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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Thyroid Antibody Status is Associated with Central Lymph Node Metastases in Papillary Thyroid Carcinoma Patients with Hashimoto's Thyroiditis

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ABSTRACT

Objective. The aim of this study was to explore the impact of thyroid antibody status on central lymph node metastases (CLNM) in papillary thyroid carcinoma (PTC) patients with Hashimoto's thyroiditis (HT).

Methods. A retrospective analysis was performed on 346 PTC patients with HT who underwent thyroidectomy and ipsilateral central lymph node dissection (CLND). Histopathological characteristics of the tumor and serum levels of thyroid hormone, as well as antibodies, were collected and analyzed.

Results. The multivariate logistic regression analysis showed that being male [odds ratio (OR) 3.269, 95% confidence interval (CI) 1.240–8.619], tumor size $>$ 1 cm [1 cm $<$ diameter $(D) \leq$ 2 cm: OR 6.947, 95% CI 2.886–16.722; 2 cm $< D$: OR 5.880, 1.937–17.846], and antibody status [thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) double negative: OR 3.791, 95% CI 1.391–10.331; TPOAb and TgAb double positive: OR 4.047, 95% CI 1.509–10.856; TgAb single positive: OR 6.024, 95% CI 2.019–17.970] were independent risk factors for CLNM. Additionally, a risk-score scale, including sex, antibody status, and tumor size, was established to predict CLNM. The sensitivity, specificity, positive predictive value, and negative predictive value were 55.7%, 84.4%, 74.4%, and 70%, respectively, when the cut-off point was chosen as 3.

Conclusions. Antibody status is a critical independent risk factor for CLNM in PTC patients with HT. For the CLND strategy, a more conservative option could be considered in a low-risk cohort with the following characteristics: female sex, smaller tumor size, and TPOAb single positive.

With a rapidly increasing incidence over the past decades, papillary thyroid carcinoma (PTC) has been the most common endocrine malignant tumor worldwide.[1,2] Hashimoto's thyroiditis (HT), otherwise known as chronic lymphocytic thyroiditis (CLT) is the most prevalent of the thyroid autoimmune diseases, accounting for approximately 0.3–1.5 cases per 1000 persons.[2,3] Recently, the crosstalk between PTC and HT has become an interesting field of great concern. Numerous studies identified HT as a risk factor for developing PTC, but as a protective factor for PTC aggressive prognostic characteristics, with regard to lymph node metastases (LNM), tumor stage, multifocality, and BRAF mutations.[1,4–8] However, some investigators reported conflicting results that HT had no significant protective effects, while others even argued its adverse effects on PTC prognosis, especially on the central lymph node metastases (CLNM).[9–12] Therefore, the relationship between PTC and HT remains controversial.

Thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) are important clinical markers for the diagnosis of HT, and were positive in 75% and 90% of HT cases, respectively.[2] The antigen-specific humoral immune responses induced by TPOAb and TgAb are considered to be associated with the development and prognosis of PTC.

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Paparodis et al.[13] reported that high levels of TPOAb appeared to protect against PTC in patients with HT. In contrast, Vasileiadis et al.[9] found a positive correlation between TgAb and LNM in patients with PTC. A further study by Shen et al.[10] revealed a double-edged sword effect of HT when thyroid antibody status varied: TPOAb or TgAb positivity was associated with more metastatic cervical lymph nodes, while single TgAb positivity and combined TgAb and TPOAb positivity, but not single TPOAb positivity, were shown to be related to less distant metastasis. The results of the above studies revealed that the inconsistent conclusions on the relationship between PTC and HT might be due in part to different antibody statuses, despite that the specific correlations are still unclear to date. Therefore, more studies on the effect of thyroid antibody status on the development and metastatic activity of PTC are needed.

The purpose of this study was to explore and analyze the clinicopathological characteristics of PTC patients with HT, mainly to answer the following questions: (1) What are the significant differences in clinical characteristics among PTC patients with different thyroid antibody statuses? (2) Is thyroid antibody status an independent risk factor for prognostic characteristics of PTC patients with HT, especially for CLNM? (3) How can a risk-score scale be established and how can it evaluate the ability to predict CLNM in PTC patients with HT, if results are available?

