European Journal of Surgical Oncology 49 (2023) 560–567

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

A retrospective study of papillary thyroid carcinoma: Hashimoto's thyroiditis as a protective biomarker for lymph node metastasis

Yu Wang [1], Jianwei Zheng [1], Xiaomeng Hu , Qing Chang , Yu Qiao , Xiaofeng Yao **, Xuan Zhou *

Department of Maxillofacial and Otorhinolaryngological Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, 300060, China

ARTICLE INFO

Article history:
Received 28 July 2022
Received in revised form
2 November 2022
Accepted 7 November 2022
Available online 11 November 2022

Keywords:
Papillary thyroid carcinoma
Hashimoto's thyroiditis
Central lymph node metastasis
Lateral lymph node metastasis
Risk factor

ABSTRACT

Purpose: There is approximately 10%–50% of papillary thyroid carcinoma (PTC) patients with Hashimoto's thyroiditis (HT). In this research, we sought to better understand the role of HT in PTC progression as well as lymph node metastasis.

Methods: It is a retrospective and cross-sectional study, and 4131 PTC patients who underwent thyroidectomy were finally enrolled. Chi-square test, univariate and multivariate logistic regression analyses were employed to evaluate both the risk factors and the critical roles of HT during PTC metastasis.

Result: In this cohort, 1555 patients (37.6%) were diagnosed with HT. According to multivariate analysis, male sex, high levels of TG and TPOAb, tumor extrathyroidal extension, maximum diameter >1 cm, and multifocality were independent risk factors for both central lymph node metastasis (CLNM) and lateral lymph node metastasis (LLNM). In addition, age <55 years and smoking were risk factors for CLNM, while CLNM was one of the risk factors for LLNM. Furthermore, HT was suggested a valuable protective factor for both CLNM and LLNM. In patients with HT, the total number of central lymph nodes was higher, while the positive rate was lower. Compared with those without HT, age and sex did not predict CLNM and LLNM in patients with HT.

Conclusion: HT is considered a protective factor for both CLNM and LLNM in PTC. For patients with HT, surgeons should pay more attention to the preservation of parathyroid gland and the protection of recurrent laryngeal nerve due to less lymph node metastasis. Otherwise, radical operation is highly recommended.

1. Introduction

The morbidity of thyroid cancer has been increasing for the past few years [1–3], and papillary thyroid carcinoma (PTC) is the commonest pathological type [4]. Although PTC is an indolent tumor, the frequency of lymph node metastasis, as the most important clinical feature, has been a major concern of head and neck cancer researchers [5]. It is widely believed that the high rate of lymph node metastasis of PTC is a vital reason for the cancer recurrence as well as poor prognosis [6,7]. Although previous studies have preliminarily explored the related factors for central lymph node metastasis (CLNM) or lateral lymph node metastasis (LLNM) in PTC, the results have drawn unsatisfactory or inconsistent conclusions. Therefore, the risk factors related to CLNM and LLNM need to be further explored.

Hashimoto's thyroiditis (HT) is a chronic autoimmune inflammation of the thyroid influenced by genetic and environmental factors [8]. According to researches and statistics, HT is more common in females and is associated with genetic background, thyroid antigens and sulfur intake [9]. Elevated thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) levels, atrophy of follicular cells, and lymphocyte infiltration are pathological characteristics of HT [10]. At present, the role of HT, along with high levels of TGAb and TPOAb, in inducing thyroid cancer tumorigenesis and lymph node metastasis, and their prognostic value in PTC

* Corresponding author.
** Corresponding author.
E-mail addresses: wangyu1991@tmu.edu.cn (Y. Wang), zhengjw1997@163.com (J. Zheng), huxiaomeng1232021@163.com (X. Hu), changqing_tmu@163.com (Q. Chang), tjyzsky@hotmail.com (Y. Qiao), yaoxf1980@163.com (X. Yao), xuanzhou@tmu.edu.cn (X. Zhou).
[1] These authors contributed equally.

https://doi.org/10.1016/j.ejso.2022.11.014
0748-7983/

patients are still unclear [11–13]. Some studies indicated that the invasion and metastasis of PTC may induce specific immune response and then increase the TGAb level [14]. Besides, the relationship between HT and PTC is still controversial. Although some studies suggested that there was no clear link between HT and PTC based on fine-needle needle biopsy (FNAB) data [15,16], previous studies have pointed out that the oxygen free radicals generated by HT inflammatory reaction are associated with the development of PTC [17], and a number of retrospective studies have confirmed that the incidence of PTC is higher in HT patients [15]. In addition, whether HT contributes to thyroid tumor CLNM and LLNM remains controversial [18,19]. Mounting evidence suggested that patients with HT may have different clinical characteristics than those without HT, and HT may have a protective effect on cervical lymph node metastasis [20,21]. However, these studies were designed based on preoperative ultrasound, thus lacking the support of postoperative pathology.

