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Prediction model for lateral lymph node metastasis of papillary thyroid carcinoma in children and adolescents based on ultrasound imaging and clinical features: a retrospective study

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Abstract

Background The presence of lateral lymph node metastases (LNM) in paediatric patients with papillary thyroid cancer (PTC) is an independent risk factor for recurrence. We aimed to identify risk factors and establish a prediction model for lateral LNM before surgery in children and adolescents with PTC.

Methods We developed a prediction model based on data obtained from 63 minors with PTC between January 2014 and June 2023. We collected and analysed clinical factors, ultrasound (US) features of the primary tumour, and pathology records of the patients. Multivariate logistic regression analysis was used to determine independent predictors and build a prediction model. We evaluated the predictive performance of risk factors and the prediction model using the area under the receiver operating characteristic (ROC) curve. We assessed the clinical usefulness of the predicting model using decision curve analysis.

Results Among the minors with PTC, 21 had lateral LNM (33.3%). Logistic regression revealed that independent risk factors for lateral LNM were multifocality, tumour size, sex, and age. The area under the ROC curve for multifocality, tumour size, sex, and age was 0.62 ($p=0.049$), 0.61 ($p=0.023$), 0.66 ($p=0.003$), and 0.58 ($p=0.013$), respectively. Compared to a single risk factor, the combined predictors had a significantly higher area under the ROC curve (0.842), with a sensitivity and specificity of 71.4% and 81.0%, respectively (cutoff value = 0.524). Decision curve analysis showed that the prediction model was clinically useful, with threshold probabilities between 2% and 99%.

Conclusions The independent risk factors for lateral LNM in paediatric PTC patients were multifocality and tumour size on US imaging, as well as sex and age. Our model outperformed US imaging and clinical features alone in predicting the status of lateral LNM.

Keywords Papillary thyroid cancer, Lymph node metastasis, Ultrasound, Prediction model, Children

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Background

Although thyroid nodules are relatively rare in children and adolescents, the incidence of malignancy within these nodules is higher than that recorded in adults [1]. Compared to adults with papillary thyroid cancer (PTC), paediatric patients exhibit significant clinicopathological differences, such as higher rates of lymph node involvement, extrathyroidal extension, and pulmonary metastasis [2, 3]. Moreover, even in the paediatric PTC cohort with clinically negative lymph nodes, the prevalence of central lateral lymph node metastases (LNM) reaches as high as 75% [4].

LMN is one of the most important risk factors associated with the recurrence rate in minors with PTC [5–7]. Historically, treatment strategies for paediatric patients have been based on guidelines for adults. The American Thyroid Association guidelines recommend [8] therapeutic lateral lymph node dissection (LND) only for patients classified as cN1b. For patients with cN0 or cN1a, preventive lateral LND is typically not recommended. In other words, only paediatric patients suspected of having lateral LNM based on preoperative ultrasound (US) examination or intraoperative lymph node exploration receive treatment with lateral LND. However, accurately assessing lateral LNM is crucial for determining patient prognosis and determining the appropriate extent of lymph node dissection. Therefore, developing a non-invasive and efficient method for preoperatively predicting lateral LNM is of great significance.

Studies investigating the potential predictive value of US features in PTC have shown that the presence of US features indicative of malignancy is associated with more advanced disease stage, extrathyroidal extension, and an increased risk of lymph node metastasis recurrence in PTC tumours > 1 cm [9, 10]. A study by Park et al. indicated that an increased number of suspicious US features is associated with lateral lymph node metastasis in patients with PTC [11]. However, previous studies on risk factors for lateral LNM have primarily focused on adult patients, with limited literature addressing the risk factors specifically relevant to the paediatric population. Therefore, we aimed to develop a prediction model using US features and clinical characteristics to predict the presence of lateral LNM in minors with PTC.