MATERIALS AND METHODS

The medical records of patients with a final histopathological diagnosis of PTC with HT at Shanghai Changzheng Hospital (Shanghai, China), between December 2014 and November 2018, were retrospectively reviewed. The protocol for this research was approved by the local clinical Ethics Committee, and written informed consent was obtained from each participant. Pathologically proven HT was defined as the presence of diffuse lymphocytic and plasma cell infiltrate, as well as oxyphilic cells, and the formation of lymphoid follicles or reactive germinal centers in the area of normal thyroid tissue. Notably, peritumoral lymphocytic infiltration was not considered as HT.[14,15] Patients with unilateral PTC underwent total thyroidectomy (TT) or unilateral lobectomy plus isthmusectomy and ipsilateral central lymph node dissection (CLND), whereas patients with bilateral PTC underwent TT and bilateral CLND. Patients with isthmus PTC underwent TT and bilateral CLND. To eliminate potential confounding bias, the following exclusion criteria were applied: (1) serious medical record deficiency; (2) a history of thyroidectomy or radiotherapy to the head and neck region; (3) a history of long-term antithyroid or thyroid hormone replacement therapy; and (4) it had been pathologically proven that none of the lymph node was found in the CLND.

Age, sex, preoperative serum levels of triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), thyrotrophin (TSH), TPOAb, and TgAb, as well as postoperative pathological characteristics of concomitant nodular goitre (NG), tumor size, multifocality, bilaterality, extrathyroidal invasion, and CLNM were recorded for each patient. The normal ranges for serum levels of T3, T4, FT3, FT4, TSH, TPOAb, and TgAb were 1.3–3.1 nmol/L, 62–164 nmol/L, 3.1–6.8 pmol/L, 12–22 pmol/L, 0.27–4.2 mIU/L, 0–34 IU/L, and 0–115 IU/L, respectively, at our institution. Thyroid antibody status was considered positive if its serum level was over the upper range. Multifocality was defined as two or more tumor foci within the thyroid gland. For multifocal tumors, tumor size was calculated as the sum of the diameters of all tumor foci, which was reported as a more accurate predictor of node status than primary tumor size.[16,17] Bilaterality was considered as tumors located in both lobes.

All patients were divided into the training and validation cohorts according to the operation time. The cases between May 2018 and November 2018 were defined as the validation cohort, while cases prior to April 2018 were defined as the training cohort, and were classified into four groups based on antibody status: (a) TPOAb single positive (TPOAb+); (b) TPOAb and TgAb double negative (Tab−); (c) TPOAb and TgAb double positive (Tab+); and (d) TgAb single positive (TgAb+). The clinicopathological characteristics of the training cohort were compared, primarily to identify the potential dependent variables influenced by different antibody statuses. Second, univariate analysis of the selected dependent variables was performed. The multivariate analysis of significant factors was then implemented to determine the independent risk factors. Finally, we attempted to establish and validate a risk-score scale based on the independent risk factors.

Statistical Analysis

The Kruskal–Wallis H test was used to compare the mean values among the groups, and Pearson's Chi square test was used to compare categorical variables. Student's t test, Mann–Whitney U test, and Pearson's Chi square test were used to perform univariate analysis of the selected dependent variables. Variables with a p value < 0.100 in the univariate analysis were considered significant and were hence included in the multivariate analysis. Logistic regression analysis was applied to identify the independent risk factors. The predictive value of the risk-score scale was evaluated by receiver operating characteristic (ROC) curve analysis. A probability (p) value of < 0.050 was

considered significant. All data were processed using IBM SPSS Statistics for Windows version 23.0 (IBM SPSS, Inc., Chicago, IL, USA), and the figures were generated using Graph Pad Prism 5 for Windows version 5.01 (Graph Pad Software, Inc., San Diego, CA, USA).

RESULTS

Overall, 346 cases were included in this study (Fig. 1). All clinicopathological characteristics of the training cohort are presented in Table 1, and reveal that the different antibody statuses of TPOAb and TgAb have no effects on thyroid function and some aggressive features, such as multifocality ($p = 0.616$), bilaterality ($p = 0.957$), and extrathyroidal invasion ($p = 0.462$). However, there were significant differences in tumor size and CLNM among the groups. The incidence of CLNM was only 22.2% in the TPOAb+ group, strikingly lower than that in the TAb+ group (50%) and the TgAb+ group (57.1%; $p = 0.009$). The data shown in Table 1 suggest the different HT types based on antibody status have no effects on thyroid function, but obvious effects on CLNM.

