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Nomogram for predicting the risk of cervical lymph node metastases and recurrence in papillary thyroid carcinoma based on the thyroid differentiation score system and clinical characteristics

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Abstract

Background This study aimed to identify independent predictors of cervical central lymph node metastasis (CLNM), cervical lateral lymph node metastasis (LLNM), and recurrence in patients with PTC, which could help guide the surgical management of these patients.

Methods This retrospective study analyzed data from 542 patients with PTC, who underwent thyroid surgery and were enrolled in The Cancer Genome Atlas and Gene Expression Omnibus databases. Patients were categorized into two groups based on the presence or absence of cervical LNM, classified as CLNM or LLNM. Data were randomly partitioned into training and validation sets in a ratio of 7:3. Age, sex, thyroid differentiation score (TDS), and other relevant attributes, were compared between the two groups using univariate and multivariate analyses and reported as odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CI). Independent predictors were identified and used to develop nomograms. To assess the accuracy, discrimination, and clinical utility of the prediction model, calibration, receiver operating characteristic (ROC), and decision curve analysis (DCA) were performed for both the training and validation sets.

Results Of the 542 patients, 261 (48.15%) and 130 (23.99%) presented with CLNM and LLNM, respectively. The analyses identified several independent predictors for CLNM, including the presence of extrathyroidal invasion (OR 2.53, 95% CI 1.60–4.00), larger tumor dimension (OR 1.17, 95% CI 1.02–1.34), age over 55 years (OR 0.52, 95% CI 0.33–0.82), non-classic papillary subtype (OR 0.38, 95% CI 0.23–0.61), and lower TDS (OR 0.50, 95% CI 0.33–0.76). A greater number of excised cervical LNs (OR 12.30, 95% CI 4.35–34.77), the presence of CLNM (OR 1.07, 95% CI 1.04–1.10), and lower TDS (OR 0.09, 95% CI 0.04–0.21) were independent predictors for LLNM. Additionally, the independent

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predictors for relapse included age greater than 55 years (HR 1.87, 95% CI 1.00–3.49) and lower TDS (HR 0.35, 95% CI 0.20–0.62). These predictors were used to develop nomograms for CLNM, LLNM, and recurrence. ROC and DCA confirmed the discrimination and clinical utility of the models.

Conclusions This study identified independent predictors of cervical CLNM, LLNM, and recurrence. Clinically relevant nomograms were developed that can assist in guiding cervical lymph node dissection and prediction of recurrence in patients with PTC.

Keywords Papillary thyroid carcinoma, Cervical lymph node metastasis, Recurrence, Thyroid differentiation score, Prediction model

Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine cancer. Over the past three decades, the incidence of thyroid cancer has more than doubled in several countries, including China, with PTC accounting for the majority of the increase. This trend is particularly notable in cases of PTC, where the maximum tumor diameter is less than 1 cm [1–3]. Although cervical lymph nodes in PTCs with diameters under 1 cm are typically classified as clinically negative (cN0), the prevalence of cervical lymph node metastasis (LNM) remains significantly elevated, with reported incidence rates ranging from 20 to 60% [4, 5]. In the context of thyroid cancer, cervical LNM includes both central lymph node metastasis (CLNM) and lateral lymph node metastasis (LLNM). Research has demonstrated that LNM is a critical predictor of increased recurrence rates, highlighting the importance of lymph node status in determining appropriate therapeutic strategies [6]. Given the high prevalence of cervical LNM and limitations associated with preoperative diagnostic accuracy in China, routine prophylactic central lymph node dissection (RCLND) is often recommended and performed in patients classified as cN0 [7]. However, the clinical advantage of RCLND for patients with cN0 PTC have yet to be definitively established [8]. Furthermore, RCLND carries a significant risk of postoperative complications, including damage to the recurrent laryngeal nerve, transient or permanent hypoparathyroidism, and chyle leakage, which may complicate the surgical procedure [9–11]. Consequently, it is essential to identify the indicators of cervical LNM in patients with PTC and develop effective predictive models. This strategy aims to facilitate targeted lymph node dissection, thereby reducing patient costs and optimizing therapeutic outcomes.

Dedifferentiation during thyroid oncogenesis is characterized by the progressive loss of lineage-specific attributes in neoplastic cells originating from the thyroid, particularly thyroid follicular cells. This phenomenon is associated with a decline in cellular mechanisms relevant to iodine metabolism and the complex regulation of thyroid hormone synthesis [12, 13]. Oncological literature has extensively documented dedifferentiation as a critical transformative event in the progression of thyroid carcinomas that exhibit increased aggressiveness, with a particular focus on poorly differentiated and anaplastic variants of the disease [13–15]. Thyroid differentiation score (TDS) is a quantitative metric based on the mRNA expression profiles of 16 genes essential for thyroid metabolic and hormonal pathways, which was developed by The Cancer Genome Atlas (TCGA) initiative to evaluate the degree of cellular differentiation in PTCs [16]. TDS demonstrates significant variability depending on the mutation status of tumor driver genes. Specifically, tumors harboring the BRAFV600E mutation tend to exhibit a lower average degree of differentiation [16]. Notably, differences in TDS and global expression levels were not significantly influenced by alterations in the tumor stroma or lymphocyte infiltration levels, thereby reinforcing the reliability of TDS [16]. Recent studies have indicated that PTCs harboring the BRAFV600E mutation and a concomitant low TDS are predominantly associated with a malignant phenotype. These tumors are particularly susceptible to metastasis, exhibit resistance to radioactive iodine therapy, and are surrounded by a challenging immune microenvironment [17–19]. Furthermore, TDS has been shown to possess prognostic value in PTCs with BRAFV600E mutations, as a reduction in differentiation, indicated by a lower TDS, correlates with decreased progression-free survival [20].

Numerous studies have examined risk factors associated with cervical LNM in patients with PTC [21–23]. However, existing predictive models frequently demonstrate inconsistencies and often neglect to incorporate the significant impact of the expression of key genes as prognostic indicators. In light of these limitations, our research aimed to identify critical predictors from clinical data and develop nomograms for the precise prediction of cervical LNM and patient prognosis. Advancement of these refined predictive models is expected to enhance surgical decision-making, thereby improving patient outcomes through the implementation of tailored clinical strategies designed to mitigate potential complications.

