Cancer Management and Research

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ORIGINAL RESEARCH

Fibrinogen-to-Neutrophil Ratio as a New Predictor of Central Lymph Node Metastasis in Patients with Papillary Thyroid Cancer and Type 2 Diabetes Mellitus

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Background: Many patients have a higher risk of thyroid cancer if they have both papillary thyroid carcinoma (PTC) and Type 2 diabetes mellitus (T2DM). Meanwhile, the primary reason for local PTC recurrence is cervical lymph node metastasis. Therefore, the prognosis of patients affects how cervical lymph nodes are managed during surgery. Due to surgical complications such as laryngeal nerve palsy and hypocalcemia, it is still debatable whether to prevent central lymph node dissection (CLND). Predicting central lymph node metastasis (CLNM) is crucial to direct CLND. It is unclear how important the fibrinogen-to-neutrophil ratio (FNR) is in thyroid cancer, so we looked into how it might help patients with PTC and T2DM predict CLNM.

Patients and methods: Wenzhou Medical University's First Affiliated Hospital provided us with 413 patients with PTC and T2DM, randomly divided into a training set (N = 292) and a validation set (N = 121). Univariate and multivariate logistic regression analyses were used to identify independent risk factors. After constructing a nomogram, the validity of the model was evaluated.

Results: The maximum tumor diameter, high-density lipoprotein, thyroxine, triglyceride, lymphocyte, and FNR were all identified as independent risk factors by multivariate logistic regression analysis. The C index of the training set was 0.775, and the validation set was 0.654.

Conclusion: In patients with PTC and T2DM, preoperative FNR was an independent risk factor for CLNM.

Keywords: FNR, PTC, nomogram, CLNM, predictor

Introduction

Thyroid cancer is a common endocrine malignancy.[1] According to cancer statistics, thyroid cancer is now the ninth most common cancer globally, with 586,000 new cases reported yearly. Women are three times more likely than men to experience the condition globally.[2] The high incidence of thyroid cancer may be primarily attributed to improved papillary thyroid carcinoma (PTC) detection and diagnosis.[3,4] Worldwide, diabetes mellitus (DM) incidence and mortality are rising.[5] Both thyroid cancer and diabetes affect a large number of patients. Therefore, we cannot disregard the substantial number of such patients. This justifies the target population of this study is patients with PTC and T2DM.

PTC is the most important type of thyroid cancer.[1,6] Cervical lymph node metastasis occurs in 40–90% of the cases.[7] Although PTC lymph node metastasis most commonly occurs in the central region, it is also possible to skip metastasis.[8] LNM is an important indicator of the prognosis, scope, and surgical method of PTC, as well as an important risk factor for both a high recurrence rate and a low patient survival rate.[9] However, prophylactic central lymph node dissection

Received: 13 March 2022
Accepted: 23 July 2022
Published: 20 December 2022

(CLND) is still debatable because it can lead to surgical complications such as laryngeal nerve palsy and hypocalcemia caused by resection of CLND.[10] Therefore, it is crucial to accurately predict the likelihood of preoperative central lymph node metastasis (CLNM) so that some patients with PTC can avoid preventive CLND.

Cancer occurrence, development, and metastasis are closely linked to inflammation.[11,12] Numerous inflammatory indicators, such as neutrophil,[13] lymphocyte,[14] C-reactive protein,[15] fibrinogen,[16] the neutrophil-to-lymphocyte ratio,[17] the platelet-to-lymphocyte ratio,[18] etc., are linked to cancer. Fibrinogen, a glycoprotein, is an essential clotting factor in the inflammatory response.[19] Increased fibrinogen has recently been associated with the progression and poor prognosis of some malignancies, such as gastric cancer,[20] gallbladder cancer,[21] and bladder cancer.[22]

The fibrinogen to the neutrophil ratio (FNR), a new predictive marker, was identified in our study, and its predictive value for CLNM in patients with PTC and T2DM was evaluated.