To identify whether thyroid antibody status was a risk factor for CLNM in PTC patients with HT, all clinicopathological characteristics were compared based on the presence of CLNM (Table 2). As detailed in Table 2, the majority of clinicopathological features, except thyroid hormone levels and extrathyroidal invasion, had significant differences ($p < 0.100$). Older patients (age > 45 years) and males both had a higher probability of CLNM (older: 52.5% vs. 39.1%, $p = 0.033$; male sex: 14.8% vs. 7.1%, $p = 0.046$), and larger tumor size was strongly associated with CLNM ($p < 0.001$). Multifocality and bilaterality were more common in the CLNM+ group compared with the CLNM − group (multifocality: $p = 0.005$; bilaterality: $p = 0.011$).

As shown in Table 2, age, sex, concomitant NG, thyroid antibody status, tumor size, multifocality, and bilaterality were included in the multivariate analysis, after univariate analysis. It was found that male sex, antibody status, and tumor size were independent variables for the prediction of CLNM. Specifically, male sex, compared with female sex, increased the risk of CLNM more than threefold [OR 3.269, 95% confidence interval (CI) 1.240–8.619, $p = 0.017$]. Focusing on tumor size, there was no significant difference between $0.5 < D \leq 1$ cm and $0 < D \leq 0.5$ cm ($p = 0.371$). However, $1 < D \leq 2$ cm and 2 cm $< D$ increased CLNM risk by 6.947- and 5.880-fold to $0 < D \leq 0.5$ cm, respectively ($p < 0.05$). Encouragingly, antibody status presented an appreciable predictive value of CLNM: TgAb+ was a strong risk factor and showed a greater than sixfold significantly increased risk of CLNM compared with TPOAb+ (OR 6.024, 95% CI 2.019–17.970, $p = 0.001$). In summary, multivariate analysis revealed that antibody status and tumor sizes > 1 cm were considerable predictive factors for CLNM in PTC patients with HT, rather than multifocality, bilaterality, and extrathyroidal invasion.

A risk-score scale was established for the preoperative prediction of CLNM in PTC patients with HT (Table 3). This scale contained items of sex, antibody status, and tumor size, based on the results of the logistic regression

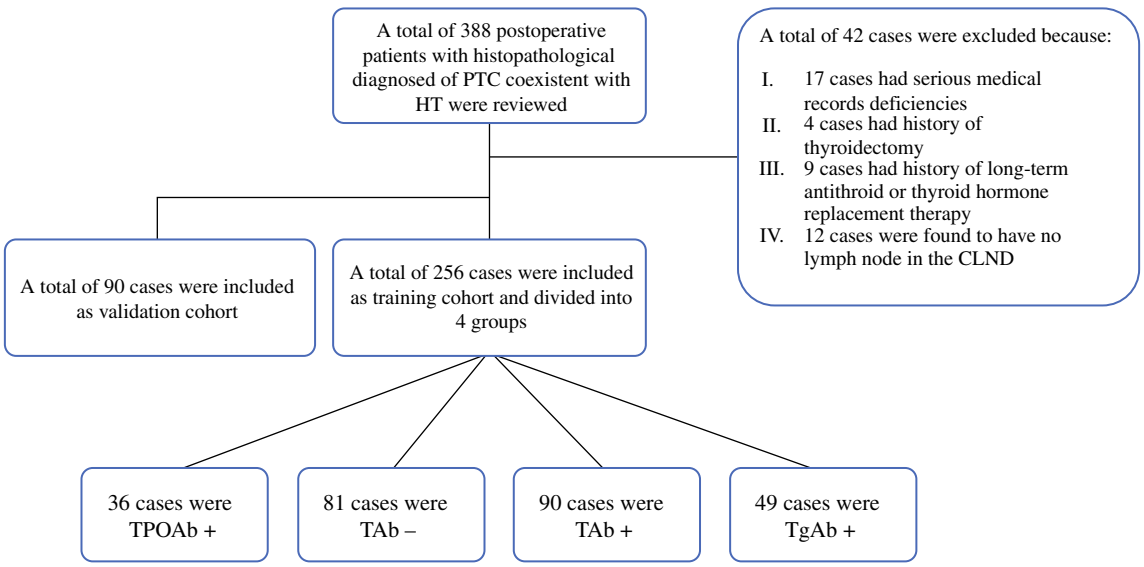

FIG. 1 Case selection process for this study. *PTC* papillary thyroid carcinoma, *HT* Hashimoto's thyroiditis, *CLND* central lymph node dissection, *TPOAb+* thyroid peroxidase antibody single positive, *TAb−* TPOAb and TgAb double negative, *TAb+* TPOAb and TgAb double positive, *TgAb+* thyroglobulin antibody single positive

