Comparison and Analysis of Clinical Features of Papillary Thyroid Cancer Complicated With Hashimoto's Thyroiditis

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ABSTRACT

BACKGROUND: Hashimoto thyroiditis (HT) combined with papillary thyroid cancer (PTC) is more common in clinical practice, maybe posing a serious threat to the health of patients. It is uncertain whether HT is a risk factor or protective factor for PTC. The aim of the study was to retrospectively explore the effect of HT on the biological behavior of PTC.

METHODS: A total of 200 patients were included in the study. Among them, 100 patients with PTC without HT were in the control group (PTC group), and 100 cases diagnosed as PTC with HT were in the experimental group (HT + PTC group). The following data were counted and analyzed, respectively: (1) the basic clinicopathologic characteristics of patients; (2) postoperative thyroid function indicators; (3) blood biochemical indicators; (4) liver function indicators; and (5) histopathological report.

RESULTS: Compared with the PTC group, women were predominant in the PTC + HT group ($P < .05$). In addition, the central lymph node metastasis rate, the number of cervical lymph node metastases, and the lateral cervical lymph node metastasis rate were significantly decreased ($P < .05$). Thyroid peroxidase antibody (TPOAb), thyroid-stimulating hormone (TSH), and thyroglobulin antibody (TGAb) of the thyroid function index were significantly increased, while the thyroglobulin (TG) value was significantly decreased ($P < .05$). The alkaline phosphatase (ALP) level of the liver function index was significantly decreased, while the lactate dehydrogenase (LDH) level was significantly increased ($P < .05$). In the pathological examination, a large number of mononuclear cells infiltrated in the lymphocyte follicular stroma. In an ultrasound examination, the boundary definition rate is lower.

CONCLUSION: Women may be more susceptible to PTC or PTC and HT than men. Patients under 55 years old accounted for a larger proportion in PTC + HT than PTC. Hashimoto thyroiditis may play an inhibitory role in the occurrence of PTC, and the presence of HT is a protective factor for PTC.

KEYWORDS: Hashimoto's thyroiditis, PTC, inflammation, relationship, clinical features

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Introduction

The main histological types of thyroid cancer are differentiated thyroid cancer (DTC), anaplastic thyroid cancer, and medullary carcinoma.[1] Differentiated thyroid cancer includes papillary thyroid carcinoma (PTC) and follicular thyroid cancer (FTC). Initial treatment for DTC is usually surgery (ie, lateral lobectomy or total thyroidectomy), radioactive iodine therapy, and lifelong thyroid-stimulating hormone (TSH) suppression.[2] Previous studies have shown that chronic lymphocytic infiltration may often be found in PTC patients, suggesting that autoimmune factors may be involved in tumor development.[3] Hashimoto thyroiditis (HT) is the most common autoimmune thyroid disease and the most common cause of hypothyroidism which usually occurs in young women.[4] The thyroid function is mostly normal, but it can occur in a few cases. Abnormalities, of which hypothyroidism is the most common. Clinically, HT patients with normal thyroid function usually do not have any symptoms with the main sign being goiter. Ultrasonography results showed that the echogenicity of the glandular parenchyma is reduced, and the uneven grid-like changes. Laboratory tests showed that thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) were both positive and the levels were significantly elevated.[5] The pathological features of HT are diffuse lymphocytic infiltration, fibrosis, and atrophy of the thyroid parenchyma.[6] At present, whether there is a relationship between HT and PTC has attracted the attention of many researchers. Previous studies revealed that there are some common molecular pathway changes between PTC and HT, such as phosphatidylinositol 3-hydroxy kinase (PI3 K)/protein kinase B (AKT), CD98, p63, and so on.[7] Therefore, some researchers believed that there is a connection between PTC and HT. It has been found that the

incidence of HT in patients with PTC has increased sharply, but its pathogenesis is still unclear. At present, there are still many controversial points about the relationship between HT and PTC, especially the complex mechanisms, and various clinical features have not yet been elucidated. In the present study, the clinical characteristics of PTC patients were analyzed by comparing patients with PTC combined with HT and those without HT to explore the effect of HT on the biological behavior of PTC.