Methods

Patients

We enrolled 413 patients with PTC and T2DM who underwent thyroid lobectomy and lymph node dissection at the First Affiliated Hospital of Wenzhou Medical University from 2018 to 2021. The following were our exclusion criteria:

1. Insufficient clinical data.
2. Non-thyroid papillary carcinoma was suggested by intraoperative rapid freezing and postoperative paraffin specimens or pathologically confirmed by PTC without CLND.
3. History of hyperthyroidism, thyroid radiation, and thyroid surgery.
4. History of other malignant tumors.
5. Patients with hemoglobin A1c >7% or who had poor preoperative blood glucose control were not eligible for surgery.
6. Preoperative imaging tests revealed evidence of enlargement of central or lateral lymph nodes or distant tumor metastasis.

Information Collection

All enrolled patients received complete information. Basic information including name, hospitalization number, age, sex, history of diabetes, medication use, etc. Prior to surgery, all patients underwent a thorough evaluation that included a preoperative thyroid ultrasound, computed tomography (CT) scan, blood routine, blood biochemistry, blood glucose monitoring, and thyroid function examination. Additionally, surgical records, intraoperative rapid freezing, and postoperative paraffin pathology were collected.

Data Analysis

Receiver operating characteristic (ROC) curve analysis, which converts continuous variables into dichotomous variables for straightforward analysis, helps us determine the optimal cut-off values. By entering a random seed number, the 413 cases were randomly divided into a training set (N = 292) and a validation set (N = 121). The two cohorts were then compared using the chi-square test to determine whether they were comparable. To further assess the independent risk factors for CLNM in the training set, factors with $P < 0.1$ were included in multivariate logistic regression analysis based on the binary logistic regression analysis results. Then, to create nomogram plots, factors with $P < 0.05$ in the multiple regression analysis were selected. The prediction performance of the training and validation sets was measured using the area under the curve (AUC) under the ROC curve. We used a calibration plot to show the consistency between predictions and results. The calibration plot's p-value was also evaluated using the Hosmer-Lemeshow test (a score of $p > 0.05$ indicated a good model fit). The clinical result of the model was assessed using decision curve analysis (DCA). To determine whether the new model's predictive ability had increased, we compared it to the original model and used the integrated discrimination improvement (IDI) and net reclassification index (NRI) measures; if IDI >0, the new model's predictive power was considered to have increased compared to the original model. If IDI <0, it had decreased predictive

power; if IDI = 0, there had been no improvement. NRI and IDI had similar significance. R 4.0.2 and statistical package for social sciences 25.0 were used.

Result

Clinical Characteristics of Patients

The First Affiliated Hospital of Wenzhou Medical University from 2018 to 2021 included 413 patients with PTC and T2DM. In the R package, 413 cases were randomly divided into a training set (N = 292) and a validation set (N = 121) in a 7:3 ratio. The data were processed if the ROC curve identified the ideal cut-off value for a continuous variable. Table 1 shows the chi-square analysis of the two data groups; the results suggested that the two data groups were consistent and comparable.

Table 1 Baseline Characteristics of the Training Dataset and the External Validation Dataset

Variables	Training Dataset N=292	Validation Dataset N=121	P-value
Age			
>55Y	165	66	0.715
≤55Y	127	55	
Gender			
Female	200	72	0.08
Male	92	49	
Medicine for diabetes			
Metformin (-)	149	64	0.73
Metformin (+)	143	57	
BMI (kg/m^2)			
>29.7	28	9	0.486
≤29.7	264	112	
Maximum diameter of mass			
>9.5 mm	106	34	0.109
≤9.5 mm	186	87	
Multifocality			
Solitary	206	83	0.694
Multiple	86	38	
CLNM			
CLNM (-)	161	70	0.613
CLNM (+)	131	51	
Laterality			
Unilateral	245	103	0.757
Bilateral	47	18	
Hashimoto's thyroiditis			
Absent	259	106	0.752
Present	33	15	
TC (mmol/L)			
>5.585	75	26	0.366
≤5.585	217	95	
TG (mmol/L)			
>2.325	101	41	0.891
≤2.325	191	80	
HDL (mmol/L)			
>1.245	76	30	0.794
≤1.245	216	91	

(*Continued*)

Table 1 (Continued).

