Scientific Reports

https://doi.org/10.1038/s41598-026-39630-0

Article in Press

Clinical characteristics and risk analysis of lymph node metastasis in patients with cN0 differentiated thyroid carcinoma

Received: 30 July 2025

Accepted: 6 February 2026

Published online: 13 February 2026

Cite this article as: Wei M., Hu K., Qiu G. *et al.* Clinical characteristics and risk analysis of lymph node metastasis in patients with cN0 differentiated thyroid carcinoma. *Sci Rep* (2026). https://doi.org/10.1038/s41598-026-39630-0

Meng Wei, Kaipeng Hu, Gaolin Qiu, Qing Lin, Jincan Qian, Yao Lu & Rui Wang

Clinical Characteristics and Risk Analysis of Lymph Node Metastasis in Patients with cN0 Differentiated Thyroid Carcinoma

Author(s): Meng Wei[1#], Kaipeng Hu[2#], Gaolin Qiu[3#], Qing Lin[1], Jincan Qian[2], Yao Lu[3]*, Rui Wang[4]*

#Contributed equally

Affiliation(s): 1. Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China;

2. First Clinical Medical College, Anhui Medical University, Hefei, China;

3. Department of Anesthesiology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

4. Department of oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

***Corresponding author:**

Dr. Yao Lu, Department of Anesthesiology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

E-mail: luyao@ahmu.edu.cn

Dr. Rui Wang, Department of oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

E-mail: wrwm416@126.com

ABSTRACT

To examine the clinical attributes and likelihood of lymph node metastasis (LNM) in patients with differentiated thyroid carcinoma classified as clinically lymph node-negative (cN0) , with a minimum tumor diameter >0.5 cm and maximum tumor diameter <3.0 cm. Clinical data of 232 patients who underwent radical thyroidectomy and satisfied the inclusion and exclusion criteria were collected, and we found that average age of the LNM-positive group was younger than that of the LNM-negative group (40.9 ± 10.8 *vs*. 45.3 ± 11.8, *P*=0.0031), sex distribution also showed a statistically significant difference, with male patients being more prone to LNM (*P*=0.0436). Patients with positive LNM exhibited higher ultrasound thyroid imaging reporting and data system (TI-RADS) scores for thyroid nodules (*P*<0.001). In terms of maximum tumor diameter and RET fusion, the LNM-positive group was higher in LNM-negative group (1.11 ± 0.832 cm vs. 0.808 ± 0.616 cm, *P*=0.0034 and 16.3% vs. 2.7%, *P*=0.0026), showing a statistically significant difference, The proportion of multifocal lesions was also higher in the LNM-positive group (26.8% *vs*. 20.2%). Patients in the LNM-positive group had higher levels of peripheral blood thyroid stimulating hormone (2.68 ± 2.88 μIU/L *vs*. 2.12 ± 2.07 μIU/L). Notably, statistically

significant differences were observed between the LNM-positive and negative groups in terms of prothrombin time activity (PT%) (110 ± 13.0% *vs*. 107 ± 11.5%, *P*=0.034) and white blood cell (WBC) count (6.11 ± 1.76 × 10^9/L *vs*. 6.59 ± 1.85 × 10^9/L, *P*=0.0495), and further investigations revealed that BMI (R=0.19) and blood urea nitrogen (R=0.17) were positively correlated with PT%, whereas PT% was negatively correlated with peripheral blood T3 (R= −0.17) and T4 (R= −0.13) levels, which has not been reported in previous studies. We observed that for patients with cN0 differentiated thyroid cancer, we should also pay attention to the influence of factors such as gender, age, tumor diameter, RET fusion, and even PT and WBC on lymph node metastasis.

Keywords: thyroid cancer, lymph node metastasis, clinical indicators

1. Introduction

Over the past two decades, thyroid cancer has emerged as the most rapidly increasing solid malignancy in China. Recent statistics have revealed that thyroid cancer incidence ranks third among all cancers, surpassed only by lung and colorectal cancers, thereby constituting a significant public health concern[1]. In 2022, China reported approximately 466,100 new cases of thyroid cancer, representing more than

half the global incidence[2]. Most cases are well-differentiated malignancies classified as differentiated thyroid cancer (DTC). The primary treatment for DTC is surgical resection, which may be supplemented with adjuvant radioactive iodine therapy in specific cases. Furthermore, BRAF, MEK and RET inhibitors have emerged as promising therapeutic options for patients with locally advanced DTC[3].

Although most patients with thyroid cancer have a favorable prognosis, instances of lateral cervical lymph node metastasis (LNM) or tumor recurrence are common in clinical practice, presenting patients with greater therapeutic risks and challenges. LNM is frequently associated with poor prognosis in individuals with thyroid cancer[4]. The reported postoperative detection rate of LNM in patients with differentiated DTC is between 13.4–60%[5,6]. Univariate and multivariate analyses consistently demonstrated that LNM plays a critical role in predicting disease recurrence. Patients with LNM are five times more likely to experience tumor recurrence than those without LNM[4]. In recent years, early detection and prediction of LNM have emerged as significant challenges in clinical practice[7]. Although numerous predictive methods for LNM have been proposed[8-10], limitations, such as false-positive and false-negative rates persist, and regional differences among patient populations further complicate treatment strategies[11,12]. These factors may adversely affect treatment decisions, patient quality of life, and long-term survival[13]. Therefore, accurate preoperative

assessment of LNM and complete surgical dissection of metastatic lymph nodes are of paramount importance in the management of patients with thyroid cancer[14].

For patients with thyroid cancer, differences in clinical parameters and gene mutation (such as BRAF, RAS, and RET genes) between those with LNM (LNM-positive) and those without (LNM-negative) are particularly critical because they are closely related to disease progression, treatment strategies, and prognosis[15]. Previous studies have suggested that thyroid cancer exhibits regional variability, and that commonly used clinical indicators possess significant diagnostic and prognostic value in tumor management[16,17]. Therefore, investigating the clinical characteristics of newly diagnosed differentiated patients with DTC in a specific region, especially those without suspicious LNM on preoperative evaluation, may help identify predictive indicators associated with LNM risk and prognosis. These findings are of great importance in guiding personalized treatment and clinical decision-making.

2. Materials and Methods

2.1. Study Population and Inclusion Criteria

Patients with DTC who underwent surgery by the same surgical team at the Department of Thyroid Surgery, First Affiliated Hospital of Anhui Medical University, between December 31, 2022 and December 31, 2024 were enrolled. This study was

approved by the Institutional Ethics Committee (Approval No.: Exp-AYYFY-EC-PJ2022-13-44). All methods were performed in accordance with the relevant guidelines and regulations, including the Chinese Guidelines for the Diagnosis and Treatment of Thyroid Cancer (2022 Edition) and 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer.

Inclusion criteria: i) DTC with a minimum tumor diameter (Dmin) of >5 mm and maximum diameter (Dmax) of <30 mm, clinically node-negative (cN0) on preoperative imaging; ii) Treatment-naïve DTC without chronic thyroid diseases (e.g., thyroiditis) or prior interventions (e.g., thermal ablation); iii) Age between 18–75 years, with no history of malignancies, hematologic diseases, or metabolic disorders; iv) Ultrasound by a single physician, with malignancy confirmed by preoperative fine-needle aspiration (FNA) cytology or intraoperative frozen section; all underwent central compartment neck dissection with postoperative pathologic confirmation; and v) Signed informed consent and documented treatment compliance.