Methods

Patients

This multicentre, retrospective study was conducted from January 2014 to June 2023 in three different hospitals: the Sixth Affiliated Hospital of Sun Yat-sen University, the First People's Hospital of Foshan, and Guangzhou Panyu Central Hospital. The research protocol was approved by the Ethics Committee of the three institutions. Informed consent for participation was exempted by the ethics committee. The study included a total of 63 children and adolescents (defined as individuals ≤ 21 years of age [12–14]); 15, 35, and 13 participants were enrolled from the Sixth Affiliated Hospital of Sun Yat-sen University, First People's Hospital of Foshan, and Guangzhou Panyu Central Hospital, respectively. All the patients were diagnosed with PTC via pathological examination through fine-needle aspiration or surgery. Each patient underwent a near-total or total thyroidectomy with central LND. Collected data included demographics, preoperative physical examinations, US tumour features, and postoperative pathological outcomes.

Exclusion criteria were as follows: (*1*) Patients diagnosed with alternative pathological types of thyroid cancer; (*2*) patients who had previously undergone thyroid surgery or irradiation involving the neck region; (*3*) presence of recurrent PTC; (*4*) cases with incomplete clinical data or absent US images.

US image acquisition and interpretation

All patients underwent preoperative US examinations of both thyroid glands and the cervical regions, using a range of high-frequency transducers: a 5–8 MHz transducer (GE, Vingmed Ultrasound AS, Norway), a 3–12 MHz transducer (Esaote, mylab twice, Italy), a 5–18 MHz transducer (Canon, Aplio i800, Japan), a 6–15 MHz transducer (GE, LOGIQ E9, USA; GE, LOGIQ E8, USA), or a 6–18 MHz transducer (Siemens, ACUSON Sequoia, Germany; Siemens, ACUSON Sequoia, USA). US images of both thyroid glands and the cervical regions were collected and stored using various brands of ultrasonic equipment.

All sonographic images were independently reviewed by two experienced radiologists (L.S.Y. and Z.Y., with 9 and 8 years of experience in US imaging, respectively) who were blinded to the pathological data. In case of disagreement, a resolution was achieved through a re-evaluation by a third radiologist (L.G.J., with 20 years of experience in US).

The following sonographic features were evaluated: background (Hashimoto's thyroiditis or others), multifocality (multifocal tumours or unifocal tumours), primary tumour size [measured as the longest diameter of the largest lesion (> 1 cm or < 1 cm)], location (upper pole, middle part, inferior pole, or isthmus), margin (smooth, ill-defined, or irregular), the relationship between tumour and capsule (tumour not contacting the thyroid capsule or tumour contacting the thyroid capsule), calcification (presence of microcalcifications or non-microcalcification), shape (taller than wide or wider than tall), and vascularization (scored as 0, 1, 2, or 3). Additionally, the co-existence of the primary tumour and Hashimoto's thyroiditis was ascertained by the increase of thyroid autoantibodies and diffuse parenchymal changes in the thyroid gland evaluated through US evaluation.

The anatomical locations within the thyroid gland were categorized as follows: upper pole refers to the upper portion, middle part denotes the central region, inferior pole indicates the lower portion, and isthmus signifies the area connecting bilateral lobes. Tumours involving the upper pole, as well as those extending to more than a single pole, were categorized under the upper pole group. Calcification was classified as microcalcification (<1.0 mm in diameter) and non-microcalcification (>1.0 mm in diameter, eggshell calcification, or none). Vascularization was graded as follows: 0 indicated no detectable blood flow within the lesion, 1 suggested minimal blood flow, 2 indicated moderate blood flow, and 3 signified abundant blood flow.

Surgical procedures

In accordance with the American Thyroid Association guidelines for children with PTC [12], all patients underwent central LND, which included the prelaryngeal, pretracheal, and unilateral or bilateral paratracheal lymph nodes. For patients with preoperative imaging examinations that suggested potential involvement of the lateral lymph nodes, preoperative fine needle aspiration was performed to establish a definitive diagnosis. An intraoperative frozen biopsy was also performed for lateral lymph nodes showing suspicious features during intraoperative exploration, particularly when such nodes were not detected in the preoperative examination. Additionally, if metastasis to the lateral neck region was suspected or confirmed, lateral LND including levels II–V was performed.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0. Statistical significance was denoted by $p<0.1$ for univariate analysis. In multivariate analysis, statistical significance was indicated by $p<0.05$. Non-normally distributed quantitative variables, such as age, were expressed as the median with interquartile range. Categorical variables were expressed as frequency. For univariate analysis, categorical variables were analysed using the $\chi2$ test, Bonferroni correction or Fisher exact test and univariate logistic regression analysis. In the univariate logistic regression analysis, the odds ratio (OR) along with its corresponding 95% confidence interval (CI) was calculated.