TABLE 1 Clinicopathological features of 256 PTC patients with HT stratified by antibody status

Variables	TPOAb+ [*n* = 36]	TAb− [*n* = 81]	TAb+ [*n* = 90]	TgAb+ [*n* = 49]	*p* value
Age ≥ 45 years [*n* (%)]	17 (47.2)	38 (46.9)	39 (43.3)	25 (51.0)	0.855[a]
Male sex [*n* (%)]	6 (16.7)	11 (13.6)	6 (6.7)	4 (8.2)	0.267[a]
Concomitant NG [*n* (%)]	7 (19.4)	20 (24.7)	15 (16.7)	5 (10.2)	0.209[a]
T3, mmol/L [median (range)]	1.62 (1.18–2.4)	1.65 (1.00–2.35)	1.59 (1.10–2.35)	1.59 (1.19–2.24)	0.405[b]
T4, mmol/L [median (range)]	89.83 (11.3–143.9)	93.04 (65.29–133.30)	93.04 (46.7–174.0)	90.6 (63.85–115.8)	0.417[b]
FT3, pmol/L [median (range)]	4.65 (3.27–6.32)	4.59 (2.89–6.77)	4.61 (3.20–7.21)	4.51 (3.66–5.53)	0.767[b]
FT4, pmol/L [median (range)]	16.04 (10.56–20.26)	16.40 (12.01–22.66)	15.80 (7.05–27.55)	15.62 (9.00–20.76)	0.345[b]
TSH, mIU/L [median (range)]	2.39 (0.15–15.40)	2.61 (0.01–13.11)	3.07 (0.04–47.25)	2.64 (0.34–10.47)	0.263[b]
Tumor size, cm [median (range)]	0.7 (0.2–3.9)	0.7 (0.1–4.8)	1 (0.1–7.0)	1 (0.2–3.0)	**0.040**[b]
Multifocality [*n* (%)]	9 (25.0)	19 (23.5)	29 (32.2)	14 (28.6)	0.616[a]
Bilaterality [*n* (%)]	7 (19.4)	16 (19.8)	18 (20)	8 (16.3)	0.957[a]
Extrathyroidal invasion [*n* (%)]	5 (13.9)	15 (18.5)	18 (20)	5 (10.2)	0.462[a]
CLNM [*n* (%)]	8 (22.2)	34 (42.0)	45 (50.0)	28 (57.1)	**0.009**[a]

Bold values indicate statistical significance ($p < 0.05$)

PTC papillary thyroid carcinoma, *HT* Hashimoto's thyroiditis, *TPOAb+* thyroid peroxidase antibody single positive, *TAb−* TPOAb and TgAb double negative, *TAb+* TPOAb and TgAb double positive, *TgAb+* thyroglobulin antibody single positive, *T3* triiodothyronine, *T4* thyroxine, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyrotrophin, *NG* nodular goitre, *CLNM* central lymph node metastases

[a]Pearson's Chi square test

[b]Kruskal–Wallis *H* test

analysis. Standard assignment was on the basis of the regression coefficient B values, and the B value of sex ($B = 1.184$) was selected as the base value (1 point). Evaluation of the scale included internal validation of the training cohort and external validation of the validation cohort. Detailed composition of the validation cohort based on the scale items is presented in Table 3. The predictive value of the risk-score scale to discriminate CLNM was determined by ROC analysis, and the area under the curve (AUC) of the internal and external validations was 0.735 (95% CI 0.673–0.797, $p < 0.001$) and 0.763 (95% CI 0.667–0.860, $p < 0.001$), respectively (Fig. 2). The maximum Jordan index was 0.4 when the cut-off point was chosen as 3 in the internal validation, with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy scores of 55.7%, 84.4%, 74.4%, 70%, and 70.18%, respectively. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy scores from our scale in the external validation were 59.5%, 79.2%, 71.4%, 69.1%, and 70.0%, respectively, which were approximately consistent with the internal validation. The risk of CLNM in all 346 PTC patients with HT could be stratified into the low-, moderate-, and high-risk groups according to the scores, which were defined as 0–1 points, 2–3 points, and 4–5 points, respectively. The high-risk group had the highest probability (36/42, 85.7%) for occurrence of CLNM compared with the moderate-risk (79/146, 54.1%) and low-risk (42/158, 26.6%) groups ($p < 0.001$). In addition, the risk of CLNM in the 0 points group (3/29, 10.3%) was significantly lower compared with the 1-point group (39/129, 30.2%; $p = 0.028$).