Materials and Methods

Patients

The clinical data of 200 patients with PTC in the Department of Breast and Thyroid Surgery of the first affiliated hospital of Chongqing Medical University of China from August 2018 to January 2022 were retrospectively analyzed. The pathological reports of the patients after surgery all met the diagnostic criteria for PTC and HT. We randomized 100 patients of papillary thyroid carcinoma and 100 patients of papillary thyroid carcinoma complicated with Hashimoto's thyroiditis based on pathological reports. Among the 200 patients, 42 were males, while 158 were females with an average age of 41.63 ± 6.75 years, of which 198 were Han and 2 were ethnic minorities (Miao and Tujia). All 200 cases were diagnosed with PTC or its variants. A total of 100 patients with PTC and HT were included in the PTC group, and 100 patients with PTC without HT were included in the HT + PTC group.

Inclusion criteria: (1) complete case data; (2) all patients who underwent thyroidectomy for the first time were incipient patients; (3) those who did not receive chemotherapy, radiotherapy, and I131 ablation before surgery; (4) lymph node dissection in the central area of the lesion was performed, and routine lymph node pathological examination was performed; (5) total thyroidectomy or unilateral resection was performed; (6) levothyroxine sodium tablets were given orally after surgery; and (7) the clinical data were complete and the follow-up was successful.

Exclusion criteria: (1) patients with lateral cervical lymph node metastasis and distant metastasis confirmed before or during surgery (for the consistency of data comparison); (2) combined with nodular goiter; (3) combined with other thyroid disorders such as subacute thyroiditis and other autoimmune disease; (4) pathological results confirmed thyroid malignancy other than PTC and other cervical malignancies; (5) mental or intellectual disability; (6) preoperative use of drugs that affect thyroid function testing and thyroid function; and (7) patients with incomplete clinical data are easily lost to follow-up.

According to the inclusion and exclusion criteria, a total of 200 PTC patients were included in the present study, and they were divided into the PTC group (n = 100) and the HT + PTC group (n = 100) according to whether or not HT was combined, respectively. Hashimoto thyroiditis diagnostic criteria are high level of TPOAb (>35 U/mL) or TgAb (>116 U/mL); with or without diffuse thyroid enlargement; with or without clinical and biochemical hypothyroidism; TSH suppression therapy up to the target that according to the 2015 American Thyroid Association (ATA) guidelines for the diagnosis and treatment of adult thyroid nodules and DTC,[8] the recurrence risk stratification is for high-risk patients, and the guidelines recommend TSH suppression level < 0.1 mU/L; for intermediate-risk patients, TSH is recommended to be controlled at 0.1 to 0.5 mU/L; for low-risk patients, TSH is recommended to be controlled at 0.6 to 2.0 mU/L.

The pathological criteria for combined HT include the following items: cancer cells are arranged in papillary or follicular shape, lymphocyte infiltration can be seen in the papillary axis, cancer tissue and HT lesions coexist, and cancer cells are mainly small foci like "seed-like" scattered in HT. In lesions or fibrous tissue, there is a transition zone phenomenon between HT and cancer tissue, manifested as atypical proliferation of follicular epithelial cells migrating to papillary hyperplasia and papillary carcinoma cells.

Methods

Surgical methods. The operation was completed by two deputy chief physicians of the Breast and Thyroid Surgery Department of the First People's Hospital Affiliated with Chongqing Medical College. According to the 2015 edition of the ATA guidelines,[8] all patients underwent intraoperative rapid frozen pathological sections to confirm PTC, and total thyroidectomy and lesion-side central lymph node dissection were used for the surgical selection. The range of lymph node dissection in the central area is as follows: up to the lower border of the hyoid bone, the outer border of the lateral common carotid artery, the middle to the midline of the trachea, the lower border to the upper border of the thymus, and the depth reaches the third layer. During the operation, the recurrent laryngeal nerve was exposed by the upper or lower approach, and the whole process was exposed.

Detection indicators and judgment standards. Levels of thyroid function indicators, blood biochemical indicators, and liver function indicators: extract 3 tubes of 3 mL peripheral venous blood from patients on an empty stomach in the morning, after natural coagulation, centrifuge at 3000 rpm for 5 minutes, take the upper serum, and place it at −80 °C for testing. The above indicators were detected by thyroid function analyzer MN-6110 and American Beckman AU680 large-scale automatic biochemical analyzer.