Multivariate logistic regression was conducted to assess the relationship between clinical features, US features, and the presence of lateral LNM while controlling for potential confounding variables. Variables with p-values<0.1 in the univariate analysis were entered selectively into the multivariate logistic regression analysis using a forward selection approach. The combined model was derived from the regression coefficient calculated in the multivariate logistic regression analysis using SPSS.

To evaluate the clinical features (sex and age), US features (tumour size and multifocality), and the combined predictor, a receiver operating characteristic (ROC) curve was used. The area under the curve was then used to assess the diagnostic performance of the risk factors and the prediction model. By calculating the Youden index, the combined predictor corresponding to the maximum Youden index was identified, and its sensitivity and specificity were computed.

To determine the clinical usefulness of the prediction model at different threshold probabilities, decision curve analysis (DCA) was conducted. DCA was performed using the R software (Version 4.4.0). The net benefit was calculated by subtracting the proportion of false-positive patients from the proportion of true-positive patients, with consideration given to the relative harm of forgoing interventions compared with the negative consequences of an unnecessary intervention.

Results

Patient features

From January 2014 to June 2023, a total of 63 paediatric patients diagnosed with PTC were enrolled in our retrospective study; the flow chart of patient selection is shown in Fig. 1. The age of the participants ranged 13–21 years, with a median age of 19 years and an interquartile range of 3 years (lower quartile: 17 years, upper quartile: 21 years). Out of the 63 patients, 58 were older than 15 years of age, and 5 were 15 years old or younger. The study included 49 female patients (77.78%) and 14 male patients (22.22%). Lateral LNM was observed in 21 patients (33.33%). Table 1 illustrates the clinical and sonographic characteristics of these 63 patients.

Risk factors for lateral lymph node metastases

Univariate analysis ($\chi2$ test, Bonferroni correction or Fisher exact test) revealed significant associations between lateral LNM and several factors: multifocality ($p=0.032$), sex (male; $p=0.005$), and age (≤15 years; $p=0.039$). Univariate logistic regression analysis revealed significant associations between lateral LNM and several factors: tumour size ($p=0.075$), multifocality ($p=0.038$), sex (male; $p=0.008$), and age (≤15 years; $p=0.049$). Consequently, these factors were included in the subsequent multivariate analysis. In contrast, lateral LNM showed no significant correlation with tumour size ($p=0.117$), location ($p=0.810$), background ($p=0.256$), margins ($p=0.286$), the relationship between tumour and capsule ($p=0.286$), calcification ($p=1.000$), shape ($p=1.000$), or vascularization ($p=0.377$) (Table 1) by univariate analysis ($\chi2$ test, Bonferroni correction or Fisher exact test).