Variables	Training Dataset N=292	Validation Dataset N=121	P-value
LDL (mmol/L)			
>2.755	117	42	0.308
≤2.755	175	79	
Glucose (mmol/L)			
>6.1	231	98	0.665
≤6.1	61	23	
Albumin (g/L)			
>38.95	260	110	0.572
≤38.95	32	11	
Globulin (g/L)			
>32.15	92	37	0.853
≤32.15	200	84	
AGR			
>1.45	137	54	0.671
≤1.45	155	67	
Neutrophil (x10^9/L)			
>4.395	96	42	0.719
≤4.395	196	79	
Mononuclear (x10^9/L)			
>0.355	187	79	0.809
≤0.355	105	42	
Lymphocyte (x10^9/L)			
>1.695	206	85	0.951
≤1.695	86	36	
Lymphocyte (%)			
>28.1	194	83	0.671
≤28.1	98	38	
Platelet (x10^9/L)			
>255	105	41	0.688
≤255	187	80	
TSH (mIU/L)			
>0.86	231	96	0.958
≤0.86	61	25	
T4 (pmol/L)			
>11.94	82	32	0.735
≤11.94	210	89	
T3 (pmol/L)			
>4.775	176	72	0.884
≤4.775	116	49	
FNR			
>0.774	181	78	0.636
≤0.774	111	43	

Abbreviations: CLNM, central lymph node metastasis; AGR, albumin globulin ratio; FNR, fibrinogen-to-neutrophil ratio.

Correlation of FNR with Clinicopathological Features in the Two Cohorts

Using the ideal FNR cut-off value, data were divided into high FNR group (N = 259) and low FNR group (N = 154). Age (P = 0.007), maximum tumor diameter (P = 0.048), neutrophils (P < 0.001), monocytes (P < 0.001), percentage of lymphocytes (P < 0.001), T3 (P = 0.005), and fibrinogen (P < 0.001) were all significantly correlated with FNR (Table 2).

Table 2 Correlations Between FNR and Clinical Characteristics in All Cohorts

Variables	FNR≤0.774 N=154	FNR>0.774 N=259	P-value
Age			
>55Y	73	158	0.007
≤55Y	81	101	
Gender			
Female	95	177	0.168
Male	59	82	
Medicine for diabetes			
Metformin (-)	70	143	0.055
Metformin (+)	84	116	
BMI (kg/m^2)			
>29.7	18	19	0.134
≤29.7	136	240	
Maximum diameter of mass			
>9.5 mm	43	97	0.048
≤9.5 mm	111	162	
Multifocality			
Solitary	99	190	0.052
Multiple	55	69	
CLNM			
CLNM (-)	81	150	0.293
CLNM (+)	73	109	
Laterality			
Unilateral	131	217	0.73
Bilateral	23	42	
Hashimoto's thyroiditis			
Absent	140	225	0.216
Present	14	34	
TC (mmol/L)			
>5.585	40	61	0.58
≤5.585	114	198	
TG (mmol/L)			
>2.325	60	82	0.131
≤2.325	94	177	
HDL (mmol/L)			
>1.245	40	66	0.912
≤1.245	114	193	
LDL (mmol/L)			
>2.755	63	96	0.438
≤2.755	91	163	
Glucose (mmol/L)			
>6.1	116	213	0.091
≤6.1	38	46	
Albumin (g/L)			
>38.95	140	230	0.498
≤38.95	14	29	
Globulin (g/L)			
>32.15	42	87	0.18
≤32.15	112	172	

(*Continued*)

Table 2 (Continued).

