A Nomogram Predicting Central Lymph Node Metastasis for Patients with Papillary Thyroid Cancer

Yu Min

The Second Affiliated Hospital of Chongqing Medical University

Yang Feng

The Second Affiliated Hospital of Chongqing Medical University

Ke Xiang

The Second Affiliated Hospital of Chongqing Medical University

Hang Chen

The Second Affiliated Hospital of Chongqing Medical University

Xing Wang

The Second Affiliated Hospital of Chongqing Medical University

Guobing Yin (✉ yinguobing@cqmu.edu.cn)

The Second Affiliated Hospital of Chongqing Medical University <https://orcid.org/0000-0002-7031-9063>

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Abstract

Purpose

Central lymph node metastasis (CLNM) has been regarded as a predictor of relatively poor prognosis in patients with papillary thyroid carcinoma (PTC). Our study aimed to identify the risk factors for CLNM and develop a nomogram helping clinical decisions.

Method

A total of 1,054 patients underwent thyroidectomy between January 2019 and September 2020 in the Second Affiliated Hospital of Chongqing Medical University. Among these patients, 747 patients with histopathologically confirmed PTC were included in this retrospective study. The perioperative clinical data of these patients were reviewed and analyzed. Univariate and multivariate logistic regression were used to analyze the correlation between clinicopathological characteristics and CLNM. A nomogram model was subsequently established and validated by a decision curve analysis (DCA) curve.

Result

33.6% (251/747) patients with PTC were confirmed with CLNM. And the CLNM was determined in 31.4% (168/535) non-Hashimoto's thyroiditis (HT) patients and 39.2% (83/212) HT patients, respectively. 4 clinicopathological factors including gender, age, size, and HT were confirmed significantly associated with CLNM. The established nomogram showed promising discrimination and consistency in the study group with a C-index of 0.703. The decision curve analysis showed the nomogram has clinical feasibility.

Conclusion

Our data suggested that male gender, younger age, larger tumor size, and HT condition played a pivotal role in promoting the CLNM of PTC patients. And the nomogram we developed can help surgeons make the individualized clinical decision in PTC patients during preoperative and intraoperative management.

Introduction

Over the past few years, the incidence and detection rate of papillary thyroid carcinoma (PTC) was rapidly increased on a global scale, which has become the most prevalent endocrine-related malignancy ¹⁻³. Despite a favorable long-term prognosis ^{4,5}, a minority of patients with central lymph node metastasis (CLNM) and even lateral lymph node metastasis (LLNM) showed relatively poor prognosis ⁶. Currently, great achievements have been made in a range of works in determining the risk factors in the progression of PTC ⁷⁻⁹. Especially, many clinical characteristics including but not limited to the male gender, younger age, larger tumor size, multifocal lesions, and extracapsular spread were regarded as the independent risk factors involving in the lymph node metastasis of PTC.

On the other side, Hashimoto's thyroiditis (HT), known as chronic lymphocytic thyroiditis, is the most prevalent autoimmune disease nowadays¹⁰. It causes chronic inflammation and damage in thyroid tissues via over-expression of thyroid globulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb), leading to a condition of hypothyroidism in about 20–30% of patients ultimately. Although a high concurrent rate of HT and PTC has been found since last century^{11,12}, yet the relationship between these two diseases remains highly controversial. Some data from relevant literature suggested that PTC patients coexisting with HT had lower staging and better prognosis, compared with non-HT patients^{13–17}. The potential mechanisms are partly due to the modulation of the tumor microenvironment, the induction of abnormally immune responses and lymphocytic infiltrates in tumor tissue. However, some other studies have reported that the coexistence of HT has no protective effect on patient outcome^{18,19}. Furthermore, some scholars even suggested the high thyroid antibody status, especially serum TgAb level, could be a risk factor in promoting the CLNM of PTC patients^{20,21}. For this reason, more clinical trials focusing on the effect of HT on the progression of PTC are merited.

The purpose of this retrospective study was to evaluate the role of clinicopathological risk factors including HT in the predicting of CLNM for PTC patients. Besides, we aimed to establish a prediction model based on the clinicopathological features helping clinical decisions.