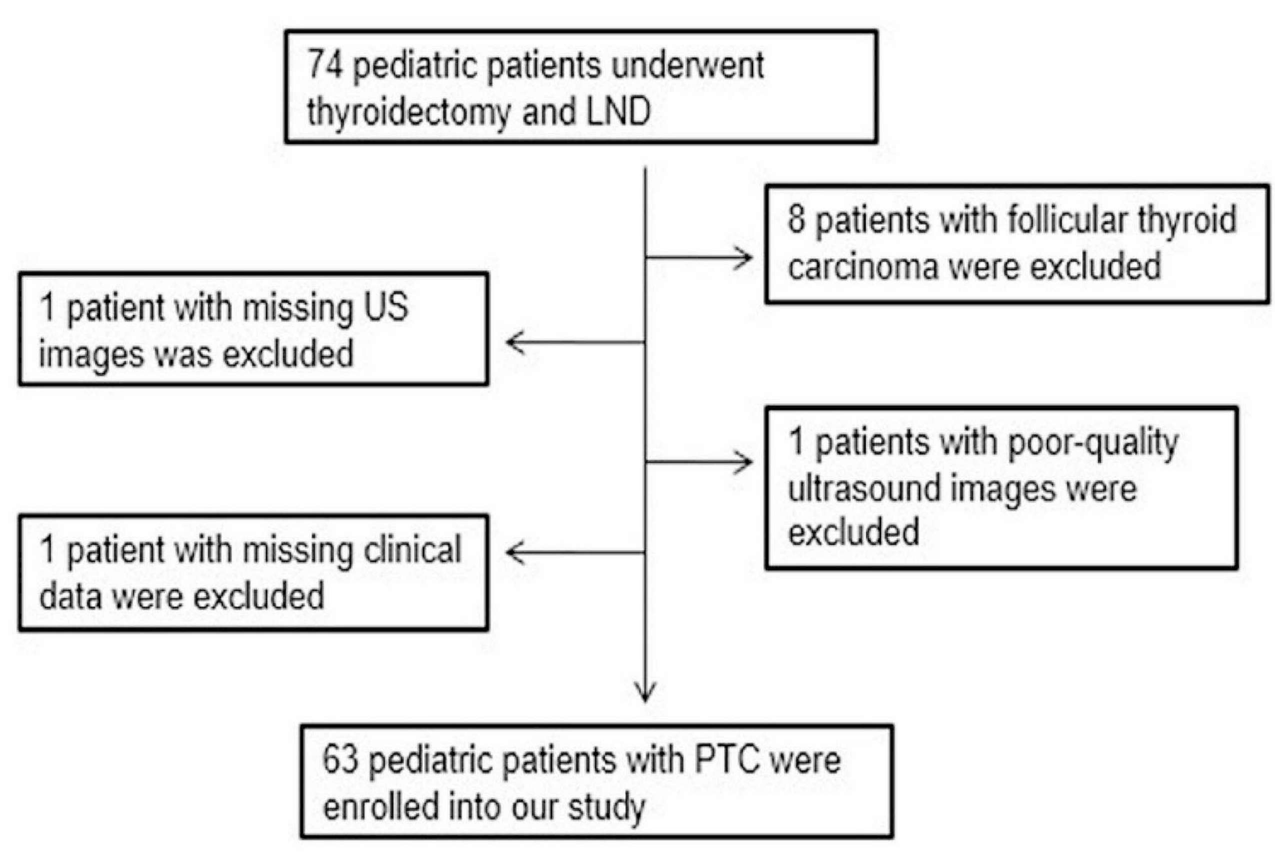

Fig. 1 Flow chart of patients' selection

Lateral LNM showed no significant correlation with location (p=0.814), background (p=0.244), margins (p=0.181), the relationship between tumour and capsule (p=0.342), calcification (p=1.000), shape (p=0.826), or vascularization (p=0.356) (Table 2) by univariate logistic regression analysis. Since previous studies have generally accepted that lateral LMN is more common in larger tumours [13, 15], and univariate logistic regression analysis revealed significant association between lateral LNM and tumour size (>10 mm; p=0.075), tumour size was also included in the subsequent multivariate analysis.

To exclude the influence of each variable factor, we performed a multivariate logistic regression analysis of lateral LNM. It revealed that multifocality, tumour size (>1 cm), age (≤15 years), and sex (male) were independent risk factors for lateral LNM in paediatric patients (Table 3).

Establishment of the prediction model

Logistic regression was employed to identify the risk factors for lateral LNM in paediatric patients with PTC (Table 3). A prediction model was established as follows: Combined predictor=6.48–2.87 × Tumour size – 1.57 × Multifocality – 2.43 × Sex – 4.06 × Age (Tumour size: ≥ 1 cm=1, < 1 cm=0; Multifocality: Yes=1, No=0; Sex: male=1, female=0; Age: ≤ 15 years old=1, > 15 years old=0). The predictive power of multifocality, tumour size, sex, age, and the combined prediction model were assessed using the ROC curve (Fig. 2). The areas under the curve for the five predictors were 0.619, 0.607, 0.655, 0.583, and 0.842 (Table 4), respectively, with the prediction model demonstrating the greatest predictive value (Fig. 3).