Papillary thyroid microcarcinoma (PTMC)/PTC positive judgment criteria: high-resolution ultrasound imaging and ultrasound-guided fine needle aspiration biopsy (FNAB). The diagnosis was based on the diagnostic criteria for thyroid nodules in the 2015 ATA guidelines for the diagnosis and treatment of thyroid nodules and DTC.[8] Ultrasound examination

items include the following: (1) the edge is rough or smooth; (2) the shape is regular (round or oval) and irregular; (3) the internal echo is extremely low echo, hypoechoic, isoechoic, slightly hyperechoic, and isoechoic; (4) the aspect ratio of the nodule is the nodule—the ratio of anterior-posterior diameter to the transverse meridian; (5) intranodular calcification: punctate tiny calcifications (calcification diameter $\leqslant 0.2$ cm), plaque-like calcifications (calcification diameter > 0.2 cm), and wheel calcifications (located in circular calcification at the edge of the nodule); (6) if the cervical lymph nodes are irregular in shape, with an aspect ratio $\geqslant 1$, and the ratio of skin to medullary is abnormal, it is regarded as cervical lymph node enlargement; (7) blood flow grading standard: according to the guidelines, the blood flow types are divided into type I (no blood flow), type II (rich blood flow signals can be detected in and around the nodule), and type III (rich blood flow in the nodule, no blood flow signal or blood flow around the nodule or less signal).

Ultrasound examination: Using the Affiniti50 color Doppler ultrasound system of Royal Philips Electronics of the Netherlands to examine the patients, and set the probe frequency to 5 to 12 MHz. The patients were placed supine on the examination bed, the neck was fully exposed, the shape, size, parenchymal echo, and calcification type of the thyroid gland were examined by two-dimensional ultrasound technology, and the distribution of blood flow signals in the glands, nodules, and surrounding areas of the thyroid gland was observed. The examination results were judged jointly by two experienced radiologists in our hospital. If there is any disagreement, the director of the imaging department of our hospital can be invited to make a diagnosis.

Observation indicators. The data of the PTC group and the HT + PTC group were recorded, respectively, and the main data of the following five groups were analyzed: (1) the preoperative age, gender, ethnicity, maximum tumor diameter, the number of lymph node metastases in the central region, the number of metastases in the lateral cervical region, the incidence of PTMC, and the incidence of BRAF positive were collected; (2) postoperative thyroid function indicators including free triiodothyronine 3 (FT3), free triiodothyronine 4 (FT4), total triiodothyronine 3 (TT3), total triiodothyronine 4 (TT4), thyrotropin (TSH), thyroglobulin (TG), TGAb, and TPOAb levels; (3) blood biochemical indicators including total white blood cells (WBC), total red blood cells (RBC), hemoglobin (Hb), mean RBC hemoglobin content (MCH), platelets (PLT), absolute value of neutrophils (NEUT), absolute value of lymphocytes (LYM), absolute value of monocytes (MONO), absolute value of eosinophils (EO), and basophilia neutrophil absolute value (BASO) levels; (4) liver function indicators including the levels of total bile acids (TBA), total bilirubin (Tbil), direct bilirubin (DB), Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), and lactate dehydrogenase (LDH); (5) postoperative histopathological report, hematoxylin-eosin (HE) stained sections of pathological tissue, immunohistochemical results; and (6) postoperative color Doppler ultrasound test results, whether PTC invaded the thyroid capsule, and so on to organize and analyze the data. The above data were combined to analyze the effect of HT on PTC.