Variables	FNR≤0.774 N=154	FNR>0.774 N=259	P-value
AGR			
>1.45	73	118	0.716
≤1.45	81	141	
Neutrophil (x10^9/L)			
>4.395	105	33	<0.001
≤4.395	49	226	
Mononuclear (x10^9/L)			
>0.355	117	149	<0.001
≤0.355	37	110	
Lymphocyte (x10^9/L)			
>1.695	113	178	0.316
≤1.695	41	81	
Lymphocyte (%)			
>28.1	71	206	<0.001
≤28.1	83	53	
Platelet (x10^9/L)			
>255	61	85	0.163
≤255	93	174	
TSH (mIU/L)			
>0.86	115	212	0.082
≤0.86	39	47	
T4 (pmol/L)			
>11.94	42	72	0.908
≤11.94	112	187	
T3 (pmol/L)			
>4.775	106	142	0.005
≤4.775	48	117	
Fibrinogen (g/L)			
>3.145	65	183	<0.001
≤3.145	89	76	

Abbreviations: CLNM, central lymph node metastasis; AGR, albumin globulin ratio.

Univariate and Multivariate Logistic Regression Analyses of Preoperative CLNM

Metformin (P = 0.087), maximum tumor diameter (P < 0.001), triglyceride (TG) (P = 0.001), high-density lipoprotein (HDL) (P = 0.009), lymphocyte (P = 0.032), thyroxine (T4) (P = 0.099), and FNR (P = 0.028) were all associated with CLNM in univariate regression analysis. Multivariate regression analysis was used to identify further the independent risk factors associated with CLNM. The larger the tumor, the lower the TG, HDL, lymphocytes, T4, and FNR, and the more likely CLNM occurred (Table 3).

Build the Predicted Nomogram

A nomogram was created to predict the risk of CLNM using the independent factors screened by multivariate analysis that was included in the analysis (Figure 1). We plotted the scores of each independent predictor and continuously added them to obtain the total score to confirm the likelihood of preoperative CLNM.

Evaluate the Effectiveness of the Nomogram

ROC curves were created using R packages to evaluate the ability of our nomogram to predict CLNM. The AUC of the training set (Figure 2A) and validation set (Figure 2B) were 0.775 and 0.654, respectively, as shown in the figure. It was

Table 3 Univariate and Multivariate Analysis of Logistic Regression in the Training Data Set

Variables	Univariate Analysis of CLNM			Multivariate Analysis of CLNM		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	0.871	0.479–1.585	0.651			
>55Y						
≤55Y						
Gender	0.943	0.483–1.841	0.862			
Female						
Male						
Medicine for diabetes	0.606	0.341–1.076	0.087	0.594	0.347–1.015	0.057
Metformin (-)						
Metformin (+)						
BMI (kg/m^2)	1.705	0.617–4.715	0.304			
>29.7						
≤29.7						
Maximum diameter of mass	6.919	3.637–13.160	<0.001	6.055	3.391–10.811	<0.001
>9.5 mm						
≤9.5 mm						
Multifocality	0.731	0.378–1.411	0.35			
Solitary						
Multiple						
Laterality	1.041	0.461–2.349	0.923			
Unilateral						
Bilateral						
Hashimoto's thyroiditis	1.25	0.514–3.043	0.622			
Absent						
Present						
TC (mmol/L)	1.216	0.519–2.852	0.653			
>5.585						
≤5.585						
TG (mmol/L)	0.28	0.136–0.579	0.001	0.349	0.189–0.647	0.001
>2.325						
≤2.325						
HDL (mmol/L)	0.377	0.182–0.783	0.009	0.316	0.164–0.612	0.001
>1.245						
≤1.245						
LDL (mmol/L)	0.72	0.354–1.463	0.363			
>2.755						
≤2.755						
Glucose (mmol/L)	1.358	0.646–2.852	0.42			
>6.1						
≤6.1						
Albumin (g/L)	0.653	0.252–1.696	0.382			
>38.95						
≤38.95						
Globulin (g/L)	0.56	0.262–1.199	0.136			
>32.15						
≤32.15						
AGR	0.661	0.318–1.374	0.267			
>1.45						
≤1.45						

(*Continued*)

Table 3 (Continued).