In this study, we first compared the clinicopathological characteristics in PTC patients with and without HT, CLNM, and LLNM. Then, we analyzed the risk factors of CLNM and LLNM in PTC patients and further divided into those with and without HT to better explore the critical role of HT in lymph node metastasis.

2. Methods

2.1. Patients

We retrospectively reviewed 4131 PTC patients who underwent central lymph node dissection (CLND) or lateral lymph node dissection (LLND) at Tianjin Medical University Cancer Institute and Hospital from 2015 to 2017. Preoperative thyroid function tests were detected for all patients, including thyroglobulin (TG), TGAb, TPOAb, T3, T4 and thyroid-stimulating hormone (TSH). LLNM was confirmed by ultrasound and fine-needle aspiration cytology (FNAC), and patients who were followed for five years and who did not undergo LLND or did not develop LLNM during the follow-up were defined as LLNM-negative. The Institutional Review Board (IRB) of Tianjin Medical University Cancer Institute and Hospital approved this study.

2.2. Patient inclusion and exclusion criteria

The inclusion criteria were complete thyroid function data, first surgery for thyroid cancer, unilateral thyroid lobule or total thyroidectomy as well as CLND or LLND, and postoperative pathology of PTC after thyroidectomy. The exclusion criteria were nonprimary thyroidectomy and inadequate basic clinical information. The diagnosis of HT was mainly based on postoperative pathology, together with thyroid function and the clinical manifestations (thyroid diffused enlargement).

2.3. Analyzed items

The basic clinical information we collected was as follows: age (between 12 and 78 years and then classified into <55 years and ≥55 years), sex, alcohol consumption, and smoking. Postoperative pathological information: HT, invasion (intraglandular, extrathyroidal extension (ETE)), CLNM, LLNM, tumor maximum diameter (≤1 cm or >1 cm), multifocality, number of central lymph nodes (CLNs) and metastatic CLNs, number of lateral lymph nodes (LLNs) and metastatic LLNs.

Thyroid function examination was performed according to the laboratory standard of Tianjin Medical University Cancer Hospital to delimit the reference range of various indicators: TSH, 0.51–4.85 mU/L; TG, 1.15–130.70 μg/L; TGAb, 0–4.10 IU/mL; and TPOAb, 0–9.00 IU/mL. According to the upper and lower limits of laboratory reference ranges, references [22], quartiles, and whether the differences between groups were statistically significant, after adjustment, TSH, TG, TGAb, TPOAb were grouped for analysis.

2.4. Statistical analysis

The Chi-squared test and Wilcoxon test were performed to investigate baseline characteristics and continuous variates, respectively. Univariate regression analysis and multivariate regression analysis were used to analyze the related risk factors. The regression model was evaluated by means of the receiver operating characteristic (ROC) curves. Forest plot was generated by R package "ggplot2". $P \leq 0.05$ was considered statistically significant in this study. All analyses were performed using the R language software (version 4.1.0).

3. Result

3.1. Clinical features of PTC patients with and without HT

To understand the clinical features of HT, we compared the clinical information of HT patients and non-HT patients (Table 1). The results showed that patients with HT were mostly female ($P < 0.001$) and younger age ($P = 0.038$). Smoking ($P < 0.001$) was associated with HT. Besides, patients with HT had higher TGAb ($P < 0.001$) and TPOAb ($P < 0.001$) levels but lower TG ($P < 0.001$) level. More importantly, patients with HT had lower incidences of both CLNM and LLNM ($P < 0.001$ and $P = 0.003$). In addition, HT disease was validated to be negatively correlated with tumor invasion ($P < 0.001$), maximum diameter ($P = 0.006$) and multifocality ($P < 0.001$). Moreover, postoperative pathology confirmed that patients with HT had more CLNs but a lower metastatic rate of CLNs. Nevertheless, HT had little effect on both the total number and metastatic rate of LLNs.

3.2. Clinical features of PTC patients with and without CLNM and LLNM

Since the incidences of CLNM and LLNM were lower in patients with HT, we further compared the clinical information of patients with and without CLNM and LLNM (Table 2). The result showed that CLND was performed in all patients, and 2070 patients (50.1%) were postoperatively diagnosed with CLNM. A total of 788 patients (19.1%) underwent LLND and were postoperatively diagnosed with LLNM. In general, there were significant differences in sex ($P < 0.001$), age ($P < 0.001$), smoking ($P < 0.001$ and $P = 0.003$), tumor invasion ($P < 0.001$), maximum diameter ($P < 0.001$), multifocality ($P < 0.001$) and HT ($P < 0.001$) between patients with and without CLNM or LLNM. In addition, the mean TG levels in patients with CLNM or LLNM were higher than those in patients without CLNM or LLNM ($P < 0.001$), whereas the mean serum TGAb and TPOAb levels in patients with CLNM were lower than those in patients without CLNM ($P < 0.001$ and $P = 0.020$). In addition, CLNM and LLNM were closely related, and there was no significant difference in T3 and T4 levels.