Material And Method

Patients

Patients with the postoperative histopathological diagnosis of PTC with or without HT at the Second Affiliated Hospital of Chongqing Medical University between January 2019 and October 2020 were reviewed and analyzed. The protocol for this study was approved by the Chongqing Medical University Ethics Committee, and written informed consent was obtained from each participant. The following information was collected to establish a retrospective database: gender, age, maximum tumor diameter, condition of extracapsular extension, the status of CLNM and LLNM, HT (histological diagnosed of diffuse lymphocyte infiltration in thyroid tissue), multifocality, and BRAF^{V600E} mutation status.

The inclusion and exclusion criteria were as follows:

Patients were enrolled during the study period using the following inclusion criteria:

- 1) aged between 18–75 years
- 2) underwent thyroidectomy and neck lymph node dissection (LND).

Patients were excluded during the study period using the following exclusion criteria:

- 1) no histologically proven PTC (n = 121)

2) no lymph nodes found in the final pathological report (n = 90)

3) history or coexistence of other head and neck cancer (n = 42)

4) incomplete or missing medical records (n = 54)

After exclusion, a total of 747(157 male; 590 female) consecutive patients that had histopathological confirmed PTC, and received thyroidectomy along with CLNM were studied.

The resected surgical specimens were processed for postoperative pathological examination (including the determination of unifocal or multifocal PTC). All acquired surgical specimens were examined by two or more board-certified pathologists from the department of pathology of the Second Affiliated Hospital of Chongqing Medical University.

Statistical Analysis

Baseline characteristics by HT were compared using chi-square tests. Univariate and multivariate logistic regression analyses were used to identify the independent risk factors in patients. A P-value of < 0.05 was defined as the criterion for variable deletion when performing backward stepwise selection. A nomogram of risk factors associated with CLNM based on the results of the multivariate logistic regression analysis was developed and validated by a decision curve analysis (DCA) curve. All analyses were performed using the R 2.15.3 software.

Results

Baseline clinicopathological characteristics

747 patients who met inclusion criteria were included in the present study. The clinicopathological characteristics of these patients stratified by HT were summarized in Table 1. Among these patients, female patients (590/747, 79%) accounted for most of the study group, compared with male patients (157/747, 21%). Additionally, based on the surgical specimens, the CLNM was ultimately confirmed in 251 (33.6%) PTC patients, and 58 (7.8%) of patients were histopathologically confirmed to have LLNM.

Table 1
Clinicopathological features of 747 PTC patients with HT or without HT

Variables	Subgroup	No. (%) of patients		
		without HT (n = 535)	with HT (n = 212)	P
Gender	male	145(27.1)	12(5.7)	< 0.001
	female	390(72.9)	200(94.3)	
Age	< 55	414(77.4)	175(82.5)	0.119
	≥ 55	121(22.6)	37(17.5)	
Tumor size (cm)	≤ 1	361(67.5)	135(63.7)	0.175
	> 1 and ≤ 2	127(23.7)	62(29.2)	
	> 2 and ≤ 4	40(7.5)	15(7.1)	
	> 4	7(1.3)	0(0.0)	
Multifocality	positive	202(37.8)	79(37.3)	0.900
	negative	333(62.2)	133(62.7)	
Extrathyroidal invasion	positive	46(8.6)	16(7.5)	0.639
	negative	489(91.4)	196(92.5)	
BRAF mutation	No	30(5.6)	15(7.1)	0.719
	Yes	421(78.7)	166(78.3)	
	NA	84(15.7)	31(14.6)	
Central LNM	No	367(68.6)	129(60.8)	0.043
	Yes	168(31.4)	83(39.2)	
Lateral LNM	No	493(92.1)	196(92.5)	0.889
	Yes	42(7.9)	16(7.5)	
TNM stage	I	504(94.2)	198(93.4)	0.462
	II	19(3.6)	11(5.2)	
	III	12(2.2)	3(1.4)	
Abbreviation: HT: Hashimoto's thyroiditis; LNM: lymph node metastasis.				
Bold values indicate statistical significance (<i>p</i> < 0.05)				

According to the postoperative histopathological examination, a total of 212 (28.4%) PTC patients were diagnosed coexisting with HT. As expected, a significantly higher proportion of the female population was found in patients with concurrent HT compared to patients without HT ($p < 0.001$). Besides, the CLNM was determined in 168 (31.4%) non-HT patients and 83 (39.2%) HT patients. However, there was no significant difference between these two datasets in terms of the prevalence of LLNM ($p = 0.889$). Furthermore, there was no significant difference in age, tumor size, multifocality, extrathyroidal invasion, TNM stage, and BRAF^{v600E} mutation