Materials and methods

Data of patients

RNA sequencing data and associated clinical information for patients diagnosed with PTC were obtained from TCGA data portal (https://tcga-data.nci.nih.gov/tcga/). The inclusion criteria were based on the availability of gene expression profiles and relevant clinical parameters, including patient age, sex, and LNM status. Follow-up included calculation of 1-, 3- and 5-year overall (OS) and relapse-free survival (RFS) rates. Gene expression data for patients with PTC were sourced from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/), specifically comprising datasets GSE33630, GSE53157, and GSE60542. A total of 542 patients with PTC were included in this study. Patient age was stratified according to the guidelines set forth by the American Joint Committee on Cancer (AJCC) 8th edition, using a threshold of 55 years. We obtained the corresponding gene mapping information between GeneSymbol and ENSG_ID from the GFF3 files and generated a transformed expression spectrum (convert_exp.txt). To address missing data, genes, and cases with missing ratios exceeding 50% were excluded from the analysis. Subsequently, data standardization was conducted using log2 (X + 1) transformation.

Thyroid differentiation score

The samples were evaluated using TDS based on the mRNA expression levels of a selected panel of 16 thyroid function genes: *DIO1*, *DIO2*, *DUOX1*, *DUOX2*, *FOXE1*, *GLIS3*, *NKX2-1*, *PAX8*, *SLC26A4*, *SLC5A5*, *SLC5A8*, *TG*, *THRA*, *THRB*, *TPO*, and *TSHR*. The TDS was developed to assess the relationship between various genetic and epigenetic processes and thyroid differentiation. It was calculated as the mean of the Log2(Fold Change) across the 16 genes [16].

Statistical analysis

Data were analyzed using SPSS Statistics 28.0. Quantitative data are reported as the mean ± standard deviation (SD) when normally distributed and as the median (25th percentile, 75th percentile) when not normally distributed. Qualitative data were described using frequencies and percentages. Variables that demonstrated statistical significance in univariate logistic regression analysis were further analyzed using multivariate logistic regression. Prognostic analyses were performed using both univariate and multivariate Cox proportional hazard regression models. A two-tailed $P < 0.05$ was considered statistically significant. Subsequently, R software (version 4.1.0), accessible at https://www.r-project.org, was used to develop a prediction nomogram based on the results of the multivariate regression analysis. Predictor variables were subjected to multivariate collinearity analysis, where a tolerance value below 0.2 or a variance inflation factor (VIF) exceeding 5 suggested the potential presence of multicollinearity among the independent variables. To evaluate the calibration of the nomogram, a calibration curve was generated, and the area under the curve (AUC) was calculated using Receiver Operating Characteristic (ROC) analysis employing both an internal validation set and a training set. Finally, decision curve analysis (DCA) was performed to assess the clinical applicability of the nomogram.

Results

Characteristics of patients included in the study

This study included 542 patients diagnosed with PTC (Table 1). Among these patients, 151 (27.86%) were male and 391 (72.14%) were female, with a mean age of 44.15 ± 17.40 years. The average tumor size was measured at 2.80 ± 1.69 cm. Preoperative lymph node scans were obtained for 336 patients (61.99%). Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) were the three main diagnostic imaging modalities. In the preoperative lymph node assessments, 257 used only ultrasonography, 51 used CT alone, 5 used MRI alone, 17 used ultrasonography and CT, 4 used ultrasonography and MRI, and 2 used all three modalities. After preoperative imaging examination of the lymph nodes, 286 (52.77%) patients were considered to have a lymph node presentation preoperatively. Postoperative pathology confirmed CLNM and LLNM in 261 (48.15%) and 130 (23.99%) patients, respectively. The median number of excised cervical lymph nodes was 6, with an interquartile range of 2.00 to 16.50, and the median TDS values were − 0.02, with an interquartile range of − 0.36 to 0.31. Pathological classification revealed that 366 patients (67.53%) were classified as classical PTC, whereas 176 patients (32.47%) were categorized as other variant subtypes of PTC. The average follow-up, median OS, and median RFS were 1752.66 ± 1703.02, 942.50, and 902.00 d, respectively. The 1-, 3-, and 5-year OS rates were 99.33%, 98.22%, and 97.33%, respectively. the 1-, 3-, and 5-year RFS rates were 96.11%, 91.53%, 90.62%, respectively. For risk factor analysis and predictive model development, the patients were randomly divided into training and validation sets in a 7:3 ratio (Table 1). No statistically significant differences were observed in the clinicopathological features of the PTC samples between the training and validation sets, indicating that random grouping was both reasonable and effective ($P > 0.05$). This methodology can be utilized to analyze independent predictors and construct a predictive model in the subsequent steps.

Independent predictors of CLNM

Table 2 shows the correlations between CLNM and various risk factors in patients diagnosed with PTC.

Table 1 Clinical characteristics of 542 PTC patients included in the present study