2.2 Clinical Data Documentation

Detailed demographic data, including patient age, sex, body weight, and body mass index (BMI), were recorded. Additional information included comorbidities, such as diabetes mellitus and hypertension, as well as behavioral factors including alcohol

abuse, smoking, and dietary habits related to long-term iodized salt consumption. Ultrasound findings were documented in accordance with the 2017 American College of Radiology Thyroid Imaging Reporting and Data System (TI-RADS) criteria, with all examinations conducted by a single designated sonographer using standardized equipment at our institution. Preoperative peripheral blood test results, including thyroid function profiles with antibody panels, coagulation studies, complete blood counts, and biochemical parameters, were collected. Furthermore, postoperative pathological characteristics, including tumor diameter (both maximal and minimal dimensions), tumor multiplicity, and LNM status, were systematically recorded. Meanwhile, we performed NGS (Next Generation Sequencing) molecular characterization on the pathological specimens of thyroid cancer patients included in the analysis to identify genetic alteration predictors that may reflect the presence of LNM.

2.3 Statistical Analysis

All statistical analyses were conducted using R software (version 4.1.2). Intergroup differences in continuous variables were assessed using the independent samples t-test or Wilcoxon rank-sum test. Categorical variables were evaluated using the chi-square test; however, the Fisher's exact test was used to ascertain statistical significance

when >25% of the cells had predicted frequencies below 5. All tests were two-tailed, with a *P*-value of <0.05 considered statistically significant.

3. Results

A total of 232 eligible patients with cN0 DTC were included in this study, comprising 109 patients confirmed to be LNM-negative by postoperative pathology and 123 patients confirmed to be LNM-positive.

3.1 Differences in Baseline Characteristics

In the LNM-negative group, 77.1% of the patients were female compared with 64.2% in the LNM-positive group. Males accounted for 22.9% of the LNM-negative group and 35.8% of the LNM-positive group. The difference in the sex distribution between the two groups was statistically significant ($P = 0.0436$). The mean age of the LNM-negative group was 45.3 ± 11.8 years, while that of the LNM-positive group was 40.9 ± 10.8 years, also showing a statistically significant difference ($P = 0.00312$), suggesting that younger and male patients are more likely to develop LNM. No statistically significant differences were observed between the two groups in terms of BMI ($P = 0.164$), height ($P = 0.861$), weight ($P = 0.266$), history of diabetes ($P = 0.342$), history of hypertension ($P = 0.243$), alcohol consumption ($P = 0.692$),

smoking history ($P = 0.683$), or long-term intake of iodized salt ($P = 0.668$) (**Figure 1 and Table 1**).

Table 1. Basic Information of Patients with Pathologically Lymph Node-Negative and -Positive Thyroid Cancer

	Overall (*N* = 232)	**Negative** (*N* = 109)	**Positive** (N = 123)	**P-value**
Sex				
Female	163 (70.3%)	84 (77.1%)	79 (64.2%)	0.0436*
Male	69 (29.7%)	25 (22.9%)	44 (35.8%)	
Age, years				
Mean (SD)	43.0 (11.4)	45.3 (11.8)	40.9 (10.8)	0.00312*
BMI				
Mean (SD)	23.9 (3.01)	24.2 (3.24)	23.6 (2.78)	0.164
Median [Min, Max]	23.7 [17.6, 33.4]	24.1 [17.6, 33.4]	23.4 [18.4, 30.4]	
Height, m				

Mean (SD)	1.64 (0.0718)	1.64 (0.0606)	1.64 (0.0806)	0.861
Median [Min, Max]	1.64 [1.49, 1.91]	1.64 [1.52, 1.80]	1.63 [1.49, 1.91]	
Weight, kg				
Mean (SD)	64.7 (11.2)	65.6 (11.6)	63.9 (10.8)	0.266
Median [Min, Max]	64.0 [45.0, 107]	65.0 [45.0, 107]	63.0 [46.0, 95.0]	
Diabetes				
No	222 (95.7%)	106 (97.2%)	116 (94.3%)	0.342
Yes	10 (4.3%)	3 (2.8%)	7 (5.7%)	
Hypertension				
No	168 (72.4%)	83 (76.1%)	85 (69.1%)	0.243
Yes	64 (27.6%)	26 (23.9%)	38 (30.9%)	
Alcohol consumption				
No	203 (87.5%)	94 (86.2%)	109 (88.6%)	0.692
Yes	29 (12.5%)	15 (13.8%)	14 (11.4%)	
Smoking history				
No	205 (88.4%)	95 (87.2%)	110 (89.4%)	0.683
Yes	27 (11.6%)	14 (12.8%)	13 (10.6%)	
Iodized salt intake >10 years				

No	5 (2.2%)	3 (2.8%)	2 (1.6%)	0.668
Yes	227 (97.8%)	106 (97.2%)	121 (98.4%)	
Ultrasound TI-RADS Score				
3	4 (1.7%)	2 (1.8%)	2 (1.6%)	<0.001*
4	1 (0.4%)	0 (0%)	1 (0.8%)	
4a	46 (19.8%)	28 (25.7%)	18 (14.6%)	
4b	128 (55.2%)	67 (61.5%)	61 (49.6%)	
4c	37 (15.9%)	9 (8.3%)	28 (22.8%)	
5	16 (6.8%)	3 (2.8%)	8 (9.6%)	
Lymph nodes on ultrasound				
No	61 (26.3%)	35 (32.1%)	26 (21.1%)	0.0728
Yes	171 (73.7%)	74 (67.9%)	97 (78.9%)	
Ultrasound calcification				
No	121 (52.2%)	62 (56.9%)	59 (48.0%)	0.19
Yes	111 (47.8%)	47 (43.1%)	64 (52.0%)	

*P < 0.05, considered statistically significant. BMI, body mass index; SD, standard deviation; TI-RADS, thyroid imaging reporting and data system

3.2 Differences between Preoperative Ultrasound and Postoperative Pathology Results

Significant differences were observed in the distribution of preoperative TI-RADS scores between the LNM-positive and LNM-negative groups. Patients in the LNM-positive group had higher TI-RADS grades, suggesting that accurate TI-RADS classification may have potential value in predicting LNM (**Table 1**). Regarding cervical lymph node findings on ultrasound, 97 (78.9%) patients in the LNM-positive group had lymph nodes, whereas 26 (21.1%) had no lymph nodes. In contrast, in the LNM-negative group, lymph nodes were reported in 74 (67.9%) patients and absent in 35 (32.1%). No statistically significant differences in ultrasound-reported nodular calcifications were observed between the two groups (**Table 1**).