Univariate And Multivariate Analysis Of Clnm

During univariate analysis, gender ($p < 0.001$), age ($p = 0.014$), tumor size ($p < 0.001$), and HT ($p = 0.044$) were found as the potential risk factors associated with CLNM in PTC patients (Table 2). Multivariate logistic regression modeling was further developed to screen for significant variables associated with CLNM. Specifically, results were as follows: male gender (OR = 2.426, 95%CI: 1.628–3.614, $p < 0.001$), the risk of CLNM increased as the diameter of the primary nodule increases, (1cm < largest diameter $\leq$ 2cm, OR = 3.315, 95%CI: 2.309–4.760; 2cm < largest diameter $\leq$ 4cm, OR = 5.270, 95%CI: 2.908–9.552; 4 < largest diameter, OR = 5.072, 95%CI: 1.083–23.748; $p < 0.001$), and present HT condition (OR = 1.678, 95%CI: 1.161–2.424, $p = 0.006$). On the contrary, aged elder than 55 years (OR = 0.583, 95%CI: 0.382–0.890, $p < 0.001$) was a protective factor in CLNM.

Table 2
Univariate and multivariate analysis of 747 PTC patients for CLNM

Univariate and multivariate analysis of 747 T1b patients for CLNM					
Variables	Subgroup	Univariable		Multivariable	
		Hazard ratio	P	Hazard ratio	P
Gender	female	1	≤ 0.001	1	≤ 0.001
	male	1.945(1.357, 2.787)		2.426(1.628, 3.614)	
Age	< 55	1	0.014	1	0.012
	≥ 55	0.607(0.409, 0.902)		0.583(0.382, 0.890)	
Tumor size (cm)	≤ 1	1	≤ 0.001	1	≤ 0.001
	> 1 and ≤ 2	3.202(2.252, 4.552)		3.315(2.309, 4.760)	
	> 2 and ≤ 4	4.752(2.667, 8.466)		5.270(2.908, 9.552)	
	> 4	4.224(0.932, 19.142)		5.072(1.083, 23.748)	
Multifocality	negative	1	0.372		
	positive	1.153(0.844, 1.574)			
BRAF ^{V600E} mutation	No	1	0.666		
	Yes	1.162(0.604, 2.234)			
	NA	0.969(0.460, 2.042)			
HT	No	1	0.044	1	0.006
	Yes	1.406(1.010, 1.957)		1.678(1.161, 2.424)	
Abbreviation: CLNM: central lymph node metastasis; HT: Hashimoto’s thyroiditis.					
Bold values indicate statistical significance (<i>p</i> < 0.05)					

As for PTC patients who suffered from LLNM (Supplementary Table 1), only male gender and tumor size were independent risk factors in LLNM (OR = 1.856, 95%CI: 1.008–3.416, $p < 0.001$; 1cm < largest diameter ≤ 2cm, OR = 2.450, 95%CI: 1.291–4.650; 2cm < largest diameter ≤ 4cm, OR = 8.987, 95%CI: 4.344–18.595; 4 < largest diameter, OR = 3.446, 95%CI: 0.039–30.236; $p < 0.001$, respectively).

Nomogram Construction For Predicting Clnm In Ptc Patients

Based on the independent risk factors determined through multivariate analysis, a nomogram was established for predicting the risk of CLNM in patients with PTC. The risk factors including gender, age, tumor size, and HT were enrolled in our nomogram model (score of each factor was shown in Fig. 1) to predict the presence of CLNM in PTC patients.

A C-index of 0.703 was achieved. Furthermore, a decision curve analysis (DCA) was performed to compare the predictive ability between the combined clinical factors nomogram and the single-factor model. The standardized net benefits of the models were comparable, and there was a significant overlap between these models. Namely, the DCA showed that the prediction ability of combined clinical factors nomogram was superior to the single-factor model in detecting CLNM for PTC patients which would be more effective than a treat-none or treat-all strategy when the threshold probability ranged from 0.2 to 0.8 (Fig. 2A). To further evaluate the clinical significance of this prediction model, the clinical impact curve (CIC) was delineated (Fig. 2B). As expected, the CIC results show that among the broad thresholds for CLNM (20–80%), the nomogram was classified as positive, and the number of true positives was greater than those of the separated factor model.