3.3. HT serves as a protective factor during lymph node metastasis in PTC

3.3.1. HT in CLNM

Univariate regression analysis showed that age, sex, smoking, TG, TGAb, and TPOAb levels, tumor invasion, maximum diameter, multifocality and HT were associated with CLNM (Supplementary Table 1). Furthermore, multivariate regression analysis was

Table 1
Clinicopathological information for patients with and without HT.

Characteristics	With HT n (%)	Without HT n (%)	*P* value
Total	1555 (37.6)	2576 (62.4)	
Sex			**< 0.001**
Female	1351 (32.7)	1907 (46.2)	
Male	204 (4.9)	669 (16.2)	
Smoking			**< 0.001**
No	1486 (36)	2351 (56.9)	
Yes	69 (1.7)	225 (5.4)	
Alcohol consumption			0.165
No	1531 (37.1)	2519 (61)	
Yes	24 (0.6)	57 (1.4)	
CLNM			**< 0.001**
No	895 (21.7)	1175 (28.4)	
Yes	660 (16)	1401 (33.9)	
LLNM			**0.003**
No	1303 (31.5)	2040 (49.4)	
Yes	252 (6.1)	536 (13)	
Invasion			**< 0.001**
Intraglandular	460 (11.1)	567 (13.7)	
ETE	1095 (26.5)	2009 (48.6)	
Multifocality			**< 0.001**
No	1136 (27.5)	1755 (42.5)	
Yes	419 (10.1)	821 (19.9)	
Age, M (P25; P75)	44 (36, 52)	45 (37, 53)	**0.038**
T3, M (P25; P75)	1.41 (1.25, 1.56)	1.41 (1.25, 1.58)	0.471
T4, M (P25; P75)	99.53 (89.72, 112.64)	100.57 (90.45, 112.32)	0.547
TSH, M (P25; P75)	2.2 (1.46, 3.21)	1.99 (1.35, 2.88)	**< 0.001**
TG, M (P25; P75)	5.42 (1.3, 14.01)	9.9 (5.04, 17.89)	**< 0.001**
TGAb, M (P25; P75)	19.82 (1.67, 139.66)	0.89 (0.44, 2.19)	**< 0.001**
TPOAb, M (P25; P75)	7.7 (1.46, 67.78)	0.92 (0.92, 1.1)	**< 0.001**
Maximum diameter, M (P25; P75)	0.8 (0.6, 1.2)	0.8 (0.6, 1.3)	**0.006**
Number of metastatic CLNs, M (P25; P75)	2 (1, 4)	2 (1, 5)	**< 0.001**
Number of CLNs, M (P25; P75)	5 (3, 8)	8 (5, 11)	**< 0.001**
metastatic CLNs/CLNs, M (P25; P75)	0.57 (0.33, 0.83)	0.33 (0.2, 0.5)	**< 0.001**
Number of metastatic LLNs, M (P25; P75)	0 (0, 2)	0 (0, 2)	0.394
Number of LLNs, M (P25; P75)	0 (0, 14)	0 (0, 15)	0.748
metastatic LLNs/LLNs, M (P25; P75)	0 (0, 0.1)	0 (0, 0.1)	0.106

HT, Hashimoto's thyroiditis; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; TG, thyroglobulin; TGAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TSH, thyrotropin; T3, triiodothyronine; T4, thyroxine; ETE, extrathyroidal extension; CLN, central lymph node; LLN, lateral lymph node; M, Median value.

applied to deeply explore the independent risk factors for CLNM. The results showed that age <55 years, male sex, smoking, TG $\leq$ 1.15 or >16.66 μg/L, TPOAb >100.00 IU/mL, ETE, maximum diameter >1 cm, and multifocality were independent risk factors for CLNM, whereas HT was a protective factor for CLNM (Fig. 1).

ROC curve demonstrated the predictive function of the CLNM logistic regression model (Fig. 2). The area under the curve (AUC) was calculated as 69.7%, and the cutoff value for the prediction of CLNM was −0.058, at which the sensitivity of the regression model was 65.4%, and the specificity was 62.6% for predicting CLNM in PTC patients.

3.3.2. HT in LLNM

Univariate regression analysis showed that age, sex, smoking, TG and TPOAb levels, CLNM, ETE, maximum diameter, multifocality and HT were associated with LLNM (Supplementary Table 2). Next, multivariate regression analysis was applied. The results showed that male sex, TG $\leq$ 1.15 or >16.66 μg/L, TPOAb >100.00 IU/mL, ETE, maximum diameter >1 cm, multifocality and CLNM were independent risk factors for LLNM, whereas HT was a protective factor for LLNM (Fig. 3).