Among the four patients diagnosed with follicular thyroid carcinoma, three presented with LNM. In comparison, the rate of LNM in patients with papillary thyroid carcinoma (PTC) was 52.63%. A statistically significant difference was observed in the maximum tumor diameter between the LNM-positive and LNM-negative groups (mean, 1.11 cm; standard deviation [SD], 0.832 cm vs. mean, 0.808 cm; SD, 0.616 cm; $P = 0.0033$), indicating a positive correlation between tumor size and the presence of LNM. Regarding multifocality, 26.8% of the patients in the LNM-positive group had multifocal lesions compared with only 20.2% in the LNM-negative

group (**Table 2**).

Table 2. Differences in Postoperative Pathological Results between Patients with Pathologically Lymph Node-Negative and -Positive Thyroid Cancer.

	Overall (N = 232)	**LNM-Negative (N = 109)**	**LNM-Positive (N = 123)**	**P-value**
Pathological Type				
FTC	4 (1.7%)	1 (0.9%)	3 (2.4%)	0.625
PTC	228 (98.3%)	108 (99.1%)	120 (97.6%)	
Maximum Tumor Diameter, cm				
Mean (SD)	0.958 (0.746)	0.808 (0.616)	1.11 (0.832)	0.00328*
Median [Min, Max]	0.800 [0.200, 5.50]	0.700 [0.200, 4.00]	0.850 [0.300, 5.50]	
Multifocality				
No	177 (76.3%)	87 (79.8%)	90 (73.2%)	0.28
Yes	55 (23.7%)	22 (20.2%)	33 (26.8%)	

*P < 0.05, considered statistically significant. LNM, lymph node metastasis; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma; SD, standard deviation

3.3 Differences in Clinical Biochemical Test Results

Patients in the LNM-positive group had higher peripheral blood thyroid stimulating hormone (TSH) levels compared with the LNM-negative group (2.68 ± 2.88 μIU/L vs. 2.12 ± 2.07 μIU/L, **Figure 2**). However, no statistically significant differences were observed between the two groups in terms of total triiodothyronine (T3, P = 0.984), total thyroxine (T4, P = 0.321), thyroglobulin antibody (TgAb, P = 0.173), thyroglobulin (Tg, P = 0.111), free T3 (FT3, P = 0.394), free T4 (FT4, P = 0.711), or parathyroid hormone (PTH, P = 0.368) levels (**Table 3**).

Table 3. Differences in Peripheral Blood Detection Indicators between Patients with Pathologically Lymph Node-Negative and -Positive Thyroid Cancer

	Overall (N = 232)	**LNM-Negative (N = 109)**	**LNM-Positive (N = 123)**	**P-value**
TSH, μIU/L				
Mean (SD)	2.76 (6.79)	2.12 (2.07)	2.68 (2.88)	0.089
Median [Min, Max]	1.86 [0.0100, 100]	1.70 [0.0100, 18.7]	2.01 [0.0500, 21]	

T3, nmol/L				
Mean (SD)	1.86 (0.368)	1.86 (0.307)	1.86 (0.417)	0.984
Median [Min, Max]	1.85 [0.670, 4.38]	1.85 [1.19, 2.77]	1.86 [0.670, 4.38]	
Missing	1 (0.4%)	0 (0%)	1 (0.8%)	
T4, nmol/L				
Mean (SD)	109 (23.3)	111 (20.4)	108 (25.6)	0.321
Median [Min, Max]	108 [14.4, 173]	110 [57.4, 171]	107 [14.4, 173]	
Missing	1 (0.4%)	0 (0%)	1 (0.8%)	
TgAb, IU/mL				
Mean (SD)	127 (382)	176 (534)	83.4 (133)	0.173
Median [Min, Max]	15.7 [10.0, 4000]	15.7 [10.0, 4000]	15.8 [10.0, 542]	
Missing	91 (39.2%)	42 (38.5%)	49 (39.8%)	
Tg, µg/L				
Mean (SD)	32.2 (94.5)	46.4 (127)	19.6 (48.2)	0.111
Median [Min, Max]	12.3 [0.0400, 841]	15.5 [0.0400, 841]	9.47 [0.0400, 410]	
Missing	92 (39.7%)	43 (39.4%)	49 (39.8%)	
FT3, pmol/L				
Mean (SD)	4.96 (1.56)	4.82 (0.843)	5.10 (2.06)	0.394
Median [Min, Max]	4.72 [2.06, 17.4]	4.80 [2.06, 7.29]	4.70 [3.04, 17.4]	

Missing	142 (61.2%)	63 (57.8%)	79 (64.2%)	
FT4, pmol/L				
Mean (SD)	17.0 (4.25)	16.8 (2.78)	17.2 (5.41)	0.711
Median [Min, Max]	16.7 [1.99, 31.7]	16.6 [9.29, 23.6]	17.0 [1.99, 31.7]	
Missing	142 (61.2%)	63 (57.8%)	79 (64.2%)	
PTH, pmol/L				
Mean (SD)	36.8 (18.9)	38.6 (21.8)	35.3 (16.0)	0.368
Median [Min, Max]	35.3 [3.00, 86.2]	39.9 [3.00, 86.2]	32.5 [3.00, 76.0]	
Missing	122 (52.6%)	58 (53.2%)	64 (52.0%)	
PT, %				
Mean (SD)	108 (14.2)	107 (11.5)	110 (13.0)	0.034*
Median [Min, Max]	107 [1.40, 160]	106 [84, 140]	110 [84.0, 160]	
Missing	7 (3.0%)	4 (3.7%)	3 (2.4%)	
D-D, µg /ml				
Mean (SD)	0.313 (0.256)	0.338 (0.339)	0.288 (0.124)	0.323
Median [Min, Max]	0.260 [0.100, 2.36]	0.260 [0.100, 2.36]	0.260 [0.160, 0.810]	
Missing	127 (54.7%)	56 (51.4%)	71 (57.7%)	
APTT, s				

Mean (SD)	36.0 (3.32)	36.3 (3.36)	35.7 (3.27)	0.196
Median [Min, Max]	35.6 [26.8, 46.4]	35.8 [30.2, 46.4]	35.4 [26.8, 45.4]	
Missing	7 (3.0%)	4 (3.7%)	3 (2.4%)	
PLT, 10^9/L				
Mean (SD)	229 (62.4)	237 (61.4)	222 (62.8)	0.0755
Median [Min, Max]	226 [87.0, 468]	230 [101, 392]	221 [87.0, 468]	
Missing	15 (6.5%)	5 (4.6%)	10 (8.1%)	
RBC, 10^12/L				
Mean (SD)	4.57 (0.481)	4.60 (0.473)	4.53 (0.488)	0.279
Median [Min, Max]	4.52 [3.22, 6.42]	4.57 [3.34, 5.69]	4.45 [3.22, 6.42]	
Missing	15 (6.5%)	5 (4.6%)	10 (8.1%)	
WBC, 10^9/L				
Mean (SD)	6.34 (1.81)	6.59 (1.85)	6.11 (1.76)	0.0495*
Median [Min, Max]	6.10 [2.57, 13.7]	6.37 [3.60, 13.7]	5.87 [2.57, 12.4]	
Missing	15 (6.5%)	5 (4.6%)	10 (8.1%)	
K, mmol/L				
Mean (SD)	4.19 (0.359)	4.18 (0.332)	4.19 (0.384)	0.881
Median [Min, Max]	4.21 [3.02, 5.18]	4.20 [3.22, 4.88]	4.22 [3.02, 5.18]	
Missing	6 (2.6%)	1 (0.9%)	5 (4.1%)	

