Patients in the Training Group

Indicators	CLNM (+) (n = 55)	CLNM (-) (n = 96)	χ^2	*P* value
Age (years)			8.708	.003[a]
< 45	38 (69.1%)	41 (42.7%)		
≥ 45	17 (30.9%)	55 (56.3%)		
BRAF V600E			10.807	.001[a]
Have	42 (64.6%)	52 (60.5%)		
None	23 (35.4%)	34 (39.5%)		
Gender			0.452	.501
Male	26 (47.3%)	27 (28.1%)		
Female	29 (52.7%)	69 (71.9%)		
Calcification			7.733	.005[a]
Have	41 (74.5%)	46 (47.9%)		
None	14 (25.5%)	50 (52.1%)		
Tumor size			24.161	.000[a]
< 5mm	14 (25.5%)	29 (30.2%)		
≥ 5mm	41 (74.5%)	67 (69.8%)		
Multifocal			8.816	.003[a]
Yes	23 (41.8%)	29 (30.2%)		
No	32 (58.2%)	67 (69.8%)		
Edge			1.592	.207
Rules	17 (30.9%)	34 (35.4%)		
Irregular	38 (69.1%)	62 (64.6%)		
Encapsular invasion			25.450	.000
Have	42 (76.4%)	32 (33.3%)		
None	13 (23.6%)	64 (66.7%)		
Significant hypoecho			0.989	.320
Yes	16 (29.1%)	29 (30.2%)		
No	39 (70.9%)	67 (69.8%)		

[a]Statistically significant ($P < .05$)

Abbreviations: CLNM, central lymph node metastasis; PTMC; papillary thyroid microcarcinoma.

Construction of PTMC CLNM Model

Multivariate logistic analysis revealed BRAF V600E mutation (OR = 3.087, 95% CI: 1.438-6.627, $P = .004$), tumor size > 5 mm (OR = 7.420, 95% CI: 3.283-16.768, $P = .000$), age < 45 years (OR = 4.034, 95% CI: 1.842-8.837, $P = .000$), capsule invasion (OR = 12.209, 95% CI: 5.167-28.846, $P = .000$), and microcalcification in tumor (OR = 3.264, 95% CI: 1.485-7.171, $P = .003$) as independent risk factors for CLNM (Table 2). However, the presence of multifocal nodules did not emerge as a significant predictive factor ($P > .05$). Based on the logistic regression analysis, the following formula was derived to predict the likelihood of CLNM:

Logit (P) = -5.125 + 0.408851704 + age < 45 years × 1.395 + microcalcification × 1.183 + BRAF V600E × 1.127 + tumor size ≥ 5mm × 2.004 + capsule invasion × 2.502.

Establishment and Validation of the Clinical Prediction Model and Nomogram

The predictive performance of the model was assessed by constructing ROC curves. In the training cohort, the area under the curve (AUC) was 0.88, with a sensitivity of 74% and a specificity of 85.7% (Figure 3). Similarly, in the validation group, the AUC of the model was 0.877, with a sensitivity of 89.2% and specificity of 74.1% (Figure 3). These findings demonstrate the model's ability to predict CLNM accurately. To facilitate the calculation of CLNM risk, a nomogram was developed by assigning scores to each variable based on their contribution (Figure 2). The individual scores were summed to determine the probability of CLNM for each patient. The Hosmer-Lemeshow goodness-of-fit test showed excellent agreement between the predicted and observed outcomes, with a slope of 0.917 for the training group and 0.835 for the validation group (Figure 4). The clinical utility of the model was assessed using DCA, and the net benefit was maximized within a threshold probability range of 0.39-0.88, as depicted in the calibration graph (Figure 5).

Figure 2. Construction of Nomogram to predict CLNM in PTMC patients. The scores corresponding to age, tumor size, BRAF V600E, calcification and capsule invasion were summed to obtain the total score. The probability of CLNM was calculated based on the total scoring scale.

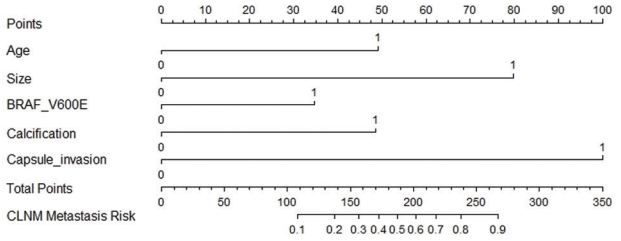


Figure 3. Construction of the ROC curves for the prediction model in the (A) training and (B) verification groups.