Clinical characteristics	Total No. (%)	Training No. (%)	Validation No. (%)		*P*
Sex					0.70
Female	391 (72.14)	276 (72.63)	115 (70.99)		
Male	151 (27.86)	104 (27.37)	47 (29.01)		
Age (year)					0.79
< 55	379 (69.93)	267 (70.26)	112 (69.14)		
≥ 55	163 (30.07)	113 (29.74)	50 (30.86)		
Dimension (median [p25, p75])	2.50 [1.50, 3.60]	2.5 [1.50, 3.52]	2.4 [1.50, 3.70]	0.92	
Multifocality					0.55
No	252 (46.49)	173 (45.53)	79 (48.77)		
Yes	222 (40.96)	158 (41.58)	64 (39.51)		
NA	68 (12.55)	49 (13.09)	19 (11.72)		
Bilaterality					0.92
No	362 (66.79)	253 (66.58)	109 (67.28)		
Yes	111 (20.48)	77 (20.26)	34 (20.99)		
NA	69 (12.73)	50 (13.16)	19 (11.73)		
Extrathyroidal invasion					0.40
No	300 (55.35)	215 (56.58)	85 (52.47)		
Yes	162 (29.89)	110 (28.95)	52 (32.10)		
NA	80 (14.76)	55 (14.47)	25 (15.43)		
Lymphocytic thyroiditis					0.11
No	340 (62.73)	232 (61.05)	108 (66.67)		
Yes	83 (15.31)	64 (16.84)	19 (11.73)		
NA	119 (21.96)	84 (22.11)	35 (21.60)		
Histological type					0.94
Classic papillary	366 (67.53)	257 (67.63)	109 (67.28)		
Other subtypes	176 (32.47)	123 (32.37)	53 (32.72)		
TDS (median [p25, p75])	-0.02 [-0.36, 0.31]	-0.02 [-0.35, 0.32]	-0.04 [-0.37, 0.29]		0.71
Excised cervical LN number (median [p25, p75])	6 [2, 16.5]	6 [3.00, 15.75]	5 [2.00, 19.00]		0.65
Radioiodine Therapy					0.32
No	73 (13.47)	46 (12.11)	27 (16.67)		
Yes	142 (26.20)	99 (26.05)	43 (26.54)		
NA	327 (60.33)	235 (61.84)	92 (56.79)		
Preoperative LN scan					0.90
No	114 (21.03)	79 (20.79)	35 (21.60)		
Yes	336 (61.99)	235 (61.84)	101 (62.35)		
NA	92 (16.98)	66 (17.37)	26 (16.05)		
OS status					0.34
Live	437 (80.63)	307 (80.79)	130 (80.25)		
Dead	13 (2.39)	7 (1.84)	6 (3.70)		
NA	92 (16.98)	66 (17.37)	26 (16.05)		
Recurrence					0.60
No	396 (73.06)	278 (73.16)	118 (72.84)		
Yes	54 (9.96)	36 (9.47)	18 (11.11)		
NA	92 (16.98)	66 (17.37)	26 (16.05)		
CLNM					0.71
No	281 (51.85)	199 (52.37)	82 (50.62)		
Yes	261 (48.15)	181 (47.63)	80 (49.38)		
LLNM					0.49
No	412 (76.01)	292 (76.84)	120 (74.07)		
Yes	130 (23.99)	88 (23.16)	42 (25.93)		

NA: not available, p25: 25th percentile, p75: 75th percentile, TDS: thyroid differentiation score, LN: lymph node, OS: overall survival, CLNM: central lymph node metastasis, LLNM: lateral lymph node metastasis

Table 2 Uni- and Mulit-logistic regression analysis for predicting risk of CLNM in the present study

Clinical characteristics	OR [95%CI]	*P* (Uni)	OR [95%CI]	*P* (Multi)	Tolerance	VIF
Age (year)		**0.01**		**0.01**	0.98	1.02
< 55	1		1			
≥ 55	0.62 [0.43,0.90]		0.52 [0.33, 0.82]			
Sex		0.076				
Female	1					
Male	1.41 [0.97, 2.05]					
Dimension (cm)		**0.00**		**0.03**	0.96	1.04
≤ 2.25	1		1			
> 2.25	1.79 [1.26, 2.54]		1.17 [1.02, 1.34]			
Multifocality		**0.01**		0.07		
No	1		1			
Yes	1.60 [1.11, 2.30]		1.55 [0.97, 2.48]			
Bilaterality		**0.01**		0.09		
No	1		1			
Yes	1.83 [1.19, 2.82]		1.62 [0.94, 2.81]			
Extrathyroidal invasion		**0.00**		**0.00**	0.95	1.05
No	1		1			
Yes	2.51 [1.69, 3.73]		2.53 [1.60, 4.00]			
Lymphocytic thyroiditis		0.53				
No	1					
Yes	0.86 [0.53, 1.38]					
Histological type		**0.00**		**0.00**	0.98	1.03
Classic papillary	1		1			
Other subtypes	0.58 [0.41, 0.84]		0.38 [0.23, 0.61]			
TDS		**0.00**		**0.00**	0.94	1.07
≤ 0.07	1		1			
> 0.07	0.31 [0.21, 0.44]		0.50 [0.33, 0.76]			
Absence of preoperative LN assessment		0.26				
No	1					
Yes	1.28 [0.83, 1.96]					

TDS: thyroid differentiation score, LN: lymph node, OR: odds ratio, CI: Confidence Interval, CLNM: central lymph node metastasis, VIF: Variance Inflation Factor

Univariate analysis revealed a significantly higher incidence of CLNM in patients aged < 55 years of age ($P < 0.05$). Additionally, factors such as larger tumor size, evidence of extrathyroidal invasion, tumor multifocality, bilaterality, and the presence of the classic papillary pathological subtype were significantly associated with an increased incidence of CLNM ($P < 0.05$). Furthermore, a higher TDS was linked to a decreased incidence of CLNM ($P < 0.05$). In the multivariate analysis, the presence of extrathyroidal invasion (OR 2.53, 95% CI 1.60–4.00, $P < 0.05$) and larger tumor dimensions (OR 1.17, 95% CI 1.02–1.34, $P < 0.05$) were identified as independent predictors of a high prevalence of CLNM (Table 2). Conversely, age over 55 (OR 0.52, 95% CI 0.33–0.82, $P < 0.05$), tumors exhibiting not-classic papillary pathological subtypes (OR 0.38, 95% CI 0.23–0.61, $P < 0.05$), and higher TDS results (OR 0.50, 95% CI 0.33–0.76, $P < 0.05$) were found to be significant independent predictors of a lower likelihood of CLNM (Table 2).

Development and validation of a predictive nomogram for assessing the risk of CLNM

By integrating the five independent predictors previously mentioned, a nomogram was developed for the model within the training set (Fig. 1a). The multivariate collinearity analysis revealed the absence of multicollinearity among the independent variables (Table 2). The total point axis of the nomogram reached a maximum value of 220, with the predictive accuracy for CLNM risk ranging approximately from 0.10 to 0.90. The calibration curve of the nomogram, which was used to predict the risk of CLNM in patients with PTC, demonstrated remarkable consistency (Fig. 1b). The calibration curve of the nomogram in the validation set is presented in Additional file: Supplementary Fig. 1a. Furthermore, the AUC for the prediction nomogram was 0.718, which was subsequently validated using the validation set, yielding a value of 0.724 (Fig. 1c and Additional file: Supplementary Fig. 1b). These results provide evidence for the robust discriminatory power of the model. DCA of the risk nomogram is indicated that utilizing this nomogram to predict the risk