Youden index=sensitivity+specificity – 1.

The largest Youden index was 0.524, and the corresponding boundary value was 0.2818. Consequently, if the combined predictor's value was ≤0.2818, it indicated an elevated risk for the occurrence of lateral LNM. Conversely, if the combined predictor's value>0.2818, it suggested a lower risk for lateral LNM. The sensitivity and specificity of the predicted value were 71.4% and 81.0%, respectively (Fig. 3).

Clinical use

The decision curve analysis for the prediction model is presented in Fig. 4. The decision curve showed that if the threshold probability>2 and <99%, respectively, using this model to predict lateral LNM risk adds more benefit than the scheme.

Table 1 The clinical features and sonographic features on univariate analysis

Variables	Total (*n* = 63)	Nonmetastatic (n)	Metastatic (n)	*P*
Sex				0.005
Female	49	37	12	
Male	14	5	9	
Age				0.039
≤15	5	1	4	
>15	58	41	17	
Background				0.256
Hashimoto's thyroiditis	3	1	2	
Others	60	41	19	
Size (mm)				0.117
≤ 10	15	13	2	
>10	48	29	19	
Multifocality				0.032
Unifocal tumor	49	36	13	
Multifocal tumor	14	6	8	
Location				0.810
Upper pole	23	14	9	
Middle part	13	10	3	
Inferior pole	24	16	8	
Isthmus	3	2	1	
Margin				0.286
Smooth or ill-defined	19	15	4	
Irregular	44	27	17	
Relationship between tumor and capsule				0.339
Not contacting capsule	20	15	5	
Contacting capsule	43	27	16	
Calcification				1.000
Microcalcification	48	32	16	
Non-microcalcification	15	10	5	
Shape				1.000
Wider than tall	50	33	17	
Taller than wide	13	9	4	
Vascularization				0.377
0	8	7	1	
1	14	10	4	
2	17	12	5	
3	24	13	11	

Table 2 The features in the univariate logistic regression analysis

Variables	*P*	OR (95% CI)
Sex		
Male	0.008	5.550 (1.555, 19.811)
Female		
Age		
≤15	0.049	0.104 (0.011, 0.996)
>15		
Background		
Hashimoto's thyroiditis	0.244	4.316 (0.368, 50.582)
Others		
Size (mm)		
≤ 10		
>10	0.075	4.259 (0.862, 21.033)
Multifocality		
Unifocal tumor		
Multifocal tumor	0.038	3.692 (1.075, 12.682)
Location		
Upper pole		1
Middle part	0.331	0.467 (0.100, 2.173)
Inferior pole	0.680	0.778 (0.236, 2.562)
Isthmus	0.846	0.778 (0.061, 9.885)
Margin		
Smooth or ill-defined		
Irregular	0.181	2.361 (0.671, 8.314)
Relationship between tumor and capsule		
Not contacting capsule		
Contacting capsule	0.342	1.778 (0.543, 5.821)
Calcification		
Non-microcalcification		
Microcalcification	1.000	1.000 (0.292, 3.421)
Shape		
Wider than tall		
Taller than wide	0.826	0.863 (0.232, 3.214)
Vascularization		
0		1
1	0.399	2.800 (0.255, 30.703)
2	0.370	2.917 (0.281, 30.298)
3	0.120	5.923 (0.628, 55.853)

Discussion

Cervical lymph node metastasis is common in PTC, even among paediatric patients with clinically node-negative (cN0) PTC, with a prevalence as high as 75%. Lateral lymph node metastasis in minors with PTC has a significant impact on tumour recurrence and the appropriate extent of therapeutic lymph node dissection [16, 17]. The objective of this study was to identify risk factors and evaluate their predictive value in accurately predicting lateral LNM before surgery.