HE staining and immunohistochemistry. Select tissue samples containing thyroid cancer cells obtained through surgical biopsy and quickly fix them in a 10% neutral formalin solution to maintain the morphology and structure of the cells and tissues. Place the fixed tissue samples in increasing concentrations of ethanol solution (70%, 80%, 90%, 95%, and 100%) for dehydration treatment in sequence. Soak each concentration for a certain period of time to remove moisture from the tissue. Place the dehydrated tissue in xylene for transparency treatment to make it transparent and facilitate subsequent wax immersion. Soak the tissue in melted paraffin to allow the paraffin to fully penetrate into the tissue. Place the tissue soaked in wax into a mold, inject paraffin wax, and solidify it into wax blocks. Cut the wax block into thin slices with a thickness of about 4 to 6 μm using a slicer. Flatten the cut slices in warm water and transfer them onto a glass slide. Place the glass slide in the oven and bake at an appropriate temperature for a period of time to firmly attach the slice to the slide. Sequentially place the slices into xylene and decreasing concentration ethanol solutions (100%, 95%, 80%, and 70%) for dewaxing and rehydration. Put the slices into HE staining solution for a certain period of time to stain the cell nucleus. Differentiate with hydrochloric acid and alcohol, remove excess staining, and then use ammonia water for blueing. Place the slices in eosin staining solution to stain the cytoplasm. Place the slices in an increasing concentration of ethanol solution for dehydration, then place them in xylene for transparency, and finally seal the slices with neutral gum.

Puncture to obtain thyroid cancer tissue samples. Fixed with formalin to maintain cell morphology and antigenicity. Dehydration, transparency, wax immersion treatment, and then embedding into paraffin blocks. Cut the paraffin block into 3 to 5 μm thick thin slices and adhere them to a glass slide. Place the glass slide in the oven to ensure that the slices adhere tightly. Remove paraffin wax sequentially with xylene and gradient ethanol, and hydrate the tissue. Using methods such as thermal repair or enzyme repair to expose the blocked antigenic determinants (HBME-1 monoclonal antibody). Use 3% hydrogen peroxide solution to reduce non-specific staining and non-specific antibody binding. Add the primary antibody and incubate at an appropriate temperature. After binding with the primary antibody, add the secondary antibody and incubate. Add 3,3′-diaminobenzidine (DAB) color reagent to color the positive area—commonly used hematoxylin to counterstain

cell nuclei. Dehydrate sequentially with gradient ethanol, make transparent with xylene, and finally seal with neutral gum. The above process is strictly carried out in accordance with the instructions.

Key indicators analysis. The sensitivity, specificity, receiver operating characteristic (ROC) curve, area under the curve (AUC), and convolutional feature heatmaps were calculated to evaluate the effect on key indicators on patients.

Ethics statement. This study was approved by the Ethics Committee of the First People's Hospital Affiliated to Chongqing Medical University (106312024-008) in August 2018. In addition to approving study protocols, informed consent was obtained from all subjects involved in this study. Furthermore, we confirm that the data associated with this manuscript are anonymized.

Statistical analysis

The SPSS 20.0 statistical software was used for data analysis, normally distributed measurement data were expressed as mean ± standard deviation ($x \pm s$), count data were expressed as case number and rate (%), and t-test was used for comparison between groups; $P < .05$ was considered a statistically significant difference. The receiver operating characteristic curve and AUC values were adopted to demonstrate the effect of key indicators and relationship with patients.

Results

Basic clinicopathological characteristics of patients

There were 100 PTC patients in this study (PTC group). There were 26 males and 74 females, with a male-to-female ratio of 1: 2.85. The age of the patients ranged from 19 to 67 years old, the median age was 43 years old, 87 patients were < 55 years old, and 13 patients were > 55 years old. Female PTC patients accounted for 74% of the total patient population, with an average age of 43.82 ± 11.74 years, and an age range of 19 to 67 years old. Male patients with PTC accounted for 26% of the total incidence of patients, the mean age was 37.08 ± 14.59 years, and the age range was 19 to 63 years old. The average age of onset in female patients was older than that in male patients, and the difference was statistically significant ($P < .05$).

There were 100 patients with PTC + HT in this study (PTC + HT group). Among them, 16 were male and 84 were female, with a male-to-female ratio of 1:5.25. The age of the patients ranged from 19 to 67 years old, the median age was 43 years old, 96 cases were < 55 years old, and 4 cases were > 55 years old. Female PTC + HT patients accounted for 84% (84 cases) of the total patient population, with an average age of 41.26 ± 10.74 years and an age range of 19 to 67 years. Male PTC + HT patients accounted for 16% (16 cases) of the total morbidity group, with an average age of 41.75 ± 11.3 years and an age range of 21 to 62 years. The mean age of onset in female patients was similar to that in male patients, and the difference between the two was not statistically significant. In addition, compared with the PTC group, the proportion of females in the PTC + HT group was significantly higher than that of the males ($P < .05$). In addition, the incidence in the PTC + HT group was significantly lower than that in the PTC group ($P < .05$) (Table 1).