Variables	Univariate Analysis of CLNM			Multivariate Analysis of CLNM		
	OR	95% CI	P-value	OR	95% CI	P-value
Mononuclear (x10^9/L)	1.577	0.802–3.103	0.187			
>0.355						
≤0.355						
Lymphocyte (x10^9/L)	0.45	0.216–0.935	0.032	0.539	0.297–0.978	0.042
>1.695						
≤1.695						
Lymphocyte (%)	1.396	0.671–2.906	0.372			
>28.1						
≤28.1						
Platelet (x10^9/L)	0.765	0.403–1.454	0.414			
>255						
≤255						
TSH (mIU/L)	1.344	0.648–2.789	0.427			
>0.86						
≤0.86						
T4 (pmol/L)	0.573	0.296–1.110	0.099	0.539	0.292–0.996	0.049
>11.94						
≤11.94						
T3 (pmol/L)	0.715	0.389–1.314	0.279			
>4.775						
≤4.775						
FNR	0.47	0.239–0.923	0.028	0.494	0.282–0.868	0.014
>3.145						
≤3.145						

Abbreviations: CLNM, central lymph node metastasis; FNR, fibrinogen-to-neutrophil ratio.

demonstrated that the method accurately predicts CLNM. Additionally, according to the Hosmer-Lemeshow test, the calibration diagrams of our recently developed model (Figure 3A and B) were well-fit between the actual and estimated probabilities of CLNM (internal training set, p = 0.677826 > 0.05 and external validation set p = 0.6933441 > 0.05). We

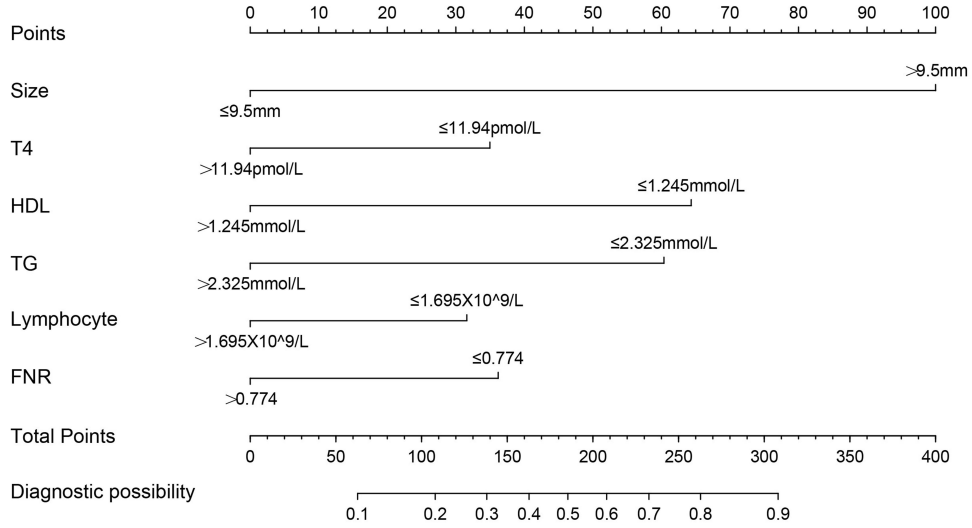

Figure 1 Nomogram for predicting CLNM in patients with T2DM PTC.
Abbreviation: FNR, fibrinogen-to-neutrophil ratio.

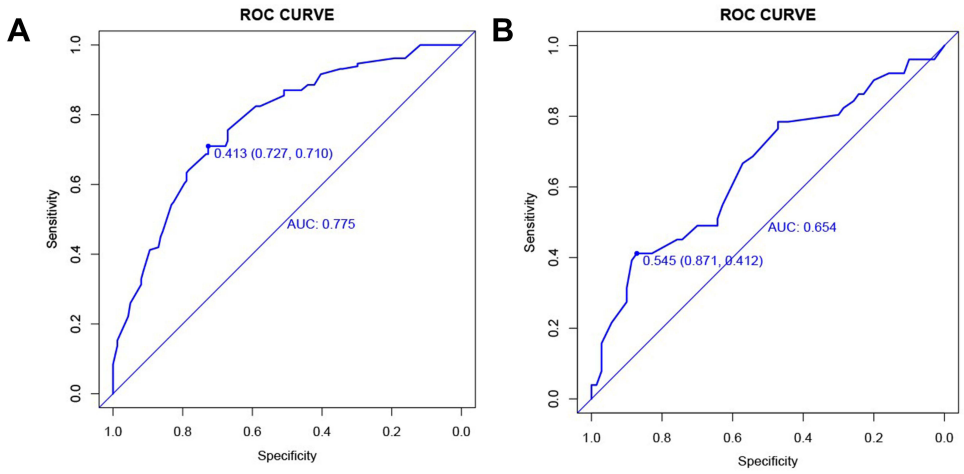

Figure 2 Receiver operating characteristic (ROC) curve analysis. (**A**) Training dataset. (**B**) External validation dataset.