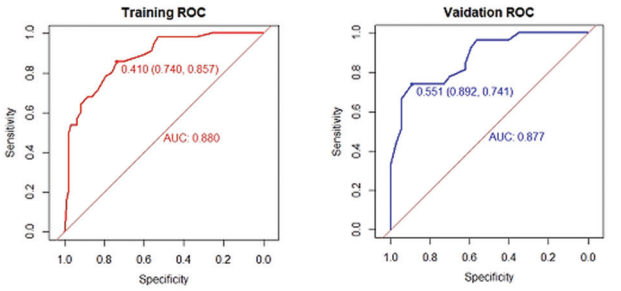


Figure 4. The Calibration curve of the prediction algorithm for CLNM in the (A) training and (B) verification sets. The ordinate is the actual probability, and the abscissa is the predicted probability. The stronger the concordance between the expected and observed outcomes, the closest the solid line is to the diagonal dotted line.

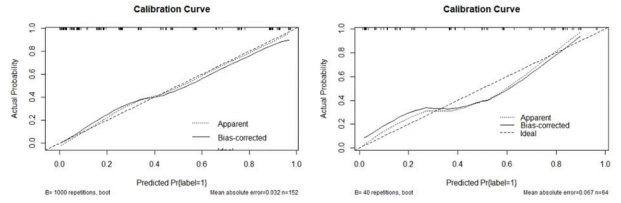
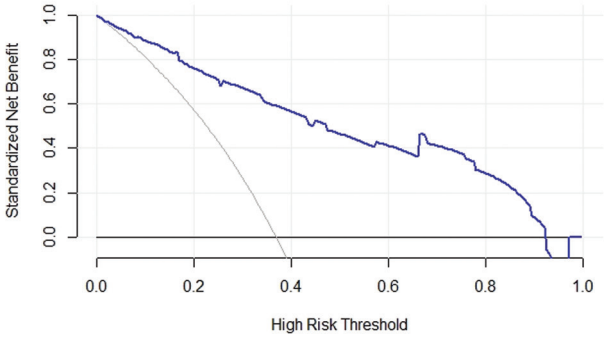


Table 2. Investigation of The Variables Determining The Prevalence Of CLNM In The PTMC Using Binary Logistic Regression

Independent variable	Beta Value	Standard Error	Wald	*P* value	OR Value	95% CI
Age < 45 years old	1.395	0.400	12.157	.000	4.034	1.842-8.837
Microcalcification	1.183	0.402	8.674	.003	3.264	1.4857-171
BRAF _ V600E	1.127	0.390	8.365	.004	3.087	1.438-6.627
Tumor size ≥ 5mm	2.004	0.416	23.214	.000	7.420	3.283-16.768
Encapsular invasion	2.502	0.439	32.533	.000	12.209	5.167-28.846
Multifocal	0.541	0.398	1.849	.174	1.718	0.787-3.750
Constant	-5.125	0.732	49.070	.000	0.006	

Abbreviations: CLNM, central lymph node metastasis; PTMC, papillary thyroid microcarcinoma.

Figure 5. DCA of the nomogram in the training set for the training and verification groups. The x-axis represents the threshold probability, while the y-axis represents the net income. The blue line represents the prediction model alignment graph. Grey lines represent the possibility that all participants have CLNM metastasis, while a black line represents the absence of CLNM metastasis in any participant. At the threshold probability between 0.39 and 0.88, the nomogram predicts that all patients will benefit more from pCLND.



DISCUSSION

Although PTMC generally carries a favorable prognosis, cancer exhibits aggressive behavior in some cases. PTMC is associated with an increased risk of central lymph node metastasis and even distant metastasis, which can have detrimental outcomes. The mortality rate for PTMC patients within the first 10 years after surgery is less than 1%, with a recurrence rate of approximately 5%.[5] Consistent with previous studies, our research found a 38.4% incidence rate of CLNM in PTMC individuals. Given that CLNM is a significant risk factor for tumor recurrence, it is crucial to understand the prognostic characteristics of CLNM to determine the optimal surgical approach.

Previous studies have reported a higher incidence of PTMC in female patients (72.5%) compared to male patients, possibly due to hormonal variations during menstruation or pregnancies. Conversely, CLNM is more common in men than women, possibly attributed to the higher basal metabolic rate in men, which may facilitate the growth and spread of cancer cells.[6] The lack of the male sex being identified as an independent predictor factor for CLNM in this study could be attributed to the limited sample size or selection bias resulting from including patients from a single center. Furthermore, in clinical practice, multiple risk factors are considered in combination to assess the risk of CLNM.

Multifocal PTMC tumors often originate from monoclonal precancerous lesions and spread throughout the thyroid gland, involving genome-wide alleles.[7] In our study, patients with multifocal PTMC had a higher incidence of CLNM (44%) compared to patients with monofocal disease (35.5%). Although multifocal tumors showed a significant correlation with CLNM incidence, it was not identified as an independent risk factor, possibly due to the confounding effect of the high prevalence of benign thyroid nodules.[8] Therefore, in patients with multifocal tumors, preoperative ultrasonography and ultrasound-guided fine needle aspiration biopsy (FNAB) can be helpful in predicting disease aggressiveness.