Discussion

To date, with an increasing prevalence and overdetected rate of PTC around the world, the management of this disease becomes more precise and particularly crucial. For preventing unnecessary diagnostic workup and possible surgical intervention, the Japan Association of Endocrine Surgery (JAES) and the American Thyroid Association (ATA) separately updated the consensus statements and guidelines about the indications and strategy for active surveillance (AS) of low-risk PTMC ($cT_1N_0M_0$) patients, especially for the elderly population^{22,23}. As the cost-effective outcomes from the long-term follow-up have been recently determined, AS is gradually accepted as a positive management option by clinicians and patients in developed countries. However, surgical intervention is still the first-line treatment for PTC patients in China²⁴, especially recommended for patients with suspicious CLNM. Besides, the role of prophylactic central lymph node dissection (CLND) in PTC is continuous to be debatable around the world, especially reviewing different guidelines from Asia and West countries^{23,24}. Furthermore, TNM staging is a common method to predict the prognosis of cancer, but TNM staging in differentiated thyroid carcinoma (DTC) has limitations as a result of “Age (55 years)” playing a significantly important role in defining the tumor stage and cannot provide clinicians with personalized prognosis prediction²⁵. Therefore, it's crucial to develop more convenient and intuitive models for making an individualized clinical decision in PTC patients.

In the present study, we aimed to establish a visualized nomogram for predicting CLNM in PTC patients. The CLNM was histopathologically confirmed in 251 (33.6%) PTC patients which were consistent with reports by other similar works^{13,14,26}. Besides, 58 (7.8%) patients were diagnosed to suffer from LLNM which was consistent with Homma et al. study (8.4%)⁶ but much lower to the observation result (25.6%) made by Yang et al.²⁶. This divergence might due to the possibly different study location, population, and number of patients. We selected seven variables including gender, age, tumor size, multifocality,

BRAF^{V600E} mutation, and HT for univariate analysis. Neither multifocality nor BRAF^{V600E} mutation was analyzed to be associated with CLNM which was believed to be the frequent risk factors in lymph node metastasis. These differences were potential due to that approximately 15% of patients did not undergo fine-needle aspiration (FNA) or BRAF^{V600E} testing before the surgery which was a common limitation in recent studies^{26,27}. Besides, a relatively smaller sample size compared with other large cohort studies also contributed to this difference. Hence, gender, age, tumor size, and HT were finally screened out for multivariable analysis, similar to the recently reported studies^{28,29}. Interestingly, it's believed that tumor size was one of the pivotal risk factors in CLNM and the risk of CLNM increased as the diameter of the primary nodule increases. However, our data suggested that the highest risk ratio was not appeared in tumors with a diameter larger than 4cm, instead of in tumors with a diameter larger than 2cm but smaller than 4cm (Fig. 1). This phenomenon was potentially associated with the limited sample size (only 7 cases) of PTC patients with a diameter larger than 4cm. Additionally, in our study, the diagnosis of HT was based on the pathology of the surgical specimen. We observed that there was a lower rate of coexistence HT in male PTC patients than in female PTC patients (94.3% vs. 5.7%, $p < 0.001$), which was consistent with that in previous studies, and no significant difference was found between PTC patients with HT or without HT except for gender and CLNM. Based on multivariate analysis, the HT condition in our study was determined to be an independent risk factor in CLNM ($p = 0.006$) which was partially different from the conclusion in the previous study. Therefore, the role of HT in the progression of PTC contained several points that were worth discussing.