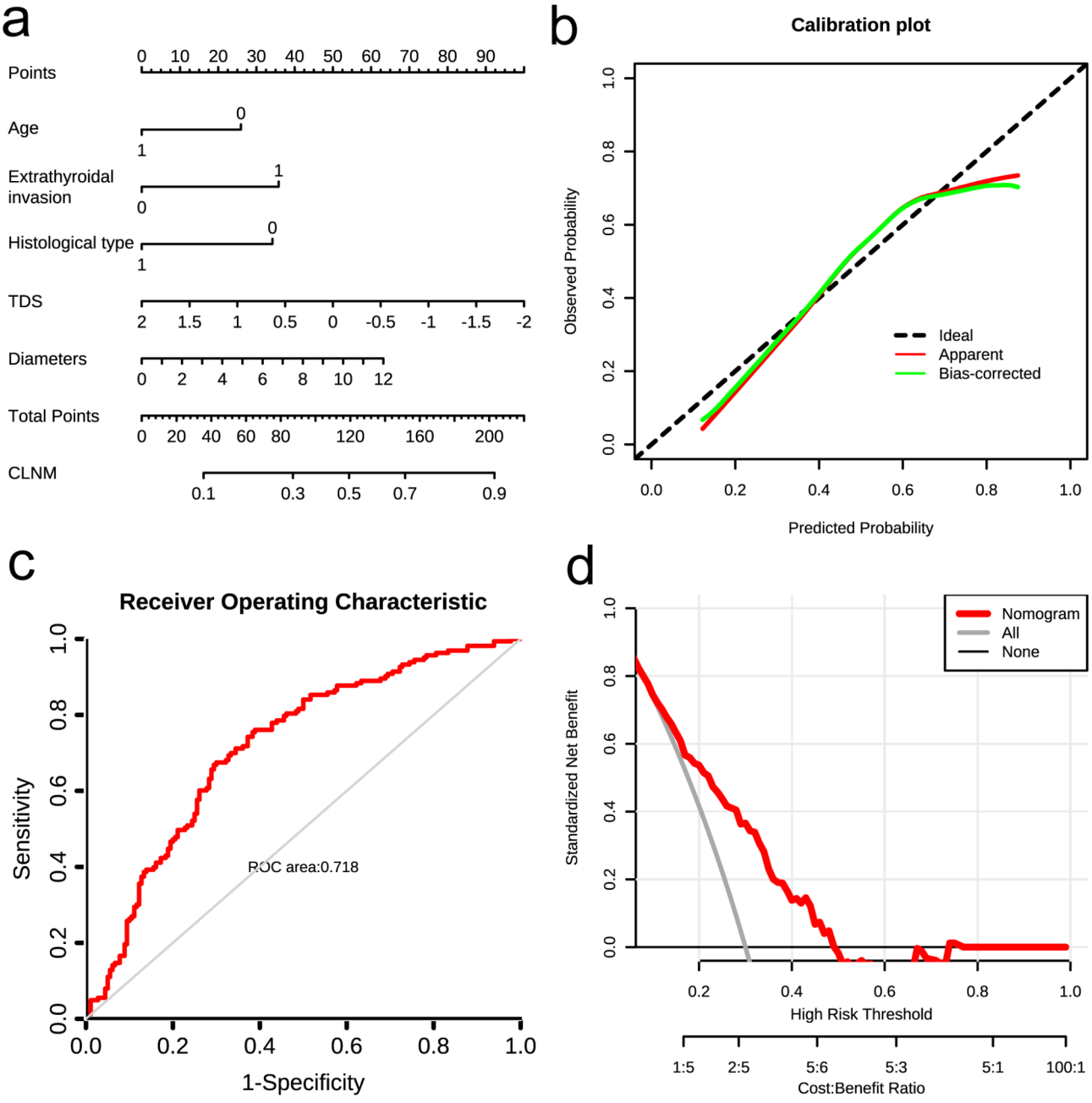

Fig. 1 Development of a nomogram for predicting the risk of CLNM in a training cohort, incorporating TDS and clinical characteristics in patients diagnosed with PTC. (**a**) Nomogram for predicting the risk of CLNM; (**b**) Calibration curve illustrating the accuracy of risk predictions derived from the risk model; (**c**) Sensitivities and specificities associated with the risk predictions, represented through ROC curves; (**d**) DCA of the risk nomogram. In this classification system, an age value of 0 indicates individuals < 55 years of age, while a value of 1 signifies individuals ≥ 55 years of age. Additionally, an extrathyroidal invasion value of 0 denotes the presence of PTC without extrathyroidal invasion, whereas a value of 1 indicates PTC with extrathyroidal invasion. A histological type value of 0 corresponds to the classic papillary subtype, while a value of 1 encompasses other variants of thyroid papillary carcinoma, including tall cell, follicular, and diffuse sclerosing subtypes. PTC, papillary thyroid carcinoma; CLNM, central lymph node metastasis; TDS, thyroid differentiation score; ROC, receiver operating characteristic; AUC, area under curve; DCA, decision curve analysis

of CLNM would be beneficial, provided that the threshold probability falls between 8% and 76% (Fig. 1d). Within this range, the net benefits derived from employing the risk nomogram were comparable, with several overlaps. DCA of the nomogram in the validation set is shown in Additional file: Supplementary Fig. 1c.

Independent predictors of LLNM

Table 3 illustrates the relationships between LLNM and various risk factors in patients with PTC. Univariate analysis indicated that male sex, presence of extrathyroidal invasion, larger tumor size, greater number of excised cervical lymph nodes, tumors of the classic papillary histological variant, and the presence of CLNM were significantly correlated with a higher prevalence of LLNM ($P<0.05$). Conversely, patients with elevated TDS exhibited a significantly lower prevalence of LLNM ($P<0.05$). The multivariate analysis identified the number of excised cervical lymph nodes (OR 12.30, 95% CI 4.35–34.77, $P<0.05$) and the presence of CLNM (OR 1.07, 95% CI 1.04–1.10, $P<0.05$) as independent predictors of a high prevalence of LLNM (Table 3). Additionally, elevated TDS (OR 0.09, 95% CI 0.04–0.21, $P<0.05$) was found to be a significant independent predictor for a reduced likelihood of LLNM (Table 3).