Ca, mmol/L				
Mean (SD)	2.34 (0.165)	2.34 (0.148)	2.34 (0.181)	0.796
Median [Min, Max]	2.35 [1.44, 2.85]	2.34 [1.74, 2.85]	2.36 [1.44, 2.62]	
Missing	27 (11.6%)	11 (10.1%)	16 (13.0%)	
Cl, mmol/L				
Mean (SD)	106 (61.2)	111 (88.4)	102 (2.89)	0.291
Median [Min, Max]	102 [94.7, 1020]	102 [94.7, 1020]	102 [95.5, 109]	
Missing	6 (2.6%)	1 (0.9%)	5 (4.1%)	
P, mmol/L				
Mean (SD)	1.21 (0.201)	1.22 (0.206)	1.20 (0.196)	0.52
Median [Min, Max]	1.21 [0.700, 1.78]	1.21 [0.820, 1.78]	1.20 [0.700, 1.71]	
Missing	28 (12.1%)	11 (10.1%)	17 (13.8%)	
Na, mmol/L				
Mean (SD)	140 (2.46)	140 (2.43)	140 (2.50)	0.685
Median [Min, Max]	140 [132, 147]	140 [134, 147]	140 [132, 146]	
Missing	6 (2.6%)	1 (0.9%)	5 (4.1%)	
Fasting glucose, mmol/L				
Mean (SD)	5.63 (1.17)	5.56 (0.892)	5.70 (1.39)	0.354
Median [Min, Max]	5.42 [4.20, 17.8]	5.40 [4.48, 11.5]	5.45 [4.20, 17.8]	

Missing	10 (4.3%)	2 (1.8%)	8 (6.5%)	
BUN, mmol/L				
Mean (SD)	5.04 (1.31)	4.94 (1.18)	5.13 (1.41)	0.278
Median [Min, Max]	5.00 [1.90, 11.6]	4.90 [2.97, 11.6]	5.08 [1.90, 11.0]	
Missing	11 (4.7%)	3 (2.8%)	8 (6.5%)	
Cr, μmol/L				
Mean (SD)	62.3 (16.5)	62.1 (18.3)	62.6 (14.6)	0.834
Median [Min, Max]	59.0 [33.0, 164]	58.1 [33.0, 164]	60.0 [40.3, 118]	
Missing	11 (4.7%)	3 (2.8%)	8 (6.5%)	
$HCO3^-$, mmol/L				
Mean (SD)	28.2 (2.78)	27.8 (2.58)	28.5 (2.92)	0.0656
Median [Min, Max]	28.0 [21.3, 36.4]	27.8 [22.0, 34.4]	28.4 [21.3, 36.4]	
Missing	6 (2.6%)	1 (0.9%)	5 (4.1%)	

*P < 0.05, statistically significant. LNM, lymph node metastasis; TSH, thyroid stimulating hormone; T3, total triiodothyronine; T4, total thyroxine; TgAb, thyroglobulin antibody; Tg, thyroglobulin; FT3, free triiodothyronine; free thyroxine; PTH, parathyroid hormone; PT, prothrombin time; D-D, D-dimer; APTT, activated partial thromboplastin time; PLT, platelets; RBC, red blood cells; WBC, white blood cells; K, potassium; Ca, calcium; P, phosphorus; Na, sodium; HCO_3; bicarbonate; BUN, blood urea nitrogen; Cr, creatinine

Notably, significant statistical differences were observed in prothrombin time activity (PT%) and white blood cell (WBC) counts between the two groups, which, to our knowledge, have not been previously reported in the literature. Mean PT% in the LNM-positive group was 110 ± 13.0%, significantly higher than 107 ± 11.5% in the LNM-negative group ($P = 0.034$). Conversely, mean WBC count was 6.11 ± 1.76 $\times 10^9$/L in the LNM-positive group, significantly lower than 6.59 ± 1.85 $\times 10^9$/L in the LNM-negative group ($P = 0.0495$) (**Table 3**). Further subgroup analysis of the LNM-positive cohort revealed several potential factors associated with elevated PT%. Notably, BMI (R = 0.19) and blood urea nitrogen (BUN, R = 0.17) were positively correlated with PT%, whereas serum T3 (R = −0.17) and T4 (R = −0.13) levels were negatively correlated with PT% (**Figures 3 and 4**).

3.4 Identify independent predictive factors and construct a nomogram

We observed significant differences in factors such as age, gender, ultrasound-defined TI-RADS score, tumor diameter, and RET gene alterations. After multivariate logistic regression analysis adjusting for potential confounding factors, age (OR = 0.96, 95% CI: 0.93 - 0.98, P = 0.002), tumor diameter (≥1 cm vs. <1 cm, OR = 2.03, 95% CI: 1.06 - 3.95, P = 0.034), and RET fusion (OR = 5.83, 95% CI: 1.44 - 39.4, P = 0.028) were identified as significant predictive factors for the presence of lymph node metastasis. Meanwhile, the gender indicator showed marginal predictive value (OR=1.79, 95% CI: 0.93-3.49, P = 0.081).**(Table 4)**

Table 4: Multivariate logistic regression analysis for the prediction of lymph node metastasis.

Characteristic	OR	95%CI	β	SEM	Wald value	P
Age	0.96	0.93，0.98	- 0.044	0.014	- 3.062	0.002*
Sex						
Female	—	—	—	—	—	
Male	1.79	0.93，3.49	0.584	0.335	1.742	0.081
TI-RADS						
3	—	—	—	—	—	
4a	0.69	0.07，6.73	- 0.369	1.099	- 0.336	0.7
4b	1.14	0.12，10.6	0.134	1.068	0.125	0.9
4c+5	3.66	0.35，38.5	1.299	1.139	1.14	0.3
Tumor Diameter, cm						
<1	—	—	—	—	—	
>=1	2.03	1.06，3.95	0.71	0.335	2.121	0.034*
RET						
Wild type	—	—	—	—	—	
gene fusion	5.83	1.44，39.4	1.762	0.804	2.193	0.028*
Missense mutation	4.43	0.55，93.8	1.489	1.191	1.25	0.2

Therefore, we incorporated age, sex, tumor diameter, and RET alterations to construct a nomogram for predicting lymph node metastasis **(Figure 5A)**. In the calibration plot, the nomogram predictions closely aligned with the reference line, indicating that the predictive nomogram is an ideal model **(Figure 5B)**. The performance of the DCA curve and clinical impact curve demonstrated high clinical net benefit, nearly across the entire threshold probability of the nomogram model **(Figure 5-C, D)**. To evaluate the predictive performance of the current model, we conducted ROC curve analysis, which yielded an AUC value of 0.724 (0.656 - 0.792). The sensitivity and specificity of this model were 82.7% and 52.9% respectively, serving as supplementary indicators for assessing the probability of lymph node metastasis in patients **(Figure 5E)**.