Previously, US features of the primary tumour have been studied [10, 18, 19] extensively as an alternative approach for detecting lateral lymph node metastasis in

Table 3 Multivariate analysis of risk factors of lateral LNM in PTC pediatric patients

Variables	*P*	OR (95% CI)
Sex (Male)	0.003	11.367 (2.335, 55.347)
Age (≤ 15)	0.013	57.784 (2.385, 1399.770)
Size (>1 cm)	0.023	17.576 (1.490, 207.337)
Multifocality	0.049	4.812 (1.006, 23.024)

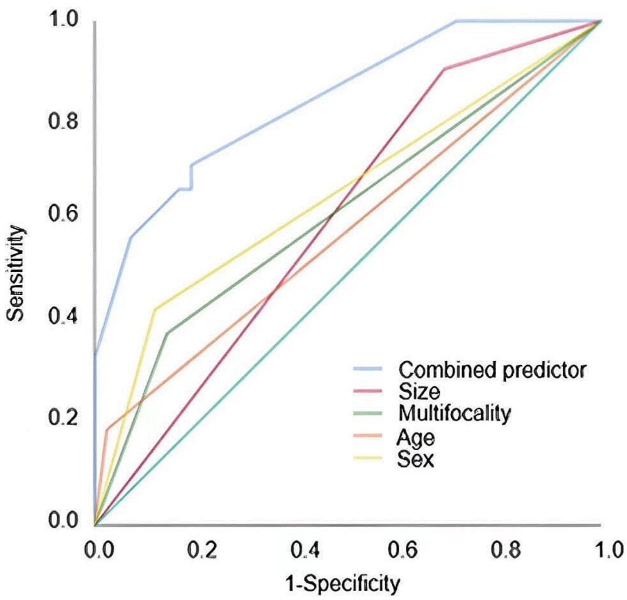

Fig. 2 ROC curve for combined predictor, tumor size, multifocality, age and sex in determining lateral LNM

Table 4 Performance of predictors for predicting lateral LNM

Predictors	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Youden Index	*P*
Size	0.61 (0.47, 0.75)	0.91	0.31	0.22	0.023
Multifocality	0.62 (0.47, 0.77)	0.38	0.86	0.24	0.049
Age	0.58 (0.43, 0.74)	0.19	0.98	0.17	0.013
Sex	0.66 (0.50, 0.81)	0.43	0.88	0.31	0.003
Combined predictor	0.84 (0.74, 0.95)	0.71	0.81	0.52	<0.001

adult patients. These risk factors are primarily associated with tumour aggressiveness, such as tumour size, the presence of Hashimoto's thyroiditis, irregular margins, microcalcifications, and taller-than-wide shape [10, 11, 20]. However, the assessment of primary tumours for predicting lateral LNM in minors remains relatively rare [21]. Previous studies on prepuberty patients have concentrated on the pathological features of the primary thyroid tumour, with findings indicating that factors such as multifocality, tumour size, and the number of central LNMs are correlated with lateral LNM [13, 15]. However, the pathological features of the primary thyroid tumour can only be evaluated postoperatively, offering no preoperative guidance for surgical therapy. In contrast, sonographic features of the primary thyroid tumour can be identified preoperatively through neck ultrasonography. Therefore, assessing the imaging features of the primary tumour to predict lateral LMN presents a more promising method for clinical practice.

In this study, we observed a higher rate of lateral lymph node metastasis in the multifocal group of PTC compared to the solitary group. This can be partially attributed to the fact that malignant neoplasms are known to be associated with an increased likelihood of lymphatic spread. A study involving 102 paediatric thyroid cancer patients concluded that multifocality (pathologically confirmed) is an independent risk factor for lateral LNM in children with PTC [13]. Another study examining sonographic features as independent predictive factors confirmed 230 cases as multifocal through histopathology, whereas 196 had been diagnosed as multifocal through preoperative ultrasonography [10]. Among the remaining 34 multifocal cases not identified by preoperative ultrasonography, 18 had a diameter of <3 mm, which made them too small for qualitative diagnosis. Therefore, ultrasonography may play a crucial role in the preoperative quantitative assessment of thyroid malignancy.