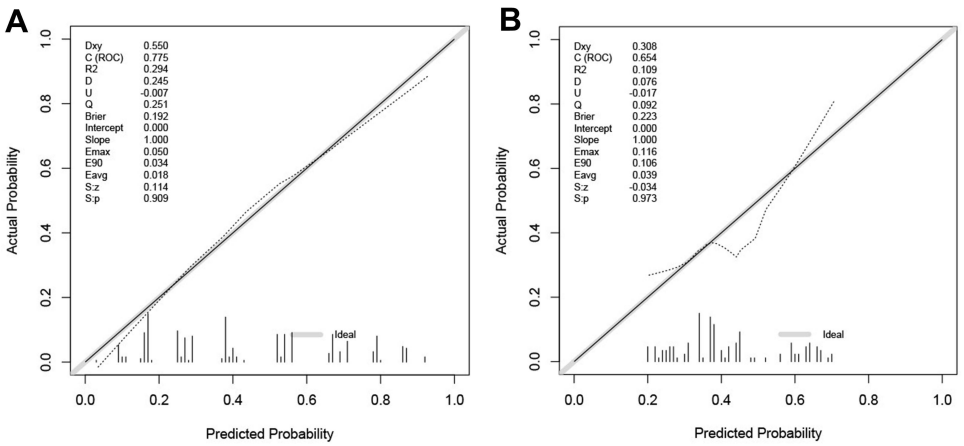

Figure 3 Calibration curve of the nomogram. (**A**) Training dataset. (**B**) External validation dataset.

used DCA to assess whether the benefits of using our predictive model in the clinic outweigh the risks (Figure 4A and B). The ordinate is threshold probability, and the ordinate is a net return. All patients did not receive net benefits from CLND, as indicated by the gray line. The gray dotted line represents the patient's net clinical benefit. The threshold probability range for this rosette was approximately 10–90% in the training set and 30–70% in the validation set, with a higher net clinical benefit when compared with all or none of the patients receiving CLND treatment.

Comparison with the Original Model

We compared our new model with the original one to determine whether it had better test performance. The model constructed by Thompson et al included age, gender, maximum tumor diameter, and multifocality.[23] Inputting our data yielded an AUC of 0.696, which was lower than the new one's AUC of 0.775 (Figure 5A). It demonstrated the new model's improved accuracy. The problem of comparing the diagnostic efficacy of the two models can be resolved by applying NRI and IDI, which quantifies the degree of improvement in the diagnostic efficacy of one index over another. Figure 5B shows NRI = 0.1283 and IDI = 0.0929. Both NRI and IDI showed that the new model's testing efficiency is higher than the original model.