The ROC curve demonstrated the predictive function of the LLNM logistic regression model (Fig. 4). The AUC was calculated as 80.2%, and the cutoff value for the prediction of CLNM was −1.354, at which the sensitivity of the regression model was 77.5%, and the specificity was 71.2% for predicting LLNM in PTC patients.

3.4. Risk factors for lymph node metastasis vary in patients with or without HT

To better understand the protective function of HT during lymph node metastasis, we divided the patients into two groups depending on HT status and further explored the risk factors for CLNM and LLNM. The multivariate results indicated that in the non-HT group, age <55 years, male sex, smoking, TG > 16.66 μg/L, ETE, maximum diameter >1 cm, and multifocality were independent risk factors for CLNM; in the HT group, TPOAb >100.00 IU/ml, ETE, maximum diameter >1 cm, and multifocality were independent risk factors for CLNM (Fig. 5). In addition, in the non-HT group, male sex, TG $\leq$ 1.15 or >16.66 μg/L, TPOAb >100.00 IU/mL, ETE, maximum diameter >1 cm, multifocality, and CLNM were independent risk factors for LLNM; in the HT group, TPOAb >100.00 IU/ml, ETE, maximum diameter, and CLNM were independent risk factors for LLNM (Fig. 6). The univariate results are presented in the supplementary materials (Supplementary Table 3 and Supplementary Table 4).

ROC curves were applied to assess the predictive value of CLNM and LLNM in patients with and without HT. For CLNM, the AUC of HT patients was 69.5%, the cutoff value was −0.169, the sensitivity was 59.4%, and the specificity was 70.9% (Supplementary Fig. 1A). The AUC of the patients without HT was 68.1%, the cutoff value was 0.401, the sensitivity was 48.8%, and the specificity was 78.9% (Supplementary Fig. 1B). For LLNM, the AUC of HT patients was 79.5%, the cutoff value was 1.767, the sensitivity was 68.7%, and the

Table 2
Clinicopathological information for patients with and without CLNM and LLNM.

Characteristics	With CLNM n (%)	Without CLNM n (%)	*P* value	With LLNM n (%)	Without LLNM n (%)	*P* value
Total	2070 (50.1)	2061 (49.9)		788 (19.1)	3343 (80.9)	
HT			**< 0.001**			**< 0.001**
Yes	1401 (33.9)	1175 (28.4)		536 (13)	2040 (49.4)	
No	660 (16)	895 (21.7)		252 (6.1)	1303 (31.5)	
Sex			**< 0.001**			**< 0.001**
Female	1535 (37.2)	1723 (41.7)		558 (13.5)	2700 (65.4)	
Male	526 (12.7)	347 (8.4)		230 (5.6)	643 (15.6)	
Smoking			**< 0.001**			**0.003**
No	1864 (45.1)	1973 (47.8)		712 (17.2)	3125 (75.6)	
Yes	197 (4.8)	97 (2.3)		76 (1.8)	218 (5.3)	
Alcohol consumption			0.069			**0.044**
No	2012 (48.7)	2038 (49.3)		765 (18.5)	3285 (79.5)	
Yes	49 (1.2)	32 (0.8)		23 (0.6)	58 (1.4)	
CLNM/LLNM			**< 0.001**			**< 0.001**
No	1383 (33.5)	1960 (47.4)		110 (2.7)	1960 (47.4)	
Yes	678 (16.4)	110 (2.7)		678 (16.4)	1383 (33.5)	
Invasion			**< 0.001**			**< 0.001**
Intraglandular	324 (7.8)	703 (17)		71 (1.7)	956 (23.1)	
ETE	1737 (42)	1367 (33.1)		717 (17.4)	2387 (57.8)	
Multifocality			**< 0.001**			**< 0.001**
No	1346 (32.6)	1545 (37.4)		458 (11.1)	2433 (58.9)	
Yes	715 (17.3)	525 (12.7)		330 (8)	910 (22)	
Age, M (P25; P75)	43 (35, 52)	46 (38, 53)	**< 0.001**	42 (34, 51)	45 (37, 53)	**< 0.001**
T3, M (P25; P75)	1.41 (1.25, 1.57)	1.41 (1.25, 1.57)	0.604	1.42 (1.26, 1.58)	1.41 (1.25, 1.57)	0.162
T4, M (P25; P75)	99.58 (90.25, 112.42)	100.64 (90.05, 112.55)	0.513	100.13 (89.5, 113.15)	99.93 (90.4, 112.32)	0.979
TSH, M (P25; P75)	2.01 (1.35, 2.91)	2.11 (1.4, 3.08)	**0.014**	2.06 (1.39, 3.01)	2.06 (1.37, 2.99)	0.950
TG, M (P25; P75)	9.34 (3.68, 18.82)	7.62 (3.14, 14.81)	**< 0.001**	10.01 (3.5, 22.74)	8.17 (3.34, 15.55)	**< 0.001**
TGAb, M (P25; P75)	1.24 (0.54, 11.23)	2.4 (0.68, 46.8)	**< 0.001**	1.05 (0.46, 10.61)	1.12 (0.34, 13.91)	0.307
TPOAb, M (P25; P75)	0.92 (0.92, 5.86)	1.16 (0.92, 8.1)	**0.020**	0.92 (0.92, 11.57)	0.92 (0.92, 6.28)	0.155
Maximum diameter, M (P25; P75)	1 (0.7, 1.5)	0.7 (0.5, 1)	**< 0.001**	1.2 (0.8, 1.6)	0.8 (0.6, 1.1)	**< 0.001**