3.5 Practical application examples of nomograms

To enhance the practical applicability of the nomogram, we provide a concrete example to illustrate its use in clinical prediction **(Figure 6)**. *For instance, in a 53-year-old male patient with thyroid cancer, we observed a tumor diameter exceeding 1 cm and the presence of RET mutation. According to the nomogram, we can identify the corresponding points for each parameter, which are 26, 40, 47, and 90 points respectively. By summing these points, we obtain a total score of 203 points, corresponding to a lymph node metastasis risk of 0.92 for this patient.*

4. Discussion

This study sought to precisely characterize the clinical features of the predominant thyroid cancer population in the region by selecting patients with DTC at cN0 stage, with a Dmin of >5 mm and Dmax of <30 mm as the study cohort. A thorough comparison and analysis of the clinical factors between patients with and without LNM was performed to provide individualized diagnostic and therapeutic options for this subset of patients with thyroid cancer.

Notable disparities in sex and age were identified between the two groups, suggesting that younger male patients have a higher propensity for LNM. This discovery has significant clinical importance in directing the diagnosis and therapy of patients with thyroid cancer. Indeed, younger age at diagnosis is associated with an increased risk of LNM in patients with PTC. Studies have shown that patients aged <30 years have the highest incidence of LNM, whereas those >60 years exhibit less

than half the risk compared with a subgroup aged <30[18]. The increased vulnerability to LNM in male patients with thyroid cancer may be ascribed to hormone-driven tumor biology, namely, the promotion of cancer cell proliferation and invasion facilitated by androgens and unique patterns of clinical metastatic behavior[19].

Thyroid nodules in patients with LNM tended to exhibit higher TI-RADS scores during preoperative ultrasound evaluations[20]. Furthermore, when experienced sonographers identify cervical lymph nodes, regardless of suspicious features, patients are still more likely to present with positive LNM. Zhong et al. reported that for each one-point increase in the TI-RADS score, the risk of central LNM correspondingly increases[21]. This study highlights the need to assess the risk of central compartment metastasis when nodules have elevated TI-RADS scores or when cervical lymph nodes are observed on ultrasonography, irrespective of their apparent suspiciousness. Nonetheless, there was a degree of divergence between ultrasonographic results and pathologically verified LNM. The sensitivity and specificity of ultrasonography are both constrained, indicating that exclusive dependence on sonographic evaluation may result in the underdiagnosis of particular LNM instances[22]. These findings suggest that although high-quality ultrasound is valuable for lymph node evaluation, cytological FNA remains indispensable for the accurate preoperative diagnosis of LNM[23].

In the present study, the LNM rate in patients with PTC was 52.63%. The mean tumor diameter in the LNM-positive group was significantly larger than that in the LNM-negative group (1.11 cm vs. 0.808 cm), and the median tumor size differed between the two groups (0.850 cm vs. 0.700 cm). Additionally, 26.8% of the patients in the LNM-positive group presented with multifocal lesions compared with 20.2% in the LNM-negative group. These data underscore a possible link between tumor size, multiplicity, and the likelihood of LNM in this particular cohort of patients with thyroid cancer. They proposed that cases involving larger or more thyroid nodules or carcinomas may require more severe surgical intervention or extensive lymph node dissection. Although BRAF and RAS are the primary mutated genes in differentiated thyroid carcinoma, with overall mutation rates of BRAF (62.1%) and RAS (2.2%) observed in our study of 232 patients, we failed to identify any correlation between BRAF mutations and LNM. This finding aligns with previous reports indicating that LNM in PTC patients is not associated with BRAF mutations but rather with PTC recurrence rates. Additionally, we observed a higher probability of LNM occurrence when RET fusion (7.8%) was present, suggesting that RET fusion may serve as an independent predictor for LNM. This is consistent with the more aggressive lymph node invasiveness exhibited by RET fusion tumors, warranting particular clinical attention. Certainly, the limited sample size included in this study may present certain

limitations, necessitating further in-depth research with larger sample sizes for comprehensive elucidation. Moreover, TSH levels were comparatively elevated in individuals with LNM, which is consistent with the results of most previous studies[21,24]. This supports the consideration of prophylactic low-dose exogenous thyroid hormone therapy in selected high-risk populations, and reinforces the importance of appropriate TSH suppression therapy following thyroid cancer surgery[25].

This study identified statistically significant differences in PT% and WBC counts between patients with and without LNM, a finding that has not been previously reported in similar studies. Further analysis of the LNM-positive group revealed that BMI and BUN were positively correlated with PT%, whereas peripheral blood levels of T3 and T4 negatively correlated with PT%. Coagulation metrics, including thrombin time, activated partial thromboplastin time, prothrombin time, fibrinogen, and platelet-related indices, are important prognostic indicators in several cancers[26]. Specifically, PT% reflects the activity of prothrombin in a patient's plasma compared with that in standard plasma, and is commonly used to assess the functionality of the extrinsic coagulation pathway[27]. An elevated PT% has been associated with poor prognosis in numerous malignancies, including clear cell renal cell carcinoma[28], bone metastases from gastric cancer[29], non-small cell lung cancer[30], and colorectal cancer[31].

This association may be linked to the proteolytic activity of tumor-induced fibrinolytic enzymes[32,33]. The correlations between PT% and BMI, BUN, and T3/T4 ratio further suggest that obesity and metabolic abnormalities may contribute to thyroid cancer progression[34]. Additionally, the elevated WBC count observed in the LNM-positive group may be attributed to the pro-inflammatory or anti-inflammatory factors such as TGF (transforming growth factor) and IL (inflammatory factors), which suppress the bone marrow and peripheral immune systems, leading to lower white blood cell counts. Additionally, Hashimoto's thyroiditis has been proven to be a risk factor for the development and progression of thyroid cancer, and Hashimoto's thyroiditis itself is an autoimmune disease that can cause leukopenia or lymphopenia[35,36]. Collectively, these findings indicate that PT% and WBC count may serve as potential clinical indicators for predicting LNM in thyroid cancer.

However, this is a single-center study, and patients from multiple medical centers need to be collected to further validate the nomogram. Additionally, the mechanisms by which patient age, gender, preoperative TI-RADS score, tumor diameter, number of lesions, RET fusion, and particularly PT and WBC counts promote lymph node metastasis in thyroid cancer require further in-depth experimental investigation. The current research represents only a small initial step.

In conclusion, for patients with preoperatively assessed cN0-stage DTC, several

factors, including age, sex, preoperative TI-RADS score, postoperative tumor diameter, multifocality, prothrombin activity, and WBC count, may be associated with the risk of LNM. These differential findings may enable clinicians evaluate disease status and prognosis more accurately, thereby guiding personalized therapeutic strategies.