Our study, found that children with tumours >10 mm were more likely to develop lateral lymph node metastasis compared to those with tumours <10 mm, which aligns with the findings in other research [13, 15]. Liang et al. claimed that the size of the primary tumour, as verified by pathology, is an independent risk factor for lateral LNM in paediatric patients with PTC [13]. More importantly, preoperative US can determine tumour size, enabling clinicians to estimate the risk of lateral LNM before surgery.

Younger age has been recognized as a risk factor for lymph node metastasis in paediatric patients with PTC. A large study involving 740 children found that those aged 10 years or younger had a higher incidence of lymph node involvement at 63%, compared to 36% in older children [22]. Consistent with these findings, our study observed that paediatric patients with PTC aged ≤15 years tended to have a higher risk of lateral LNM ($p<0.05$). Furthermore, our analysis identified age as an independent risk factor for lateral LNM in these patients, with statistical significance ($p=0.01$).

In adults, sex has been found to be significantly associated with lateral LNM, with male individuals generally exhibiting a higher rate of lymph node involvement [23, 24]. A study of children and teenagers with PTC in a region exposed to radiation after Chernobyl found that lateral LNM was associated with the sex of patients [5]. Our study's findings are in line with these results [15].

To our knowledge, this study is the first to assess the utility of US in evaluating the primary tumour to predict lateral LMN in minors with PTC prior to surgery. Additionally, the performance of US features of the primary tumour in assessing lateral LMN was compared with the clinical features of the patients. Our results show that combining conventional US with clinical features provides a more accurate prediction of lateral lymph node status before surgery than either approach alone. Moreover, the factors used in our predictive model are readily

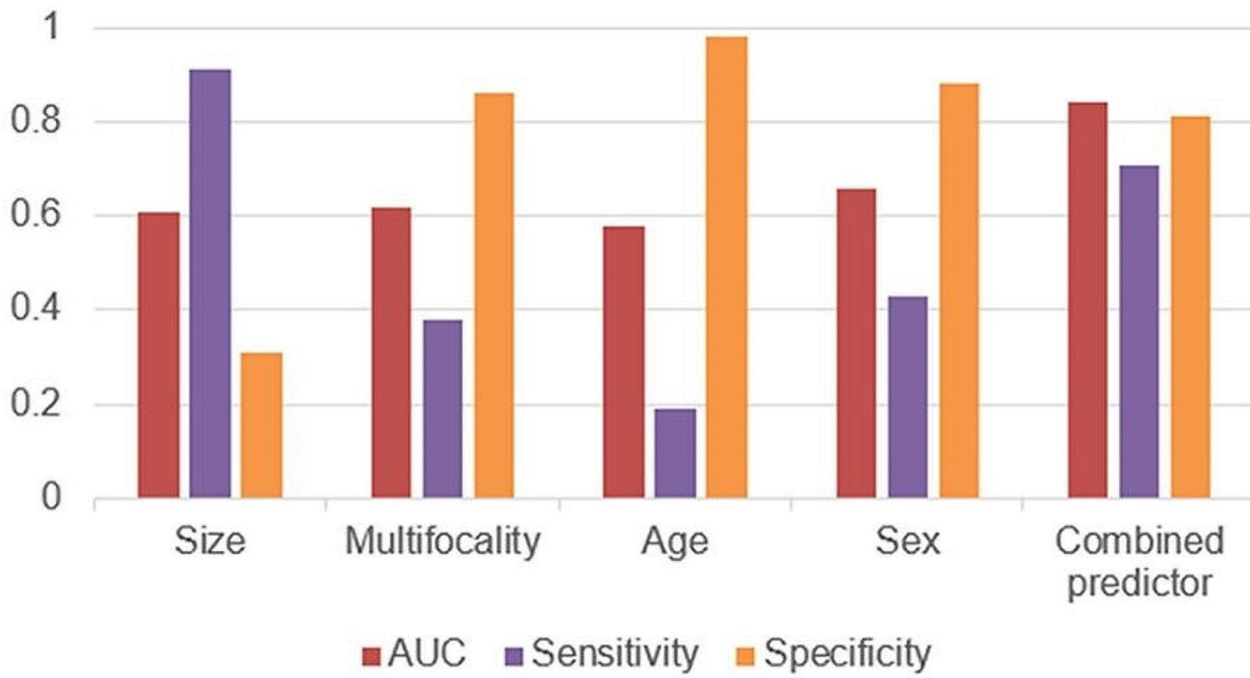

Fig. 3 A column diagram expressing predictive value of combined predictor, tumor size, multifocality, age and sex