HT, Hashimoto's thyroiditis; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; TG, thyroglobulin; TGAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TSH, thyrotropin; T3, triiodothyronine; T4, thyroxine; ETE, extrathyroidal extension; M, Median value.

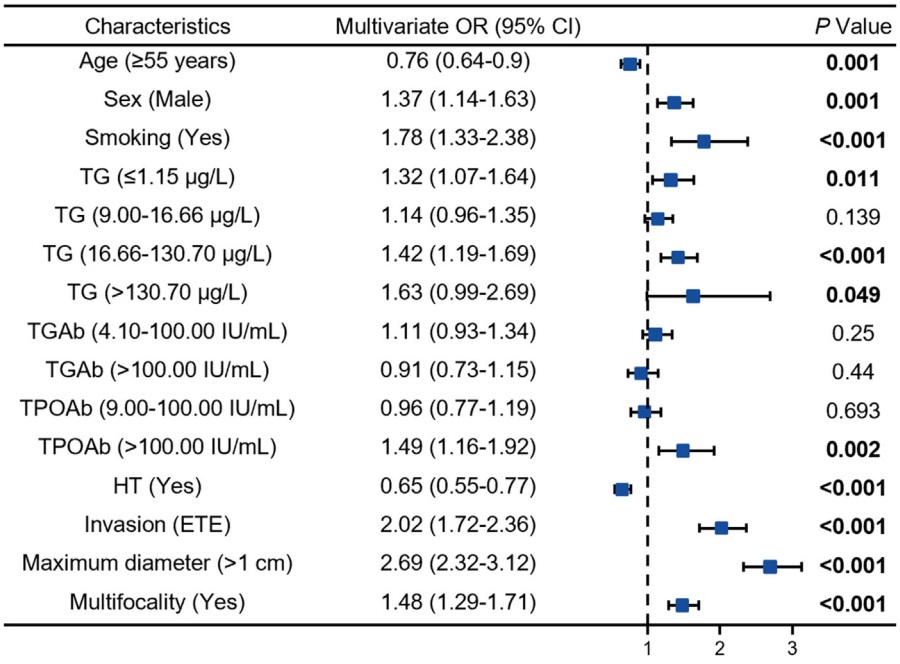

Fig. 1. Multivariate logistic regression analysis of CLNM. TG, thyroglobulin; TGAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; HT, Hashimoto's thyroiditis; ETE, extrathyroidal extension.

specificity was 79.4% (Supplementary Fig. 1C). The AUC without HT was 80.5%, the cutoff value was −1.234, the sensitivity was 77.2%, and the specificity was 72.7% (Supplementary Fig. 1D).

4. Discussion

In recent years, the relationship between HT and PTC has been a hot topic and controversial [23–25]. Ulla Feldt-Rasmussen

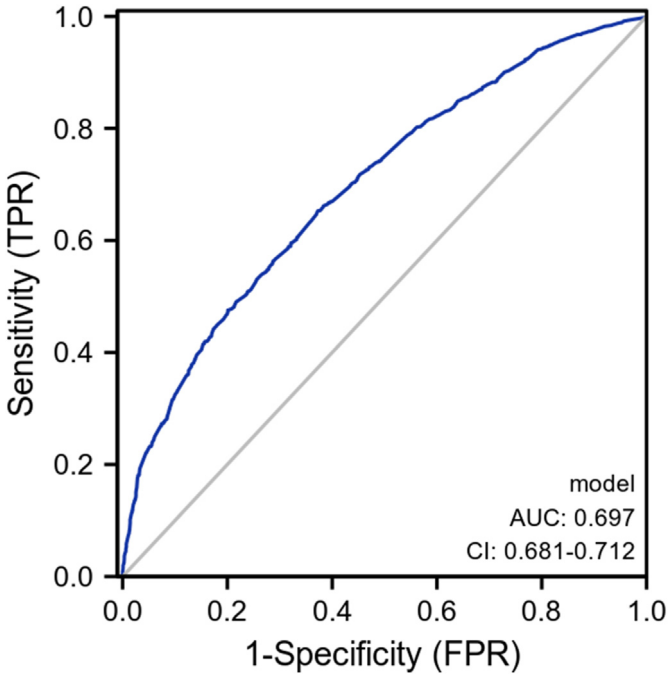

Fig. 2. The receiver operation characteristic curve demonstrated multivariate logistic models for predicting CLNM.