DISCUSSION

The present studies have documented that HT was significantly associated with development and prognosis of PTC.[1,6–8,11,13,18–20] Different antibody statuses of HT might lead to varied effects of HT on PTC, which provoked the controversy of the relationship between HT and PTC.[9,10,21,22] Karatzas et al.[21] and Vasileiadis et al.[9] reported that positive TgAb was closely associated with multifocality, bilaterality, LNM, and capsule penetration in PTC patients. In addition, Paparodis et al.[13] reported that a high level of TPOAb appeared to protect against PTC in patients with HT. These studies indicated that different HT types classified by TPOAb and TgAb may have distinctly different effects on the aggressive prognostic characteristics of PTC. Unfortunately, most studies evaluated the clinical characteristics in PTC patients stratified only by the presence of HT, or only focused on single TPOAb or single TgAb status. There are a dearth of studies assessing the four antibody statuses in PTC patients with HT; however, this is the first study to explore the significant differences in clinical characteristics in PTC patients with HT among the

TABLE 2 Univariate and multivariate analysis of 256 PTC patients with HT for CLNM

Variables	Univariate analysis			Multivariate analysis			
	CLNM+ [n = 115]	CLNM− [n = 141]	p-Value	B	OR	95% CI	p-value
Age (≥ 45 years [n (%)]	45 (39.1)	74 (52.5)	**0.033**[a]	0.0514	0.598	0.337–1.062	0.079
Male sex [n (%)]	17 (14.8)	10 (7.1)	**0.046**[a]	1.184	3.269	1.240–8.619	**0.017**
Concomitant NG [n (%)]	16 (13.9)	31 (22.0)	**0.097**[a]	−0.338	0.713	0.336–1.513	0.379
T3, mmol/L [median (range)]	1.59 (1.03–2.32)	1.64 (1.00–2.40)	0.387[b]				
T4, mmol/L[median (range)]	91.62 (11.3–174.00)	93.1 (62.04–157.30)	0.290[b]				
FT3, pmol/L [median (range)]	4.51 (3.03–6.77)	4.61 (2.89–7.21)	0.956[b]				
FT4, pmol/L) [mean (SD)]	15.95 (2.68)	16.21 (2.35)	0.407[c]				
TSH, mIU/L [median (range)]	2.64 (0.01–47.25)	2.82 (0.15–15.40)	0.941[b]				
Antibody status [n (%)]			**0.009**[a]				**0.012**
TPOAb+[e,f,g]	8 (7.0)	28 (19.9)		1.000	1.000	Reference	
TAb−[d]	34 (29.6)	47 (33.3)		1.333	3.791	1.391–10.331	**0.009**
TAb+[d]	45 (39.1)	45 (31.9)		1.398	4.047	1.509–10.856	**0.005**
TgAb+[d]	28 (24.3)	21 (14.9)		1.796	6.024	2.019–17.970	**0.001**
Tumor sizes, cm[n (%)]			**<0.001**[a]				**<0.001**
$0 < D \leq 0.5$[j,k]	17 (14.8)	49 (34.8)		1.000	1.000	Reference	
$0.5 < D \leq 1$[j,k]	32 (27.8)	63 (44.7)		0.371	1.449	0.688–3.052	0.330
$1 < D \leq 2$ [h,i]	47 (40.9)	19 (13.5)		1.938	6.947	2.886–16.722	**<0.001**
$2 < D$[h,i]	19 (16.5)	10 (7.1)		1.771	5.880	1.937–17.846	**0.002**
Multifocality [n (%)]	42 (36.5)	29 (20.6)	**0.005**[a]	−0.122	0.885	0.315–2.490	0.817
Bilaterality [n (%)]	30 (26.1)	19 (13.5)	**0.011**[a]	−0.349	1.417	0.448–4.481	0.553
Extrathyroidal invasion [n (%)]	21 (18.3)	22 (15.6)	0.571[a]				