Table 3 Uni- and Mulit-logistic regression analysis for predicting risk of LLNM in the present study

Clinical characteristics	OR [95%CI]	*P* (Uni)	OR [95%CI]	*P* (Multi)	Tolerance	VIF
Sex		**0.02**		0.08		
Female	1		1			
Male	1.68 [1.10, 2.56]		1.92 [0.93, 3.94]			
Age (year)		0.84				
< 55	1					
≥ 55	1.04 [0.68, 1.60]					
Dimension (cm)		**0.00**		0.10		
≤ 2.95	1		1			
> 2.95	2.47 [1.63, 3.72]		1.17 [0.96, 1.43]			
Multifocality		0.22				
No	1					
Yes	1.30 [0.85, 1.97]					
Bilaterality		0.25				
No	1					
Yes	1.32 [0.82, 2.13]					
Extrathyroidal invasion		**0.00**		0.72		
No	1		1			
Yes	2.33 [1.51, 3.58]		1.13 [0.56, 2.28]			
Lymphocytic thyroiditis		0.55				
No	1					
Yes	0.84 [0.48, 1.47]					
Histological type		**0.03**		0.84		
Classic papillary	1		1			
Other subtypes	0.61 [0.39, 0.95]		1.09 [0.48, 2.46]			
TDS		**0.00**		**0.00**	0.93	1.08
≤ -0.21	1		1			
> -0.21	0.17 [0.11, 0.26]		0.09 [0.04, 0.21]			
Absence of preoperative LN assessment		0.15				
No	1					
Yes	1.48 [0.87, 2.52]					
Excised cervical LN number		**0.00**		**0.00**	0.77	1.31
≤ 21.5	1		1			
> 21.5	34.76 [17.75, 68.04]		12.30 [4.35, 34.77]			
CLNM		**0.00**		**0.00**	0.78	1.29
No	1		1			
Yes	34.89 [15.86, 76.76]		1.07 [1.04, 1.10]			

TDS: thyroid differentiation score, LN: lymph node, OR: odds ratio, CI: Confidence Interval, CLNM: central lymph node metastasis, LLNM: lateral lymph node metastasis, VIF: Variance Inflation Factor

Development and validation of a predictive nomogram for assessing the risk of LLNM

A specific nomogram model was developed by integrating three previously identified independent predictors (Fig. 2a). The multivariate collinearity assessment indicated no evidence of multicollinearity among the predictor variables (Table 3). The total point axis ranged from 0 to 180, with the predictive range for the risk of LLNM metastasis ranging from approximately 0.10–0.90. The calibration curve used to predict the risk of LLNM metastasis in patients with PTC demonstrated remarkable consistency (Fig. 2b). The calibration curve of the nomogram in the validation set is shown in Additional Supplementary Fig. 2a. The AUC for the prediction nomogram was 0.935, indicating a strong discriminatory power, which was further corroborated by the validation