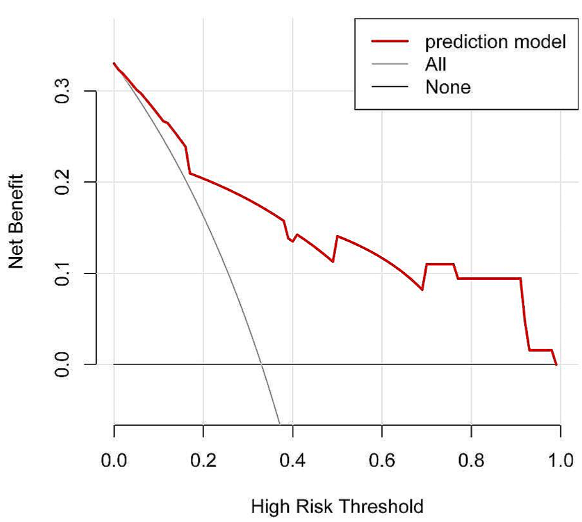

Fig. 4 Decision curve analysis for the prediction model. The *y*-axis measures the net benefit. The red line represents the prediction model. The black thick solid line represents the assumption that all patients are nonadherent to intervention. The black thin solid line represents the assumption that no patients are nonadherent to intervention. The decision curve showed that if the threshold probability is >2 and <99%, respectively, using this prediction model in the current study to predict lateral LNM risk adds more benefit than the intervention-all-patients scheme or the intervention-none scheme

available and do not require any additional invasive procedures. Therefore, due to its convenience, cost-effectiveness, and safety, the US features of the primary tumour can be effectively used as a supplement in the preoperative evaluation of lateral lymph node status for PTC when integrated with clinical factors.

It is important to acknowledge the limitations of our study. Firstly, the retrospective nature of our investigation unavoidably introduces potential selection bias. Conducting prospective randomized trials is challenging due to the low annual incidence of paediatric PTC. Secondly, while previous studies have demonstrated the predictive value of central LMN for lateral LMN in minors with PTC, the diagnostic efficacy of preoperative imaging assessments, such as ultrasonography for central LMN, remains a subject of debate. In our study, the accuracy of ultrasonographic diagnosis of central compartment lymph nodes was evaluated, with an area under the ROC curve value of 0.64, suggesting a slightly better than random chance accuracy. Specifically, the sensitivity and specificity of the test were 35.9% and 91.7%, respectively, using a cutoff value of 0.276. Consequently, lymph node metastasis in the central region was not considered a risk factor in our analysis. Overall, it appears that the precise number of central LMNs can only be determined postoperatively through histopathological examinations.

Conclusions

We concluded that US features and clinical factors could be combined to provide reliable information about lateral LMN in children and adolescents with papillary thyroid carcinoma. This study also developed a prediction model with enhanced clinical utility in predicting lateral LNM risks, outperforming other schemes within a 2−99% threshold.

Abbreviations

LNM	Lymph node metastases
PTC	Papillary thyroid cancer
US	Ultrasound
AUC	The area under the receiver operating characteristic curve
LND	Lymph node dissection
ROC curve	Receiver operating characteristic curve
OR	Odds ratio
CI	Confidence interval
DCA	Decision curve analysis

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Author contributions

Guangjian Liu and Shiyang Lin contributed to the study conception and design. Material preparation, data collection was performed by Shiyang Lin, Yuan Zhong and Yidi Lin. Data analysis was performed by Shiyang Lin and Yuan Zhong. The first draft of the manuscript was written by Shiyang Lin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The retrospective study was approved by the ethics committee of The Sixth Affiliated Hospital of Sun Yat-sen University (ethical approval number: 2023ZSLYEC-641), and informed consent for participation was exempted by the ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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