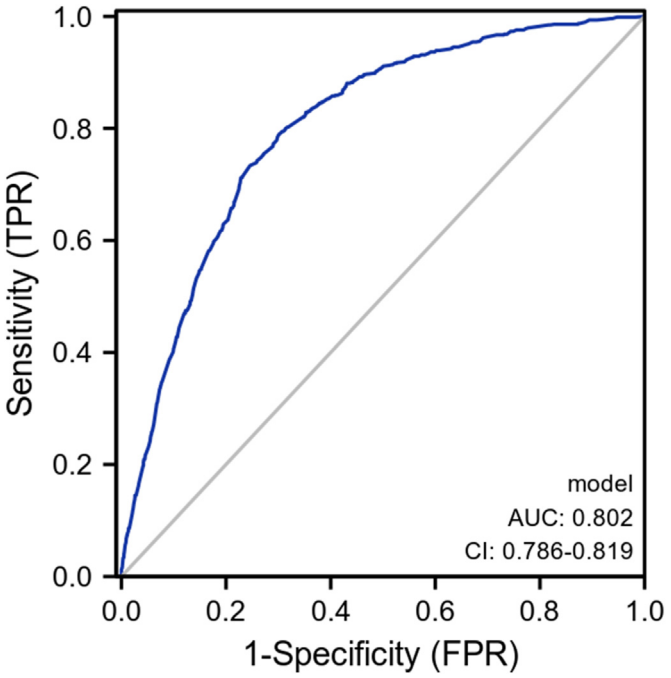

Fig. 4. The receiver operation characteristic curve demonstrated multivariate logistic models for predicting LLNM.

Characteristics	Multivariate OR (95% CI)	*P* Value
Age (≥55 years)	0.85 (0.68-1.08)	0.181
Sex (Male)	1.46 (1.17-1.82)	**0.001**
Smoking (Yes)	0.94 (0.67-1.31)	0.708
TG (≤1.15 μg/L)	1.61 (1.22-2.14)	**0.001**
TG (9.00-16.66 μg/L)	1.02 (0.8-1.31)	0.852
TG (16.66-130.70 μg/L)	1.56 (1.24-1.95)	**<0.001**
TG (>130.70 μg/L)	2.35 (1.4-3.94)	**0.001**
TPOAb (9.00-100.00 IU/mL)	1.45 (1.09-1.93)	**0.012**
TPOAb (>100.00 IU/mL)	1.76 (1.27-2.42)	**0.001**
HT (Yes)	0.74 (0.62-0.87)	**<0.001**
CLNM (Yes)	6.1 (4.89-7.61)	**<0.001**
Invasion (ETE)	2.07 (1.57-2.72)	**<0.001**
Maximum diameter (>1 cm)	2.22 (1.86-2.66)	**<0.001**
Multifocality (Yes)	1.68 (1.4-2.01)	**<0.001**

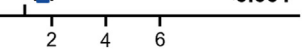

Fig. 3. Multivariate logistic regression analysis of LLNM. TG, thyroglobulin; TPOAb, anti-thyroid peroxidase antibody; HT, Hashimoto's thyroiditis; CLNM, central lymph node metastasis; ETE, extrathyroidal extension.

suggested that the inflammatory response of HT may promote the progression of thyroid cancer [26]. However, most previous studies showed that the presence of HT may be correlated with earlier diagnosis and better prognosis [19,27,28]. Even though, whether HT could affect cervical lymph node metastasis has not been confirmed. Summarizing the results of previous meta-analyses, Mao et al. suggested that HT could not affect lymph node metastasis [29], while others indicated that HT was a protective factor for CLNM [30,31]. Moreover, researchers from Korea demonstrated that HT had no confirmed association with LLNM [31,32]. At the same time, some studies assessed the relationship between HT and cervical lymph node metastasis by ultrasound [20,33]. Although previous studies have investigated some relationships between HT and lymph node metastasis, no consistent results have been obtained. Hence, we conducted a retrospective study on the clinical information of 4131 patients in our center to deeply explore the