Funding

This study was supported by the National Natural Science Foundation of China（82101349），
Anhui Provincial Special Program for Clinical Medical Research Translation.202527c10020076
Anhui Provincial New Era Education Quality Engineering Project (Graduate Education)
2024qyw/sysfkc017

Author Contributions

M.W.: Conceptualization (equal); investigation (equal); visualization (equal); writing – original draft (equal). K.H.: Data curation (equal); formal analysis (equal). G.Q.: Resources (equal); software (equal); visualization (equal). Q.L.: Investigation (equal); validation (equal); visualization (equal). J.Q.: Resources (equal); supervision (equal); validation (equal). Y.L.: Investigation (equal); supervision (equal); writing – review and editing (equal). R.W.: Conceptualization (equal); data curation (equal); writing – review and editing (equal).

Competing Interests

The authors declare that they have no competing interests.

Data availability

The datasets analyzed in the current study are available from the corresponding author on reasonable request.

References

1. Han B, Zheng R, Zeng H, et al. Cancer incidence and mortality in China, 2022. *J Natl Cancer Cent.* 2024;4(1):47-53.
2. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229-263.
3. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. *Lancet.* 2016;388(10061):2783-2795.
4. Prabhu M, Shakya S, Ballal S, Ahmed Shamim S, Bal C. RET gene mutation analysis and long-term clinical outcomes of medullary thyroid cancer patients. *Nucl Med Commun.* 2020;41(11):1136-1142.
5. Zhou SL, Guo YP, Zhang L, et al. Predicting factors of central lymph node metastasis and BRAF(V600E) mutation in Chinese population with papillary thyroid carcinoma. *World J Surg Oncol.* 2021;19(1):211.
6. Nie X, Tan Z, Ge M. Skip metastasis in papillary thyroid carcinoma is difficult to predict in clinical practice. *BMC Cancer.* 2017;17(1):702.
7. Caliskan O, Unlu MT, Yanar C, Kostek M, Aygun N, Uludag M. Predictive Factors Affecting the Development of Lateral Lymph Node Metastasis in Papillary Thyroid Cancer. *Sisli Etfal Hastan Tıp Bul.* 2023;57(3):312-319.
8. Yu J, Deng Y, Liu T, et al. Lymph node metastasis prediction of papillary thyroid carcinoma based on transfer learning radiomics. *Nat Commun.* 2020;11(1):4807.
9. Yu Y, Ouyang W, Huang Y, et al. Artificial intelligence-based multi-modal multi-tasks analysis reveals tumor molecular heterogeneity, predicts preoperative lymph node metastasis and prognosis in papillary thyroid carcinoma: a retrospective study. *Int J Surg.* 2025;111(1):839-856.
10. Liu F, Han F, Lu L, Chen Y, Guo Z, Yao J. Meta-analysis of prediction models for predicting lymph node metastasis in thyroid cancer. *World J Surg Oncol.* 2024;22(1):278.

11. Du Y, Zhang S, Zhang G, et al. Mutational profiling of Chinese patients with thyroid cancer. *Front Endocrinol (Lausanne).* 2023;14:1156999.
12. Wang C, Wu Z, Lei L, et al. Geographic disparities in trends of thyroid cancer incidence and mortality from 1990 to 2019 and a projection to 2030 across income-classified countries and territories. *J Glob Health.* 2023;13:04108.
13. Oh MY, Jung KY, Choi H, et al. Distinct Impacts of Clinicopathological and Mutational Profiles on Long-Term Survival and Recurrence in Medullary Thyroid Carcinoma. *Endocrinol Metab (Seoul).* 2024;39(6):877-890.
14. Fu R, Yang H, Zeng D, et al. PTC-MAS: A Deep Learning-Based Preoperative Automatic Assessment of Lymph Node Metastasis in Primary Thyroid Cancer. *Diagnostics (Basel).* 2023;13(10).
15. Zhu H, Yu B, Li Y, et al. Models of ultrasonic radiomics and clinical characters for lymph node metastasis assessment in thyroid cancer: a retrospective study. *PeerJ.* 2023;11:e14546.
16. Rezaei F, Mazidimoradi A, Pasokh Z, Dehghani SP, Allahqoli L, Salehiniya H. Temporal trends of thyroid cancer between 2010 and 2019 in Asian countries by geographical region and SDI, comparison with global data. *Aging Med (Milton).* 2023;6(4):386-426.
17. Zhang MB, Meng ZL, Mao Y, et al. Cervical lymph node metastasis prediction from papillary thyroid carcinoma US videos: a prospective multicenter study. *BMC Med.* 2024;22(1):153.
18. Wang J, Liu J, Pan H, et al. Young age increases the risk of lymph node positivity in papillary thyroid cancer patients: a SEER data-based study. *Cancer Manag Res.* 2018;10:3867-3873.
19. Xu FZ, Zheng LL, Chen KH, et al. Serum sex hormones correlate with pathological features of papillary thyroid cancer. *Endocrine.* 2024;84(1):148-154.
20. Lu X, Dang Y, Kondowe B, et al. Combining Thyroglobulin Levels in Lymph Node Wash-out Fluid with TI-RADS to Predict Lymph Node Metastasis in Papillary Thyroid Carcinoma. *Malawi Med J.* 2025;36(5):298-302.
21. Zhong M, Zhang Z, Xiao Y, et al. The Predictive Value of ACR TI-RADS Classification for Central Lymph Node Metastasis of Papillary Thyroid Carcinoma: A Retrospective Study. *Int J Endocrinol.* 2022;2022:4412725.
22. Zhang Y, Zhao J, Wang B, Lin Y, Meng S, Luo Y. [Contrast-enhanced ultrasonography with intra-glandular contrast injection can improve the diagnostic accuracy of central compartment lymph node metastasis of thyroid cancer]. *Nan Fang Yi Ke Da Xue Xue Bao.* 2023;43(2):219-224.
23. Chen L, Liu ZY, Zhang JS. [Clinical and cytological characteristics of primary thyroid lymphoma: a fine needle aspiration study of 10 cases]. *Zhonghua Bing Li Xue Za Zhi.* 2025;54(6):618-625.
24. Carvalho AY, Kohler HF, Gomes CC, Vartanian JG, Kowalski LP. Predictive Factors of Recurrence of Papillary Thyroid Microcarcinomas: Analysis of 2,538 Patients. *Int Arch Otorhinolaryngol.* 2021;25(4):e585-e593.