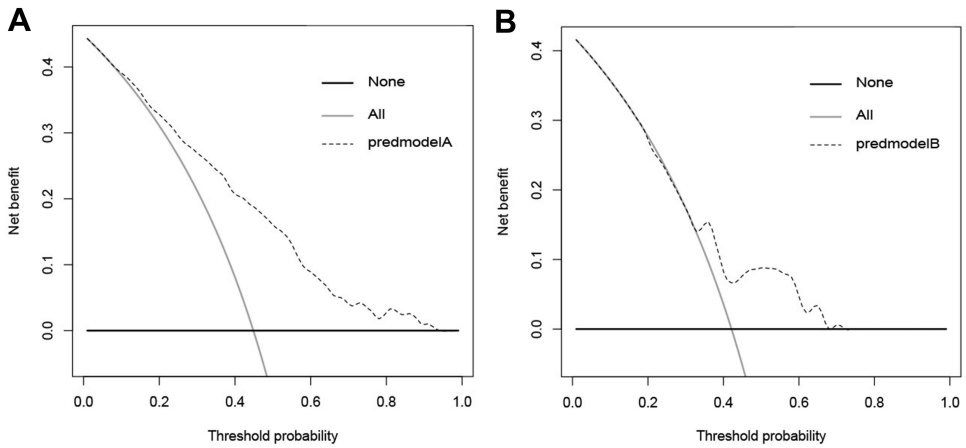

Figure 4 Decision curve analysis (DCA) of nomogram. (**A**) Training dataset. (**B**) External validation dataset.

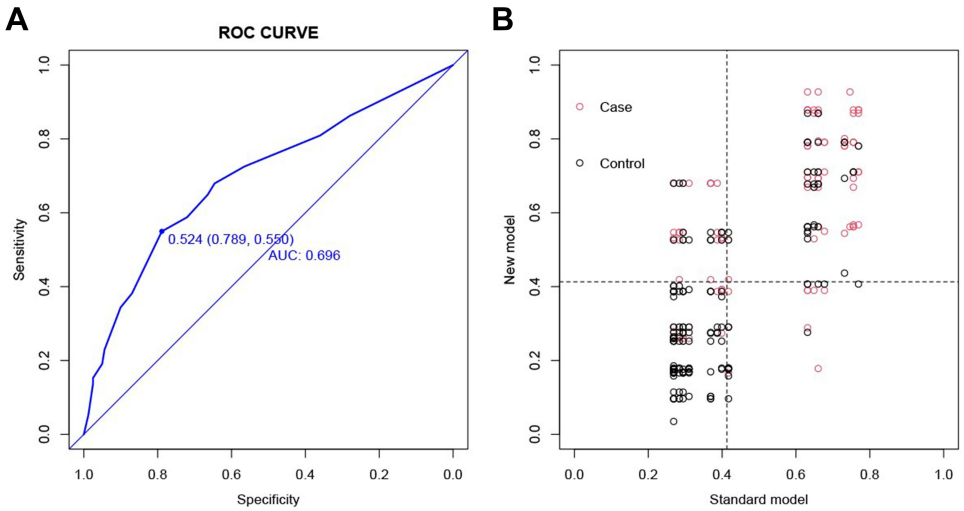

Figure 5 Comparison with original model. (**A**) Receiver operating characteristic (ROC) curve analysis. (**B**) Net reclassification index (NRI).

Discussion

To the best of our knowledge, this study is the first to focus on the relationship between preoperative FNR and CLNM in patients with PTC and T2DM, as well as the relationship between preoperative FNR and cancer FNR and cancer. FNR-related research has not yet been published. Our research remains significant and valuable.

Currently, surgeons typically perform preventive lymph node dissection in patients with PTC's central region of the neck. Still, this practice can raise the danger of postoperative hypocalcemia, which is controversial in CLND research.[10] Ultrasound is still the primary imaging technique for detecting CLNM in PTC among the commonly used clinical diagnosis and treatment approaches. When assessing CLNM of PTC, CT, magnetic resonance imaging, and other imaging techniques are not more effective than ultrasound.[24,25] However, there are high false negatives and poor diagnostic accuracy with ultrasound diagnosis of CLNM in PTC. An important factor in surgical selection is the ability to accurately identify patients who do not require preventive dissection of lymph nodes in the central region of the neck prior to surgery. This issue has become an urgent clinical problem that needs to be resolved.

There is growing evidence that inflammation is a crucial factor inextricably linked to cancer, with neutrophils, monocytes, and other inflammatory cells promoting tumor cell proliferation, survival, and migration.[26] Numerous studies have linked elevated fibrinogen to some malignant tumors' progression and poor prognosis.[20–22] However, studies on the role of FNR in cancer are lacking. According to two large studies, thyroid cancer may be influenced by a history of diabetes.[27,28] Thyroid cancer is more common in people with diabetes than those without,[29] with a 20% increase in incidence compared to those without DM.[30] What's more, according to a study by Xu et al, who used data from a cohort of 36,379 patients with Type 2 DM (T2DM), the crude incidence of thyroid cancer and T2DM in men was 5.01 per 105 person-years. The crude incidence of cancer subtypes for women was 34.97 per 105 person-years, placing women in the top 10.[31] Therefore, we boldly hypothesized that in patients with PTC and T2DM, preoperative FNR was significantly associated with CLNM.