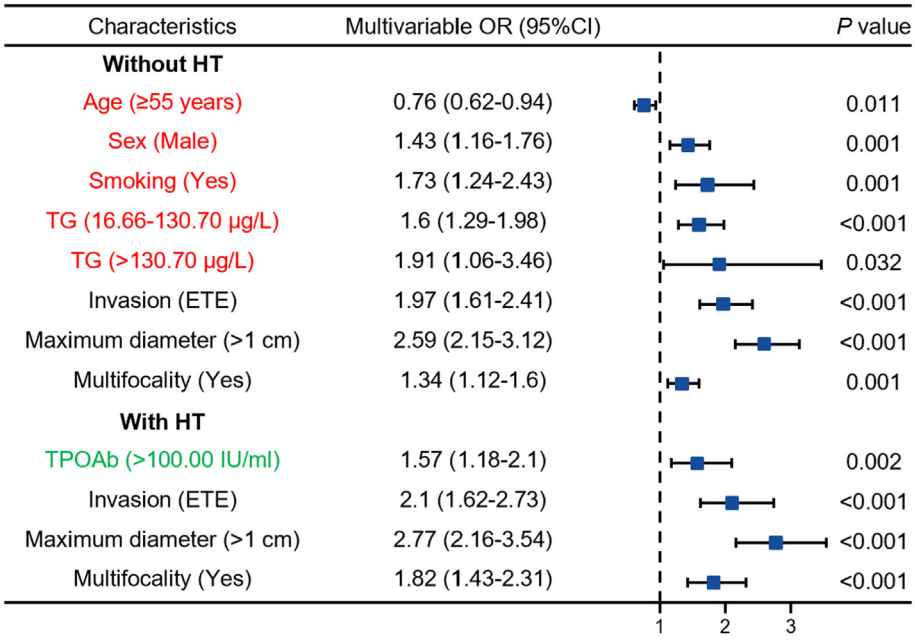

Fig. 5. Multivariate analyses showed the correlation between the clinical characteristics of CLNM in the HT group and non-HT group, with red representing the additional related factors in patients without HT and green representing the additional related factors in patients with HT. ETE, extrathyroidal extension.

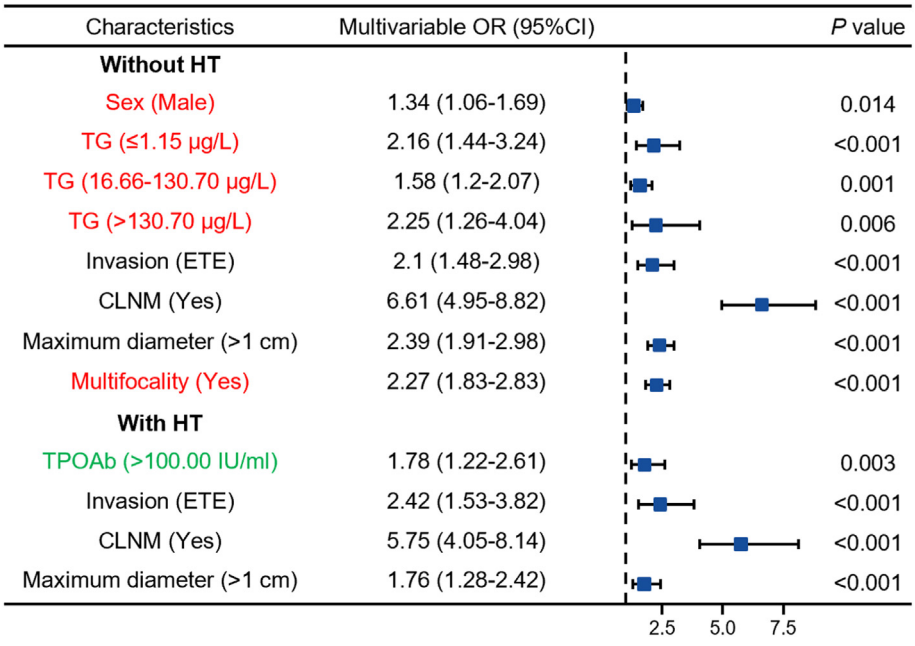

Fig. 6. Multivariate analyses showed the correlation between the clinical characteristics of LLNM in HT group and non-HT group, with red representing the additional related factors in patients without HT and green representing the additional related factors in patients with HT. ETE, extrathyroidal extension.

driving role of HT in lymph node metastasis and tumor progression in PTC. Generally, we aim to provide strong theoretical support for the clinical diagnosis, treatment and operation standards of PTC.