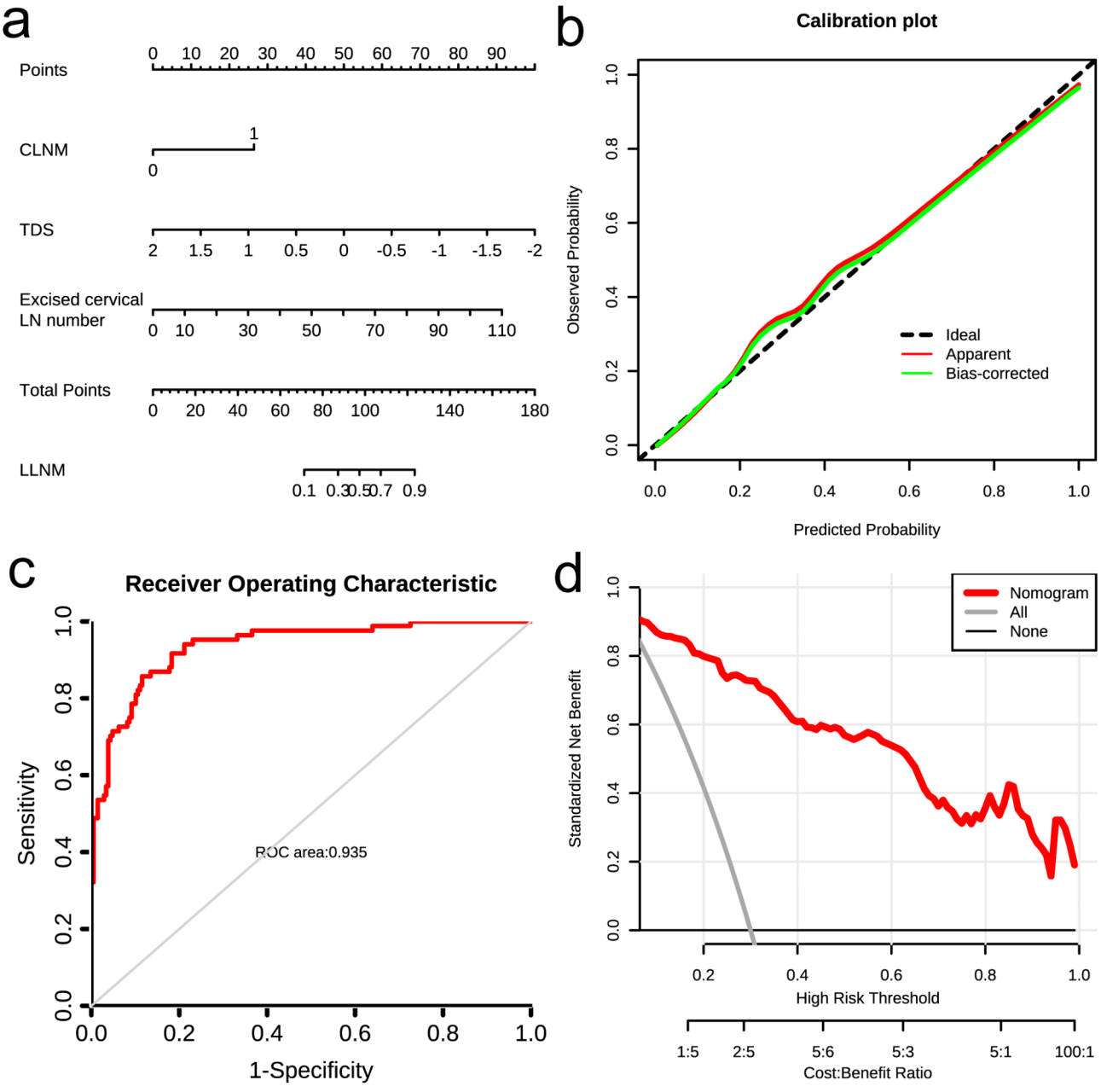

Fig. 2 Development of a nomogram for predicting the risk of LLNM in a training cohort, incorporating TDS and clinical characteristics in patients diagnosed with PTC. (**a**) Nomogram for predicting the risk of LLNM; (**b**) Calibration curve illustrating the accuracy of risk predictions derived from the risk model; (**c**) Sensitivities and specificities associated with the risk predictions, represented through ROC curves; (**d**) DCA of the risk nomogram. CLNM = 0 indicates the presence of PTC without CLNM, whereas CLNM = 1 signifies the presence of PTC with CLNM. PTC, papillary thyroid carcinoma; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; TDS, thyroid differentiation score; ROC, receiver operating characteristic; AUC, area under curve; DCA, decision curve analysis

set (Fig. 2c and Additional file: Supplementary Fig. 2b). These findings validate the efficacy of the model in predicting the risk of LLN metastasis. The DCA results support the application of the risk nomogram for forecasting LLNM risk, as evidenced by the net benefits remaining within the threshold probability range of 1–99% (Fig. 2d). The benefits associated with the use of the risk nomogram were consistent across this range, with several overlaps indicating comparable outcomes. DCA of the nomogram in the validation set is shown in Additional file: Supplementary Fig. 2c.

Independent prognostic predictors

Univariate analyses were conducted to evaluate the influence of individual variables on prognosis, with the objective of identifying factors that significantly affected the risk of OS and RFS. Larger tumor dimensions emerged as the only significant variable associated with OS ($P < 0.05$), whereas the other factors examined did not demonstrate a statistically significant impact on OS ($P > 0.05$). Univariate analyses of RFS were performed to identify individual variables that could significantly influence the risk of recurrence (Table 4). The findings indicated that age < 55 years, extrathyroidal invasion, reduced TDS, and LLNM significantly correlated with RFS ($P < 0.05$). According to the results of the multivariate analysis presented in Table 4, patients under 55 years of age exhibited a recurrence risk that was 1.87 times greater than that in patients over 55 years of age (95% CI 1.00–3.49, $P < 0.05$). Furthermore, patients with elevated TDS were found to have a 0.35-fold increased likelihood of recurrence compared to those with reduced TDS (95% CI 0.20–0.62, $P < 0.05$).

Development and validation of a predictive nomogram for assessing the risk of recurrence

A nomogram model was developed by incorporating the two independent predictors mentioned previously (Fig. 3a). The multivariate collinearity assessment indicated no evidence of multicollinearity among the predictor variables (Table 4). The total point axis of the nomogram ranges from 0 to 120 points. The predicted probabilities for recurrence were observed to range from 0.70 to 0.90, 0.50 to 0.90, and 0.30 to 0.90 in the first, third, and fifth years, respectively. The calibration curve used to predict the likelihood of recurrence in patients with PTC demonstrated a high degree of consistency (Fig. 3b, Additional file: Supplementary Fig. 3a and 3b). The AUC for the prediction nomogram was calculated to be 0.60, 0.62, and 0.65 for the first, third, and fifth year, respectively (Fig. 3c). DCA of the nomogram in the training set is shown in Fig. 3d. Furthermore, the effectiveness of the model in predicting the recurrence risk was validated using a validation set (Additional file: Supplementary Fig. 3c–3 g).

Discussion

Management of lymph nodes during initial surgical intervention is critical for determining the prognosis of patients with PTC. Accurate prediction of cervical LNM is imperative because of the elevated risk of permanent hypoparathyroidism and recurrent laryngeal nerve injury associated with reoperation as well as the potential complications of significantly reduced parathyroid hormone levels and permanent hypocalcemia. Therefore, identifying reliable predictors and developing an effective prediction model are of the utmost importance. One promising approach involves the use of nomograms, which are predictive models that incorporate biological and clinical variables to forecast tumor-related outcomes, including mortality and other high-risk events [24].

In the present study, we examined various clinical and genetic characteristics as potential predictors of cervical LNM and prognosis in patients diagnosed with PTC. To enhance the accuracy of predicting the likelihood of CLNM and LLNM, we developed predictive models specifically tailored to each type of cervical LNM. Univariate analysis indicated that tumor bilaterality and multifocality were associated with the occurrence of CLNM; however, these factors were not identified as independent variables in the subsequent multivariate analysis. Notably, multivariate analysis revealed that age, tumor size, extrathyroidal invasion, histological type, and TDS were independent predictors of CLNM. Furthermore, univariate analysis indicated that sex, tumor size, presence of extrathyroidal invasion, and histological type were correlated with the incidence of LLNM. Nevertheless, these factors were determined to be non-independent variables in multivariate analysis. Multivariate analysis identified TDS, the number of excised cervical lymph nodes, and the presence of CLNM as independent predictors of LLNM in patients with PTC. Although most patients with PTC have a favorable prognosis, some may experience recurrence. This study specifically focused on identifying the independent variables associated with recurrence to improve predictive accuracy. According to the results of both the univariate and multivariate analyses, age and TDS emerged as the only independent variables associated with recurrence.

Tumor size is a significant determinant in the prediction of LNM, because larger tumors tend to exhibit more aggressive behavior and are associated with an increased rate of metastasis, particularly in CLNM. Nevertheless, a consensus regarding the specific size threshold has yet to be established. Previous studies have indicated that varying tumor size thresholds result in different correlations when predicting LNM [22, 25, 26]. The results of this study indicated that tumor size serves as an independent predictor of CLNM. Furthermore, the threshold identified for the correlation between tumor size and CLNM

Table 4 Uni- and Mulit-Cox regression analysis for predicting risk of recurrence in the present study