Currently, a range of works^{13,21,30,31}, especially retrospective study, have determined a high concurrence rate of HT and PTC from surgical specimens but the relationship between these two diseases, as well as HT and CLNM, has been controversial. Immunologically, emerging evidence has shown that an abnormal inflammatory response, especially the imbalanced subsets of T cells, NK cells, and cytokines were presenting in HT condition^{12,32}, which could potentially affect the tumor microenvironment and subsequent prognosis. For instance, in vitro experiment, Lubin et al.³³ conducted that the presence of background HT was contributed to a higher risk of CLNM via increased programmed death ligand-1 (PD-L1). On the contrary, results from Hu et al.¹⁷ suggested that enhanced MHC class I expression in HT conditions could decrease the PD-L1 and further overcome the CLNM in PTC patients. Serologically, Wen et al.²¹ conducted that different thyroid antibody status was significantly associated with the CLNM in PTC patients concurrent with HT. They concluded single TgAb was a risk factor in CLNM, whereas TPOAb played a protective role in preventing CLNM. By contrast, a few studies hold the opposite view on the role of serum TPOAb level in CLNM, with the results they analyzed³⁴. The inconsistent result in these studies inspired us to provide our own experience in the following works.

Reviewing similar works on predicting CLNM^{13,26,27,35}, our study had a partial difference and takes it a step further. To our knowledge, compared with other works, our data indicated that HT was one of the independent risk factors in promoting CLNM which deserved further evaluation. Although the C-index in the previous study achieved 0.764 based on 914 PTC patients³⁶ and 0.854 based on a sample size of 1,252 PTC patients²⁶, the C-index of our nomogram was still more than 0.7, indicating that it has

sufficient discrimination ability. The DCA results show that the nomogram we developed has good clinical practical value. Combined with other established nomograms based on ultrasound signatures, our nomogram with clinical pathological characteristics with the strongest risk factors including gender, age, size, and HT can increase the accuracy for predicting CLNM. These prognostic factors collected from preoperative and intraoperative could further help surgeons to decide the extent of the initial thyroidectomy and whether prophylactic central neck dissection is warranted.

Nonetheless, there were still some limitations that should be mentioned. Firstly, this was a retrospective study from a single-center teaching hospital center which did introduce some selection biases. There were only 747 patients enrolled in this study which were still not large enough for the deepening predicting of the clinical risk factors in CLNM. Secondly, body mass index (BMI), ultrasound signatures, and some laboratory testing results which were determined to be associated with CLNM in PTC patients^{26,27} were not included in our study. Lastly, there were only four variables finally added to the nomogram, which indicated there might be potential variables waiting to be discovered that could make our nomogram complete and more reliable.

Conclusion

In summary, several clinical features including male gender, younger age, and larger tumor size are independent risk factors in the CLNM of PTC patients. A predicting nomogram model based on clinical risk factors is established to help surgeons make an individualized clinical decision in PTC patients during interoperative management.

Declarations

Funding

None

Conflicts of interest

The authors have no conflicts of interest to declare.

Availability of data and material

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

Code availability

The software application generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions

- (I) Conception and design: Yu Min, Yang Feng
- (II) Administrative support: Xing Wang, Guobing Yin
- (III) Provision of study materials or patients: Yang Feng, Hang Chen, Yu Min
- (IV) Collection and assembly of data: Yu Min, Ke Xiang
- (V) Data analysis and interpretation: Yu Min, Yang Feng
- (VI) Manuscript writing: All authors.
- (VII) Final approval of manuscript: All authors

Ethics approval

Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent to participate

Not applicable

Consent for publication

Not applicable

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Figures

Figure 1

Clinical factor-based nomogram used for prediction of central lymph node metastasis in PTC patients.
HT: Hashimoto's thyroiditis.

Figure 2

Determination of decision point via Decision Curve Analysis (DCA) and Clinical Impact Curve (CIC). A. DCA for the prediction model (EI-Score). The decision curve analysis graphically shows the clinical usefulness of the EI-Score based on a continuum of potential thresholds for central lymph node metastasis (CLNM) (x-axis) and the net benefit of using the EI-Score to stratify patients (y-axis). Net benefit curves are plotted across probability thresholds for 7 options: “treat all” assume all patients have

CLNM, 'treat none' assume no patients have CLNM, treat according to combined clinical factors (age, gender, tumor size, HT), Age, Gender, size, HT and EI-Score. Net benefit = (true positives/N) - (false positives/ N) *(weighting factor). Weighting factor = Threshold probability/ (1-threshold probability). B. CIC for EI-Score. The red line shows the total number who would be deemed as low risk of CLNM for each risk threshold. The blue line shows how many of those would be true positive (without CLNM).

Supplementary Files

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- [supplementaryTable1.docx](#)