25. Yang LG, Yang ZG, Zhang J, Fu YL. Effects of (131)I and TSH suppression therapy on METTL3, METTL14 levels and recurrence in thyroid cancer. *Am J Cancer Res.* 2025;15(1):42-58.
26. Li Z, Yin Z, Luan Z, et al. Comprehensive analyses for the coagulation and macrophage-related genes to reveal their joint roles in the prognosis and immunotherapy of lung adenocarcinoma patients. *Front Immunol.* 2023;14:1273422.
27. Gan D, Zeng Y, Zhang K, et al. Development of a novel prognostic assessment model for hepatitis B virus-related acute-on-chronic liver failure based on reexamination results. *Medicine (Baltimore).* 2023;102(11):e33252.
28. Bian Z, Meng J, Niu Q, et al. Prognostic Role of Prothrombin Time Activity, Prothrombin Time, Albumin/Globulin Ratio, Platelets, Sex, and Fibrinogen in Predicting Recurrence-Free Survival Time of Renal Cancer. *Cancer Manag Res.* 2020;12:8481-8490.
29. Wang X, Wang JY, Chen M, Ren J, Zhang X. Clinical association between coagulation indicators and bone metastasis in patients with gastric cancer. *World J Gastrointest Oncol.* 2023;15(7):1253-1261.
30. Li Y, Xu C, Yu Q. Risk factor analysis of bone metastasis in patients with non-small cell lung cancer. *Am J Transl Res.* 2022;14(9):6696-6702.
31. Zhang L, Ye J, Luo Q, et al. Prediction of Poor Outcomes in Patients with Colorectal Cancer: Elevated Preoperative Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT). *Cancer Manag Res.* 2020;12:5373-5384.
32. Weitz JI, Fredenburgh JC, Eikelboom JW. A Test in Context: D-Dimer. *J Am Coll Cardiol.* 2017;70(19):2411-2420.
33. Johnson ED, Schell JC, Rodgers GM. The D-dimer assay. *Am J Hematol.* 2019;94(7):833-839.
34. Pasqual E, O'Brien K, Rinaldi S, Sandler DP, Kitahara CM. Obesity, obesity-related metabolic conditions, and risk of thyroid cancer in women: results from a prospective cohort study (Sister Study). *Lancet Reg Health Am.* 2023;23:100537.
35. Mukherjee S,Sachdeva N,Sood A, et al. IL-17 A correlates with disease progression in papillary thyroid carcinoma. Diagn Pathol. 2023;18 (1):93. doi:10.1186/s13000-023-01362-4.
36. Kim EH,Kim JH,Park SB, et al. Association of the Preoperative Neutrophil-to-ymphocyte Count Ratio and Platelet-to-Lymphocyte Count Ratio with Clinicopathological Characteristics in Patients with Papillary Thyroid Cancer. Endocrinol Metab (Seoul). 2015;30 (4):494-501. doi:10.3803/EnM.2015.30.4.494

Figure Legends

Figure 1. Discrepancies in Clinical Indicators between patients with Pathologically Lymph Node Metastasis-Negative and Lymph Node Metastasis-Positive Thyroid Cancer

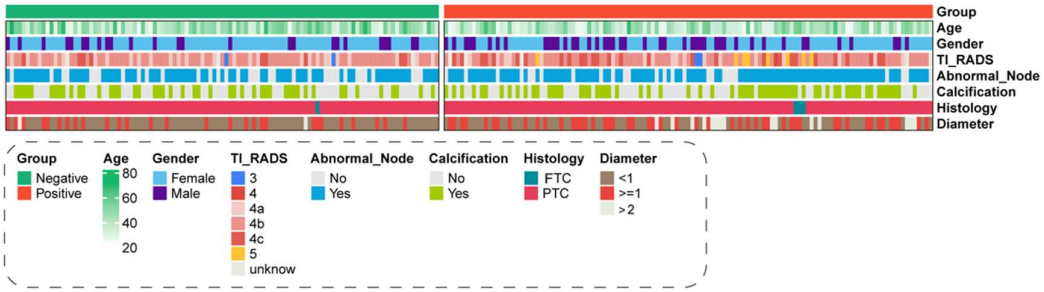

Figure 2. Differences in Thyroid-Related Hormone Levels between Patients with Lymph Node-Negative and -Positive Primary Thyroid Cancer

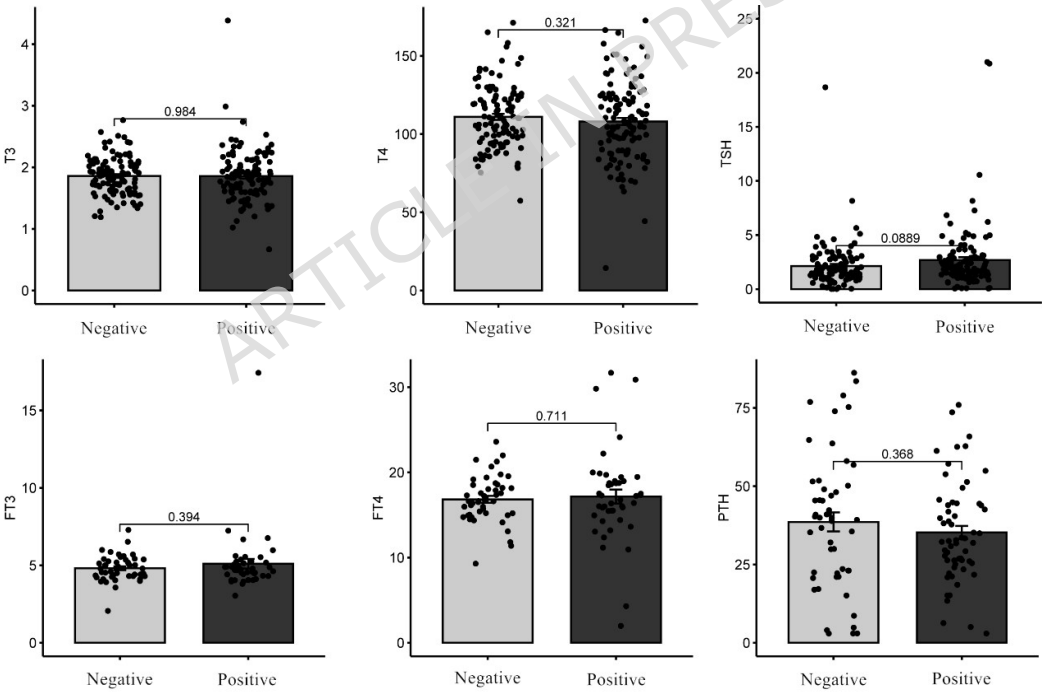

Figure 3. Correlation of Thyroid-Related Hormone Levels and Clinical Indicators in Patients with Lymph Node-Positive Cancer

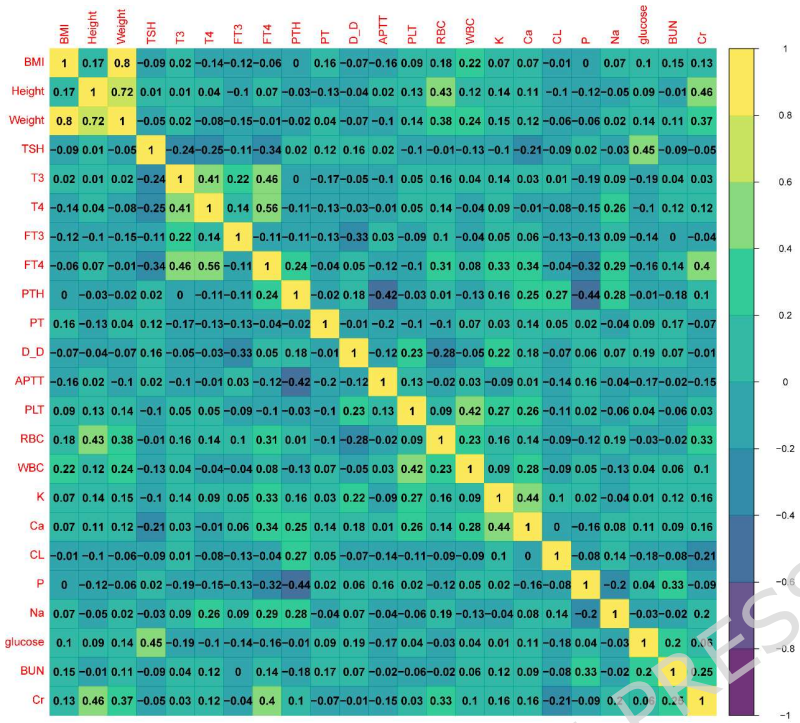

Figure 4. Differences in Prothrombin Activity between Patients with Lymph Node-Negative and -Positive Cancer and its Correlation with Thyroid-Related Hormones