Pathological and biological features

Compared with the PTC group, there were significant differences in the central lymph node metastasis rate, the number of cervical lymph node metastases, and the lateral cervical lymph node metastasis rate in the PTC + HT group ($P < .05$). Among them, the central lymph node metastasis rate, the number of cervical lymph node metastases, and the lateral cervical lymph node metastasis rate in the PTC + HT group were significantly reduced. In addition, there were no significant differences in the maximum tumor diameter, the number of lymph node metastases in the central region, the incidence of microcarcinoma, and the incidence of BRAF positive (Table 1).

Thyroid function indexes

Compared with the PTC group, the TPOAb, TSH, and TGAb of the PTC + HT group were significantly increased, while the TG value was significantly decreased, and the difference between the two groups was statistically significant ($P < .05$) (Table 2). There were no significant differences in other thyroid function indicators.

Blood biochemical indexes

Compared with the PTC group, there was no significant difference in the blood biochemical indexes which include WBC (Figure 1A), RBC (Figure 1B), PLT (Figure 1C), NEUT (Figure 1D), MONO (Figure 1E), MCH (Figure 1F), LYM (Figure 1G), Hb (Figure 1H), EO (Figure 1I), and BASO (Figure 1J) in the PTC + HT group.

Liver function indexes

The characteristics of liver function indexes between the PTC + HT group and the PTC group are shown in Figure 2. Compared with the PTC group, there were no significant differences in other liver function indexes including ALT (Figure 2A), AST (Figure 2B), GGT (Figure 2D), DB (Figure 2E), TBA (Figure 2G), and TBil (Figure 2H). In addition, the ALP level was significantly lower than the PTC group (Figure 2C), while the LDH level was significantly higher than the PTC group (Figure 2F) in the PTC + HT group.

Table 1. Clinicopathologic characteristics of the PTC group and the PTC + HT group.

VARIABLE	PTC (N = 100)	PTC + HT (N = 100)	*P* VALUE
Age/year	41.34 ± 11.74	43.92 ± 12.12	.903
Age n (%)			.031
>55	13 (13%)	4 (4%)	
Gender n (%)			.028
Male	26 (26%)	16 (16%)	
Female	74 (74%)	84 (84%)	
Central lymph node metastasis n (%)			.037
Yes	66 (66%)	49 (49%)	
No	34 (34%)	51 (51%)	
Lateral cervical region metastasis n (%)			.029 9
Yes	31 (31%)	21 (21%)	
No	69 (69%)	79 (79%)	
Size of largest focus D/mm	8.25 ± 0.42	8.45 ± 0.31	.102
Microcarcinoma (%)			.575
Yes	69 (69%)	73 (73%)	
No	31 (31%)	27 (27%)	
Number of central lymph node metastasis lymph node n	2.58 ± 1.31	2.05 ± 1.21	.217
Number of lateral cervical region metastasis	1.29 ± 2.83	0.73 ± 2.52	.000
BRAF + (%)	48 (48%)	44 (44%)	.485
Demographic race	Han (100%)	Han (98%), Miao (1%) and Tujia (1%)	

Papillary thyroid carcinoma (PTC) group; Papillary thyroid cancer complicated with Hashimoto's thyroiditis (PTC + HT) group.