Clinical characteristics	HR [95%CI]	*P* (Uni)	HR [95%CI]	*P* (Multi)	Tolerance	VIF
Sex		0.29				
Female	1					
Male	1.42 [0.74, 2.71]					
Age (year)		**0.02**		**0.04**	0.99	1.00
< 55	1		1			
≥ 55	2.07 [1.12, 3.82]		1.87 [1.00,3.49]			
Dimension (cm)		0.06				
≤ 2.55	1					
> 2.55	1.17 [1.00, 1.38]					
Multifocality		0.98				
No	1					
Yes	1.01 [0.54, 1.87]					
Bilaterality		0.70				
No	1					
Yes	1.15 [0.56, 2.35]					
Extrathyroidal invasion		**0.03**		0.23		
No	1		1			
Yes	2.03 [1.09, 3.78]		1.50 [0.78, 2.87]			
Lymphocytic thyroiditis		0.93				
No	1					
Yes	0.96 [0.40, 2.32]					
Histological type		0.74				
Classic papillary	1					
Other subtypes	1.12 [0.56, 2.24]					
TDS		**0.00**		**0.00**	0.99	1.00
≤ -0.11	1		1			
> -0.11	0.32 [0.18, 0.58]		0.35 [0.20, 0.62]			
Absence of preoperative LN assessment		0.59				
No	1					
Yes	1.23 [0.59, 2.57]					
Excised cervical LN number		0.63				
≤ 16.5	1					
> 16.5	1.00 [0.99, 1.02]					
CLNM		0.08				
No	1					
Yes	1.77 [0.95, 3.32]					
LLNM		**0.01**		0.46		
No	1		1			
Yes	2.46 [1.31, 4.62]		1.32 [0.64, 2.74]			
Radioiodine Therapy		0.21				
No	1					
Yes	2.22 [0.64, 7.70]					

TDS: thyroid differentiation score, LN: lymph node, HR: hazard ratio, CI: Confidence Interval, CLNM: central lymph node metastasis, LLNM: lateral lymph node metastasis, VIF: Variance Inflation Factor

was 2.25 cm. This finding aligns with the prevailing consensus that there is a positive correlation between tumor size and the probability of LNM, wherein larger tumors are associated with an increased likelihood of metastatic spread.

Extrathyroidal invasion, a notable characteristic of thyroid cancer, has become an important prognostic indicator that garnered substantial clinical interest in recent years. Numerous studies have shown that the presence of extrathyroidal invasion identified during preoperative assessment is a critical independent risk factor that significantly influences the recurrence rate of thyroid cancer [27–29]. The findings of our study align with those of previous studies, indicating that extrathyroidal invasion serves as an independent risk factor for the occurrence of CLNM. The 8th edition of the American Joint Committee

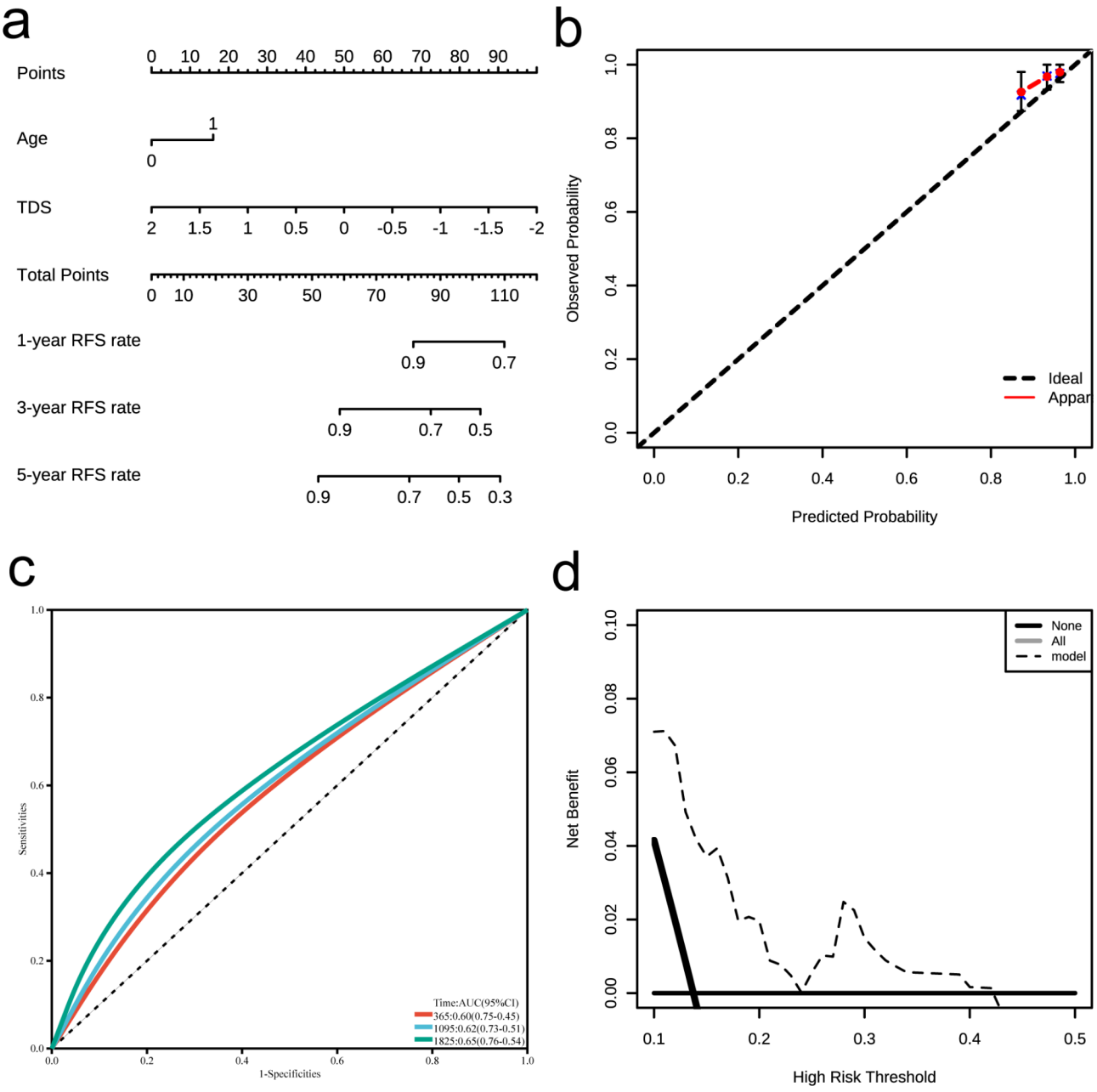

Fig. 3 Development of a nomogram for predicting the risk of recurrence in a training cohort, incorporating TDS and clinical characteristics in patients diagnosed with PTC. (**a**) Nomogram for predicting the risk of recurrence; (**b**) Calibration curve illustrating risk prediction based on the risk model at the 365-day time point; (**c**) Sensitivities and specificities of risk prediction derived from the risk model, visualized through ROC curves; (**d**) DCA of the risk nomogram. Age = 0 represents age less than 55 years; age = 1 represents age over 55 years. PTC, papillary thyroid carcinoma; RFS, recurrence free survival; TDS, thyroid differentiation score; ROC, receiver operating characteristic; AUC, area under curve; DCA, decision curve analysis