Statistics were used to screen out the independent risk factors for CLNM in 413 patients with PTC and T2DM. These risk factors included maximum tumor diameter >9.5mm, low TG, low lymphocyte, low HDL, low T4, and low FNR. A low FNR value indicated low fibrinogen or high neutrophils. Fibrinogen and neutrophils were known to be associated with poor prognosis of tumors. In our previous data analysis, it was found that there was no significant correlation between CLNM of PTC and T2DM and fibrinogen alone, and the AUC value of the ROC curve for the analysis results of neutrophil number alone was lower than that of FNR. These results indicated that in patients with PTC and T2DM, FNR was a novel and more significant indicator for predicting preoperative CLNM. Tumor size is an independent risk factor for CLNM, supporting earlier studies. Liu et al concluded that the tumor measured 1.0 cm in diameter.[32] The ideal tumor truncation measured was 1.1 cm by Wu et al.[33] In the study by Zhou et al, the ideal truncation value of the tumor was 0.7 cm.[34] In our study, the ideal truncation value was 0.95 cm. TG had various effects on various cancers.[35–39] Studies conducted in Austria showed a positive correlation between TG and thyroid cancer.[37] In our study, patients with PTC and T2DM may have increased CLNM metastasis due to low TG levels. Further studies are needed to verify the mechanism of TG in tumor development, most likely because the Austrian study was prospective, and ours was a case-control study with some selection bias. The lymphocyte's primary component of anti-tumor immunity can activate the release of cytokines such as interferon and tumor necrosis factor-α to play a protective role.[26,40] Low lymphocyte count, which has been regarded as a poor prognostic biomarker,[14,41] was associated with CLNM in this study. Low lymphocyte count may also be associated with activating reactive oxygen species-mediated apoptosis pathways.[42] Recent studies have found a negative correlation between HDL and cancer. HDL may exert anti-inflammatory and antioxidant properties by regulating cytokine production.[43] Further research must be done to determine the specific mechanism of action. In our study, low HDL levels in patients with PTC and T2DM may be associated with CLNM. Li et al found that low T4 levels were only related to capsule infiltration, and routine preoperative serum T4 determination helped identify which patients should undergo surgery.[44] Lower T4 levels were found to be correlated with an increased risk of thyroid cancer.[45]

We constructed relevant programs further to explore the clinical value of this new indicator after it was established that low FNR was an independent risk factor for CLNM in patients with PTC and T2DM. Our nomogram exhibits good discrimination and calibration. Additionally, the ROC curve shows that the rotors are more accurate predictors than the original model.[23] Both NRI and IDI suggest that our model's predictive ability has increased compared to the original model. Because routine tests like blood indicators, blood glucose, and B-ultrasound are performed before each patient is admitted to the hospital for surgery, our model is a simple to use the clinical tool. The model is universal and can facilitate patient consultation and personalized treatment.

This study has some limitations. First, this analysis uses a small sample size. To confirm this, multicenter studies are needed. Second, since this is a retrospective study, data biases such as selection bias are unavoidable. We anticipate developing more accurate indicators and tools to predict CLNM in the future.

In conclusion, FNR is a new predictor and an independent risk factor for CLNM in patients with PTC and T2DM.

Ethical Approval and Informed Consent

The approval of the clinical ethics committee was obtained from the ethics committee of the First Affiliated Hospital of Wenzhou Medical University. This study design was in accordance with the Declaration of Helsinki. All individual participants were aware and signed the informed consent for participation in this study.

Funding

Science and Technology Plan Project of Wenzhou (Y20210258); Natural Science Foundation of Zhejiang Province (LY20H160011).

Disclosure

All authors declare no potential conflicts of interest in this work.

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