Postoperative histopathological results

In terms of pathological examination results, the mean number of central lymph node metastases in the PTC + HT group was 2.05 ± 1.21, while that in the PTC group was 2.58 ± 1.31, with no significant difference ($P = 0.217$; Table 1). The average number of lymph node metastases in the lateral cervical region in the PTC + HT group was 0.73 ± 2.52, while the average in the PTC group was 1.29 ± 2.83, which was significantly higher than that in the PTC + HT group ($P = .000$, Table 1). In addition, the pathological features of HE pathological sections of PTC are as follows: the papilla has many branches, there is a fibrovascular interstitium (true papilla) in the center of the papilla, and there are common concentric calcified bodies in the interstitium, that is, the psammoma body. The papillary epithelium can be single or multi-layered, and the cancer cells can be differentiated in different degrees, with little nuclear chromatin, often clear or ground glass, and no nucleoli (Figure 3A). In the HE pathological section of HT combined with PTC, lymphocytes can be seen infiltrated by a large number of mononuclear cells in the follicular interstitium, mainly lymphocytes, plasma cells, and macrophages, forming true lymphoid follicles. Hashimoto thyroiditis cells are located in peripheral cortical areas, often with prominent germinal centers (Figure 3B). HBME-1 monoclonal antibody is a useful adjunct immunostain to differentiate papillary and follicular carcinomas of thyroid from benign lesions. Immunostaining was performed with Leica Bond-Max automatic immunostainer by HBME-1 staining. The positive expression of immunohistochemistry was brown-yellow granules, which were distributed in the envelope and cytoplasm (Figure 3C and D).

Postoperative ultrasound result

Ultrasonography plays an important role in the detection of thyroid nodules, the identification of benign and malignant

Table 2. Comparison of postoperative thyroid function between PTC group and PTC + HT group.

GROUP	TOTAL CASES	FT_3(PMOL/L)	FT_4(PMOL/L)	TT_3(NMOL/L)	TT_4(NMOL/L)	TPOAB(IU/ML)	TSH(μIU/ML)	TGAB(IU/ML)	TG(μG/L)
PTC group	100	3.14 ± 0.45	0.90 ± 0.12	1.02 ± 0.24	8.51 ± 1.43	33.91 ± 1.95	2.23 ± 1.94	15.67 ± 2.17	19.46 ± 3.48
PTC + HT group	100	3.21 ± 0.56	0.85 ± 0.13	1.04 ± 0.16	7.94 ± 2.32	137.52 ± 2.15*	3.08 ± 1.28*	112.67 ± 7.89*	8.57 ± 1.25*
P		.915	.895	.986	.754	.000	.021	.000	.000

[1]Papillary thyroid carcinoma (PTC) group; papillary thyroid cancer complicated with Hashimoto's thyroiditis (PTC + HT) group.
[2]Free triiodothyronine 3 (FT3); free triiodothyronine 4 (FT4); total triiodothyronine 3 (TT3); total triiodothyronine 4 (TT4); thyroid peroxidase antibody (TPOAb); thyroid-stimulating hormone (TSH); thyroglobulin antibody (TGAb); thyroglobulin (TG).
[3]The data represent the mean ± SD (n = 100) per group.
*$P < .05$, versus PTC group.

nodules, and follow-up monitoring. In the present study, the ultrasound images of 200 patients were analyzed, respectively (Figure 4). The main features included: (1) papillary carcinomas were mostly manifested as substantive hypoechoic nodules (85.6%; Figure 4A); (2) most of the nodules of PTC were irregular in shape, with indistinct borders (70.5%), often burr-like, without obvious halo or capsule around (Figure 4B); (3) there were microcalcifications in cancer nodules (78.1%; Figure 4C); (4) there were abundant and tortuous blood flow signals in or around the nodules detected by Doppler ultrasonography (67.1%; Figure 4D); and (5) some PTCs were accompanied by cervical lymph node metastasis and enlargement (9.2%; Figure 4E). Combined with relevant studies, if there are abundant cells in the fine needle aspiration smear, and the nucleus-to-cytoplasmic ratio is increased, the nuclei overlap, combined with the characteristic manifestations of ground glass-like nuclei, nuclear grooves, and papillary structures, PTC can be diagnosed. However, in the B-ultrasound examination of PTC + HT patients, the boundary definition rate was lower, and the results of the study showed that the boundary definition rate was 0.00% (Figure 4F). B-ultrasound examination with clear borders can be used as the basis for the diagnosis of thyroid cancer with Hashimoto's thyroid gland.