on AJCC/Tumor/tumor node metastasis staging system for thyroid cancer includes the T3b classification, which pertains to tumors that exhibit macroscopic extrathyroidal invasion limited to the strap muscles [30]. Although gross extrathyroidal invasion, defined as the macroscopic spread of a tumor observable through imaging or during surgical procedures, is an established risk factor for both disease recurrence and survival, the prognostic significance of minimal extrathyroidal invasion, identified solely through histological examination, remains a contentious issue among medical professionals. Due to inconsistent data regarding the risk of recurrence associated with minimal extrathyroidal invasion, this study was conducted to assess its impact on patient outcomes. The results indicate that the presence of minimal extrathyroidal invasion serves as a statistically significant and

independent risk factor for predicting relapse through lymph nodes and distant metastases in patients diagnosed with papillary thyroid microcarcinoma [31].

Many predictive models developed for the preoperative assessment of LNM do not adequately integrate genetic factors. However, advances in preoperative fine-needle aspiration biopsy techniques have facilitated the possibility of conducting genetic testing prior to surgery. Consequently, it is essential to incorporate genetically related factors into these models. Some studies have focused on the expression of a single gene as a risk factor in the development of LNM prediction models, which may introduce specific biases [32]. This study incorporated the TDS system as a risk factor for the development of a reliable predictive model. Compared to prediction models based solely on individual genes, the TDS system offers superior evaluation and prediction of LNM, including CLNM and LLNM, from the standpoint of thyroid differentiation. Furthermore, the TDS system exhibits advantages in terms of comprehensiveness and precision. Different values were observed between the high- and low-TDS groups when assessing the risk of CLNM, LLNM, and RFS. These differences reflect the varying severities and biological characteristics of the different indicators. CLNM, LLNM, and RFS represent different clinical stages and prognostic indicators. CLNM and LLNM pertain to the status of lymph node metastasis, whereas RFS pertains to the duration of recurrence-free survival. They play distinct roles in tumor progression. CLNM and LLNM are associated with local regional control, whereas RFS is associated with long-term survival and disease recurrence. Therefore, the observed differences in the predictive effects of TDS across these indicators may stem from their individual relationships to distinct biological behaviors of the tumor and the response to treatment. CLNM and LLNM are more involved in lymph node metastasis, which may be related to tumor invasiveness and ability to spread locally. RFS is a more comprehensive indicator, encompassing not only local control but also distant metastasis and the overall health status of the patient. Thus, the differences in TDS across these indicators may reflect distinct biological characteristics and therapeutic strategies for tumors. The findings of this study also indicate a significant correlation between the degree of PTC differentiation and recurrence in patients. Therefore, evaluating the risk of recurrence based on the degree of PTC differentiation has substantial clinical significance.

Age is recognized as a significant factor in PTC staging, with patients over the age of 45 typically exhibiting a slightly poorer prognosis and elevated recurrence rate [33]. Several studies have identified age as a risk factor for LNM and have reported a higher incidence of LNM in patients younger than 55 years [34]. Additionally, sex serves as an important indicator, as females generally present with a higher incidence of PTC; however, some studies have indicated that male sex may be a risk factor for CLNM [35]. In contrast, our study found that age and sex were not independent predictors of LLNM, a finding that differs from previous reports. Consequently, we emphasize the importance of incorporating gene-related indicators as risk factors in the development of predictive models. Compared to fundamental gene-level factors, the influence of age and sex on LLNM appears to be significantly diminished, rendering them non-independent risk factors. Nonetheless, these conclusions remain speculative, and we intend to further validate our hypotheses through follow-up studies.

This study has several limitations. First, the research was conducted retrospectively and relied on data obtained from publicly available databases, which may have introduced a risk of selection bias. Second, the study did not incorporate any ultrasonographic features because the results of ultrasonography are significantly dependent on the diagnostic expertise of the operator. Although most sonographers were highly experienced, subjective factors may have influenced the collected data. Consequently, this decision may have further contributed to a potential selection bias. Additionally, the reliability of TDS as a predictive factor requires further validation. To improve our methodology, we plan to collect additional cases and conduct further validations in future research.

In summary, this study identified five significant independent predictors of CLNM: age, tumor size, extrathyroidal invasion, histological type, and TDS. Additionally, three significant independent predictors of LLNM were identified: number of excised cervical lymph nodes, presence of CLNM, and TDS. Age and TDS scores were significant independent predictors of recurrence. Using these independent predictors, prediction nomograms were developed to provide a quantitative risk assessment. These nomograms can assist surgeons in accurately evaluating cervical lymph node status preoperatively, thereby facilitating appropriate treatment decisions, including the avoidance of unnecessary RCLND, and enabling the formulation of suitable management strategies. Moreover, they can enhance the accuracy of predicting recurrence in patients with PTC.

Abbreviations

PTC	Papillary thyroid carcinoma
TCGA	The Cancer Genome Atlas
ROC	Receiver operating characteristic
AUC	Area under curve
LNM	Lymph node metastasis
CLNM	Central lymph node metastasis
LLNM	Lateral lymph node metastasis
RCLND	Routine prophylactic central lymph node dissection
TDS	Thyroid Differentiation Score
GEO	Gene Expression Omnibus
DCA	Decision curve analysis

Supplementary Information

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Supplementary Material 1

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Author contributions
Conceptualization, YL, HL, and LW; Methodology, YL, HL, and LW; Investigation, XW and XS; Resources, YL, HL, and LW; Writing– Original Draft Preparation, YL; Writing– Review & Editing, HL, and LW; Supervision, HL, and LW. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The public datasets analyzed in this study were publicly available and therefore did not require ethics approval.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
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