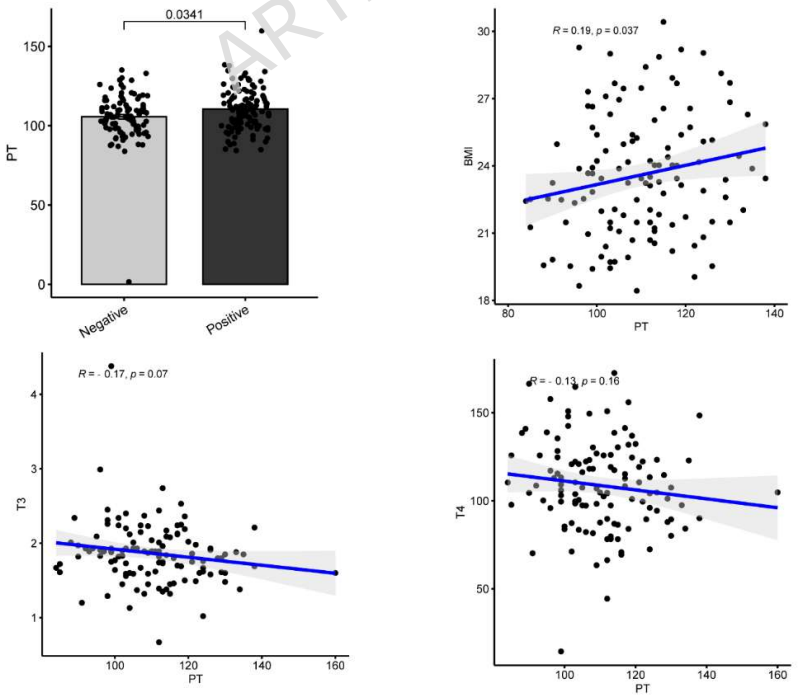

Figure 5. Construction of a nomogram for predicting lymph node metastasis and evaluating the clinical application of the nomogram.（A）Nomogram for the prediction of lymph node metastasis for thyroid cancer patients with the factors of age, gender, tumor diameter, and RET genetic alteration. （B）Calibration plot for the nomogram. （C）DCA showed that our nomogram has a greatest net benefit. （D）Clinical impact curve of the nomogram plots the number of lymph node metastasis patients classified as high risk, and the number of cases classified as high risk with the event at each risk threshold. （E）ROC curve showed the preferable prognostic value of the nomogram.

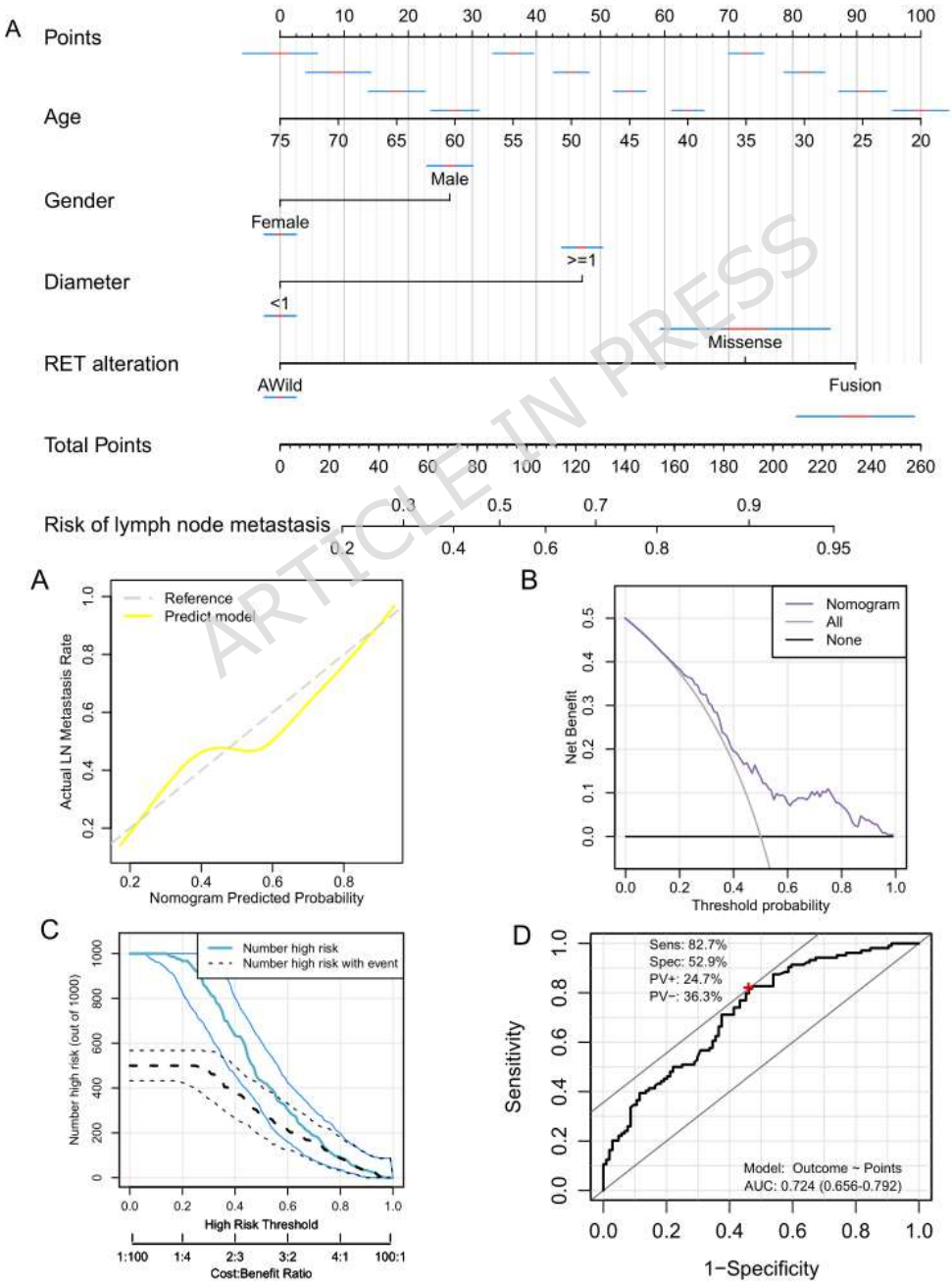

Figure 6. Application reference diagram of the newly constructed nomogram for predicting lymph node metastasis in patients with thyroid cancer.