Through comprehensive studies, female patients were found to have a higher prevalence of HT and higher TSH levels [34], which is consistent with the findings of our study. TSH could promote the growth of follicular epithelial cells of the thyroid and thus promote PTC cell progression [35,36]. Hence, elevated TSH levels may be the reason why HT promotes the tumorigenesis of thyroid cancer [37,38]. Our results showed that patients with HT had higher TSH levels, which may be one of the predisposing factors for the increased incidence of PTC. In contrast, multivariate analysis showed that HT may be a protective factor for both CLNM and LLNM. In detail, the total number of metastatic lymph nodes in patients with HT was significantly less than that in non-HT group. Besides, to better understand the relationship between HT and CLNM, we analyzed the lymph node metastatic rate (metastatic lymph nodes/total lymph nodes) in both groups. Similarly, the

metastatic rate in HT group was also lower than that in non-HT group, similar to other published data [39,40]. We hypothesize that such a relatively low metastatic rate might be one hand due to the less metastatic lymph nodes, other hand resulting from the HT-related Inflammatory lymph node hyperplasia. More importantly, we further explored the similarities and differences in risk factors for cervical lymph node metastasis in HT patients and non-HT patients. The results indicated that, unlike non-HT patients, age, sex, smoking, and TG were no longer independent risk factors for CLNM in HT patients. However, TPOAb was a significant biomarker specifically for the group of HT patients. Similar results were obtained in the analysis for LLNM. Hence, HT was indicated to significantly protect PTC patients from more risk factors for both CLNM and LLNM. According to the clinical characteristics of less ETE, CLNM and LLNM in patients with HT, we recommend that clinicians pay more attention to function preservation and rapid postoperative rehabilitation for patients with HT. As much as possible, all parathyroid glands should be retained, and the laryngeal recurrent nerve should be protected, which will enable patients with fewer postoperative complications to have a better quality of life. In contrast, for PTC patients without HT, as a result of a higher rate of lymph node metastasis, surgeons should perform radical neck lymph node dissection as much as possible and pay more attention to achieving a lower recurrence rate and better local tumor control rate.

In addition to the influence of HT, we investigated many other regulatory factors for CLNM. In this study, 50.1% of patients were found to have CLNM, consistent with that in previous studies [41]. Navika Shukla et al. suggested that children and adolescents are risk factors for CLNM [42], similar to our conclusion that age $\geq$55 years was a protective factor for CLNM. In addition, smoking was suggested a risk factor for CLNM, while alcohol consumption was not, reflecting that personal habits were also partially related to the incidence of CLNM. TGAb and TPOAb are thyroid autoimmune antibodies that are closely related to the occurrence of thyroid cancer [43,44]. Wen et al. suggested that thyroid antibodies are one of the key factors affecting CLNM [45]. Our results suggested that when TG is $\leq$ 1.5 or >16.66 μg/L or TPOAb is > 100.00 IU/mL, the probability of CLNM will increase. Feng et al. pointed out that multifocality increased the risk of CLNM [46], which was confirmed in our study, and ETE, multifocality and tumor maximum diameter >1 cm were found to be independent risk factors for CLNM. On the other hand, there have been many previous studies on LLNM risk factors during PTC progression. Dou et al. reported that papillary microcarcinoma (PTMC) in the upper pole of the thyroid is one of the risk factors for LLNM [47]. In addition, Shan and colleagues suggested that higher TSH levels, CLNM and higher tumor numbers could significantly predict LLNM [48]. Our study and that of Liu et al. [49] reached similar conclusions that sex, TG and TPOAb levels, HT, ETE, maximum tumor diameter, multifocality and CLNM could affect LLNM.

However, this study still has several limitations. Imaging data such as ultrasound and CT were not collected for comprehensive evaluation, which needs to be further improved. Moreover, since the current study was a retrospective analysis, further prospective studies are needed to better investigate the risk factors for lymph node metastasis of PTC as well as the relationship between PTC and HT.

5. Conclusion

In summary, our study confirmed that HT, which is negatively correlated with tumor invasion and metastasis, may serve as a valuable protective factor for both CLNM and LLNM during PTC progression. Therefore, we recommend that functional preservation, such as the protection of both the recurrent laryngeal nerve and parathyroid gland, should be priorities to consider during surgery for HT patients, while both tumor extensive resection and radical neck dissection may be the better choice for non-HT patients.

Funding

This work was supported by the China National Natural Scientific Fund No. 81872206 (to X.Z.), 82073010 (to X.Z.) and 82002892 (to Y.W.); the Tianjin Education Commission Funded Projects No.2019KJ188 (to Y.W.).

CRediT authorship contribution statement

Yu Wang: Conceptualization, Methodology, Writing – original draft. **Jianwei Zheng:** Visualization, Software, Writing – original draft. **Xiaomeng Hu:** Data curation, Investigation. **Qing Chang:** Data curation, Investigation. **Yu Qiao:** Methodology, Validation. **Xiaofeng Yao:** Conceptualization, Writing – review & editing. **Xuan Zhou:** Conceptualization, Writing – review &.

Declaration of competing interest

There are no potential conflicts of interest, financial or otherwise, for the participating authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.11.014.

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