Bold values indicate statistical significance ($p < 0.05$)

B regression coefficient, *OR* odds ratio, *CI* confidence interval, *D* sum of the diameter of all lesions' diameters, *CLNM+* positive central lymph node metastases, *CLNM−* negative central lymph node metastases, *SD* standard deviation, *PTC* papillary thyroid carcinoma, *HT* Hashimoto's thyroiditis, *NG* nodular goitre, *TPOAb+* thyroid peroxidase antibody single positive, *TAb−* TPOAb and TgAb double negative, *TAb+* TPOAb and TgAb double positive, *TgAb+* thyroglobulin antibody single positive, *T3* triiodothyronine, *T4* thyroxine, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyrotrophin

[a]Pearson's Chi square test

[b]Mann–Whitney *U* test

[c]Student's *t* test

[d]Pearson's Chi square test $p < 0.05$ vs. TPOAb+

[e]Pearson's Chi square test $p < 0.05$ vs. TAb−

[f]Pearson's Chi square test $p < 0.05$ vs. TAb+

[g]Pearson's Chi square test $p < 0.05$ vs. TgAb+

[h]Pearson's Chi square test $p < 0.05$ vs. $0 < D \leq 0.5$

[i]Pearson's Chi square test $p < 0.05$ vs. $0.5 < D \leq 1$

[j]Pearson's Chi square test $p < 0.05$ vs. $1 < D \leq 2$

[k]Pearson's Chi square test $p < 0.05$ vs. $2 < D$

four different antibody status groups, and to investigate whether antibody status is an independent risk factor for prognostic characteristics of PTC, especially for CLNM.

In this study, there were significant differences among four different antibody status groups in terms of tumor size ($p = 0.040$) and CLNM ($p = 0.009$). Moreover, the TgAb+ group presented the highest incidence of CLNM (57.1%), while the TPO+ group showed the least incidence of CLNM (22.0%) among different antibody status groups. This finding suggested TgAb might be a risk factor of CLNM in PTC patients with HT. A previous study by Liang et al.[23] demonstrated that multifocality and age < 45 years were independent risk factors of CLNM in PTC patients with HT; however, antibody status was excluded in the multivariate analysis. Nevertheless, our multivariate analysis found that male sex, antibody status, and tumor

TABLE 3 The risk-score scale of CLNM in PTC patients with HT and the frequency composition of 90 patients in the validation cohort

Variables	Value (points)	Verification cohort		
		CLNM+ [n = 42]	CLNM− [n = 48]	p value
Sex				
Female	0	35	45	0.218[b]
Male	1	7	3	
Antibody status				
TPOAb+	0	3	17	**0.010**[a]
TAb−	1	13	11	
TAb+	1	12	12	
TgAb+	2	14	8	
Tumor size, cm				
$D \leq 1$	0	15	33	**0.002**[a]
$D > 1$	2	27	15	

Bold values indicate statistical significance ($p < 0.05$)

TPOAb+ thyroid peroxidase antibody single positive, *TAb−* TPOAb and TgAb double negative, *TAb+* TPOAb and TgAb double positive, *TgAb+* thyroglobulin antibody single positive, *D* sum of the diameter of all lesions

[a]Pearson's Chi square test

[b]Correction of continuity Chi square test

size > 1 cm were considerable predictive independent risk factors of CLNM in PTC patients with HT, rather than age, multifocality, bilaterality, and extrathyroidal invasion. These inconsistent results might be due to the differences in the inclusion of variables.