The age of 45 serves as a cutoff in the TNM staging system for thyroid cancer defined by the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC). Age has been recognized as a significant prognostic factor for survival in patients with papillary thyroid cancer larger than 1 cm, according to Jovanovic et al.[9] Our study also revealed that patients younger than 45 had a higher rate of CLNM compared to older individuals (69.1% vs 30.9%), and age was identified as an independent predictor of CLNM. Therefore, careful examination of lymph nodes before surgery is essential for younger PTMC patients. Additionally, therapeutic approaches may need to be tailored differently for younger and older patients.[10] For example, pCLND might be more appropriate for young individuals, while observation may be recommended for older patients.

In previous studies, tumor size has been established as an independent predictor of the likelihood of CLNM. Although there is no universally defined criterion for PTMC tumor size to predict CLNM, many studies have used a cutoff of 0.5 cm. Consistent with these findings, our study also found that PTMC tumors larger than 0.5 cm were significantly associated with CLNM.[11] We used the same size threshold in our study and found that the probability of CLNM increased with tumor size.

Thyroid capsule invasion is another important factor that indicates poor prognosis in PTMC and can serve as a predictor of CLNM. In our study, we defined thyroid capsule invasion as an incomplete thyroid capsule or close proximity between the tumor and thyroid capsule, and we found it to be an independent ultrasound predictor of CLNM. Tumor calcification, characterized by the focal accumulation of calcium salts due to rapid tumor cell proliferation,[12] was also identified as a risk factor for cervical lymph node involvement

in our study. Microcalcification, specifically, has been recognized as a highly specific feature of suspected malignant nodules by the American Thyroid Association in 2015. While some studies have associated CLNM with hypoechoic, lobulated, or irregularly margined tumors, the results have been inconsistent due to variations in diagnostic criteria and subjective interpretations among researchers and sonographers,[13] In our study, the tumors exhibited significant hypoechoic features with shallow lobulated or irregular margins. Further investigation is needed to elucidate the predictive value of microcalcification for CLNM.

The BRAF V600E mutation has been extensively studied in relation to the poor prognosis of papillary thyroid carcinoma. Molecular alterations associated with BRAF mutations and the inactivation of tumor suppressor genes significantly influence the initiation, progression, and metastatic spread of PTMC, leading to higher recurrence rates and increased mortality.[14] However, the role of BRAF V600E as a predictor of CLNM in PTMC remains controversial. While some studies have reported a higher incidence of cervical lymph node metastases in PTMC patients with BRAF mutations.[15] Virk et al.[16] have found that BRAF V600E is not a reliable predictor of CLNM in PTMC. Our study identified BRAF V600E as a significant and independent risk factor for CLNM in PTMC patients. The predictive model incorporating the independent risk factors for CLNM demonstrated good discriminatory ability, suggesting its potential utility in guiding personalized follow-up treatment for PTMC patients.

Study Limitations

It is important to acknowledge the limitations of our study. Firstly, the retrospective nature of the study and the use of data from a single center introduces the possibility of selection bias and limit the generalizability of our findings. A multicenter study with a larger and more diverse sample would be valuable to confirm the robustness of our statistical method. Secondly, the sample size of our study was relatively small, which may affect the precision of our estimates and limit the statistical power to detect certain associations. Future studies with larger cohorts are warranted to enhance the reliability of our results. Thirdly, we did not consider additional potential risk factors for CLNM, such as family medical history, localized recurrence, and disease-specific survival. These variables could provide valuable insights into the comprehensive assessment of CLNM risk in PTMC patients. Further research incorporating these factors is needed to obtain a more comprehensive understanding of the predictive model. Lastly, our study design focused on a retrospective analysis, which has inherent limitations in establishing causality and temporality. To further validate the effectiveness and applicability of our statistical model, a well-designed prospective cohort study involving a larger number of PTMC patients is essential. This would allow for the evaluation of the model's performance over time and enable a more robust assessment of its clinical utility in guiding treatment decisions.

CONCLUSION

In conclusion, our study aimed to identify and develop a predictive model for the risk of central lymph node metastasis in patients with papillary thyroid microcarcinoma. We constructed a clinical model based on preoperative ultrasound features, BRAF V600E mutation status, and clinical information. Our findings revealed that BRAF V600E mutation, tumor size, age, thyroid capsule invasion, and tumor calcification were independent risk factors for CLNM in PTMC patients. The developed predictive model demonstrated good discrimination ability in differentiating between patients at high and low risk of CLNM. This model could assist clinicians in making informed decisions regarding the appropriate management and follow-up strategies for PTMC patients. The use of this model may contribute to personalized and tailored treatment approaches, potentially reducing unnecessary interventions while ensuring adequate surveillance and management for patients at higher risk. However, Future studies with larger prospective cohorts and external validation are warranted to validate further and refine the predictive model.

DATA AVAILABILITY

On request, the corresponding author will provide the relevant data that supports this research work.

CONFLICTS OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHORS' CONTRIBUTIONS

All authors contributed equally; they read and approved the final manuscript.

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