It is worth noting that the TgAb+ group showed a greater than sixfold significantly increased risk of CLNM compared with the TPOAb+ group (OR 6.024, 95% CI 2.019–17.970, $p = 0.001$), which confirmed the tumor-progressing feature of TgAb in PTC patients with HT. Concordant with our data, Vasileiadis et al.[9] revealed that the incidence of LNM in PTC patients with positive TgAb (20.3%) was significantly higher than that in patients with negative TgAb (10%). In contrast, Paparodis et al.[13] reported that high titers of TPOAb led to a decreased risk of developing PTC. Interestingly, our data also demonstrated that the TAb− group (OR 3.791, 95% CI 1.391–10.331, $p = 0.009$) and the TAb+ group (OR 4.047, 95% CI 1.509–10.856, $p = 0.005$) had a similar significantly increased risk of CLNM—by almost fourfold compared with the TPOAb+ group. Together, these observations suggest that the tumor-progressing effect of TgAb might be counteracted by the tumor-protecting effect of TPOAb. This interesting counteraction might be explained by (1) TPOAb-dependent complement-mediated cell death;[24] and (2) TPOAb-dependent cell toxicity via Fc-g receptor I (CD64), which is known to be expressed on monocytes.[25]

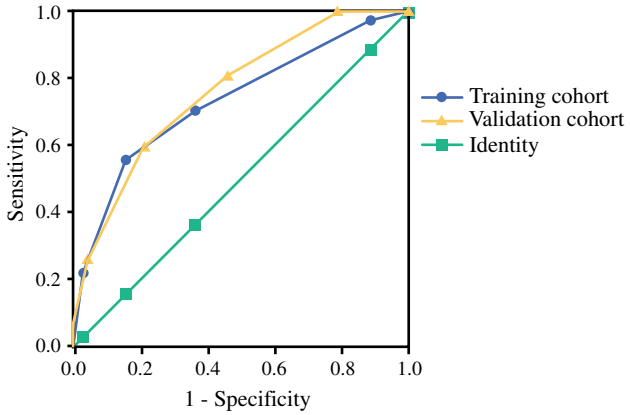

FIG. 2 Receiver operating characteristic curve of the risk-score scale for the prediction of central lymph node metastases in papillary thyroid carcinoma patients with Hashimoto's thyroiditis. The area under the curve of the training and validation cohorts was 0.735 and 0.763, respectively

Our study provided the first risk-score scale for preoperatively predicting CLNM in PTC patients with HT. As we know, CLNM is a critical predictor for risk of locoregional recurrence and lateral LNM of PTC.[26–28] However, several studies have confirmed that HT is linked to an increased number of benign hyperplastic cervical lymph nodes.[6,29,30] Whether prophylactic CLND should be routinely performed may be a dilemma to surgeons with regard to the potential risks of technical difficulty and complications in the background of HT. Therefore, our risk-score scale, with an accuracy of 70.18% in internal validation and 70.0% confirmed in external validation, can be applied to assess the possibility of CLNM in PTC patients with HT. We stratified the risk of CLNM into low-, moderate-, and high-risk groups, with a 26.6%, 54.1%, and 85.7% possibility of CLNM, respectively. According to our data, CLND should be strongly recommended in the high-risk group. However, in contrast, a more conservative option could be considered in the low-risk group, composed of individuals who were female, had a smaller tumor size, and were TPOAb+, especially in the 0 points group, which had a significant lower proportion of CLNM compared with others (3/29, 10.3%).

This study has some limitations. First, some clinicopathological characteristics, such as BRAF and TERT mutation status, were not investigated due to selective screening, which might reduce the identical degree of multivariate analysis for CLNM. Second, the sample size was small, which might have interfered with selection of the independent risk factors of CLNM in PTC patients with HT. For example, age < 45 years ($p = 0.079$) may become

an independent risk factor if the sample is expanded. Third, the proportion of CLNM in the low-risk group (26.6%) was still not low enough to avoid CLND in the case of the above two limitations. The accumulation of the sample and inclusion of more potential risk factors were in progress to improve the AUC and accuracy of our scale, and a further prospective large sample study is still needed to evaluate the tumor-protecting and tumor-progressing effects of specific thyroid antibody status, focusing on LNM, recurrence, and mortality. These limitations remain to be studied in subsequent work.

CONCLUSIONS

This retrospective study showed that with regard to the incidence of CLNM, significant differences were found among different antibody statuses in PTC patients with HT. The TgAb+ group presented the highest incidence of CLNM, while the TPO+ group showed the lowest. Additionally, multivariate analysis for CLNM suggested that male sex, tumor size, and antibody status are independent risk factors for CLNM. Moreover, a simple scale, with an accuracy of 70.18%, can be applied to assess the possibility of CLNM in PTC patients with HT. CLND should be strongly recommended in the high-risk group, and a more conservative option could be considered in the low-risk group, which is composed of individuals who are female, have a smaller tumor size, and are TPOAb+.

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