Result of key indicators on patients

Receiver operating characteristic and AUC curves are important indicators to determine whether the results predicted by the dichotomous model are good enough. $0.5 < AUC < 1$, better than a random guess. This classifier (model) can have predictive value if the threshold value is properly set. The comparison of the ROC curves, sensitivities, and specificities of the 200 patients (HT, HT + PTC) is presented in Figure 5. The AUC value was 0.927, 0.896, 0.813, 0.786, 0.689, and 0.922 corresponding to age (Figure 5A), gender (Figure 5B), central lymph node metastasis (Figure 5C), lateral cervical region metastasis (Figure 5D), number of central lymph node metastasis (Figure 5E), and number of lateral cervical region metastasis (Figure 5F), respectively.

Discussion

Hashimoto thyroiditis, also known as autoimmune thyroiditis, is considered to be a disease caused by the destruction of epithelial cells by autoimmune tissue and is one of the important causes of hypothyroidism.[9] Serological test results showed the presence of a large number of lymphocytes and antibodies in the thyroid tissue.[10] Hashimoto thyroiditis is more common in females, and there is a significant difference in the ratio of males and females.[11] Previous research results showed that part of the thyroid parenchyma was atrophied, and the thyroid tissue showed diffuse lymphocytic infiltration changes in HT patients.[12] Because HT is a chronic disease, its disease progresses slowly, and patients may have masses in the thyroid gland. A small number of patients may have a lump with

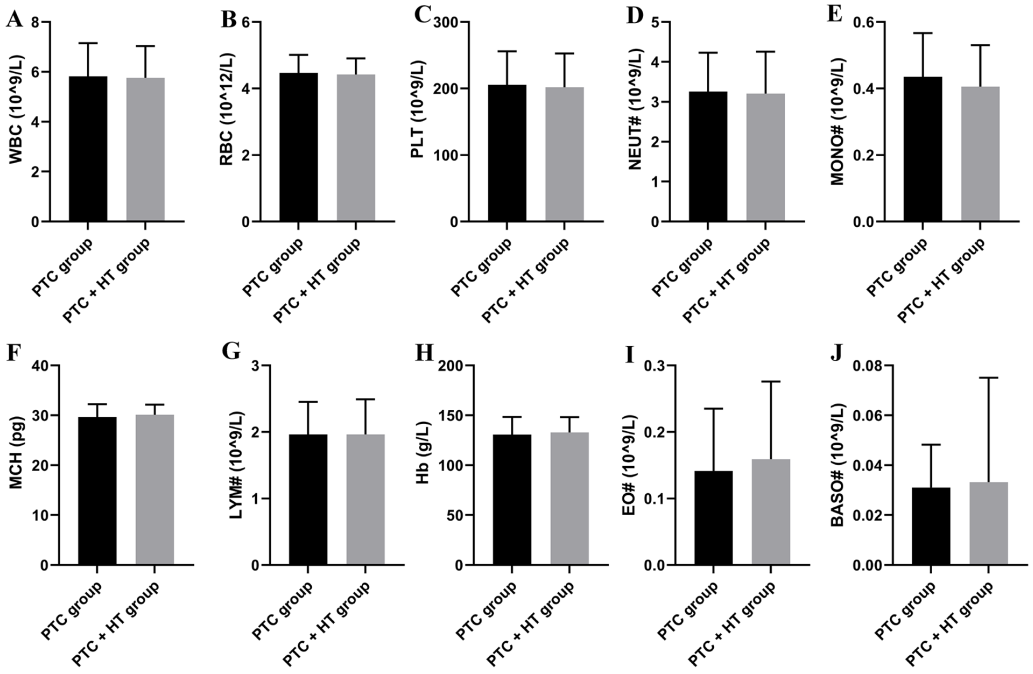

Figure 1. Comparison of characteristics of blood biochemical indexes between PTC group and PTC + HT group: (A) white blood cells (WBC), (B) red blood cells (RBC), (C) platelets (PLT), (D) neutrophils (NEUT), (E) monocytes (MONO), (F) mean RBC hemoglobin content (MCH), (G) lymphocytes (LYM), (H) hemoglobin (Hb), (I) eosinophils (EO), and (J) basophilia neutrophil absolute value (BASO).
The data represent the mean ± SD (n = 100) per group.
*$P < .05$, versus PTC group.

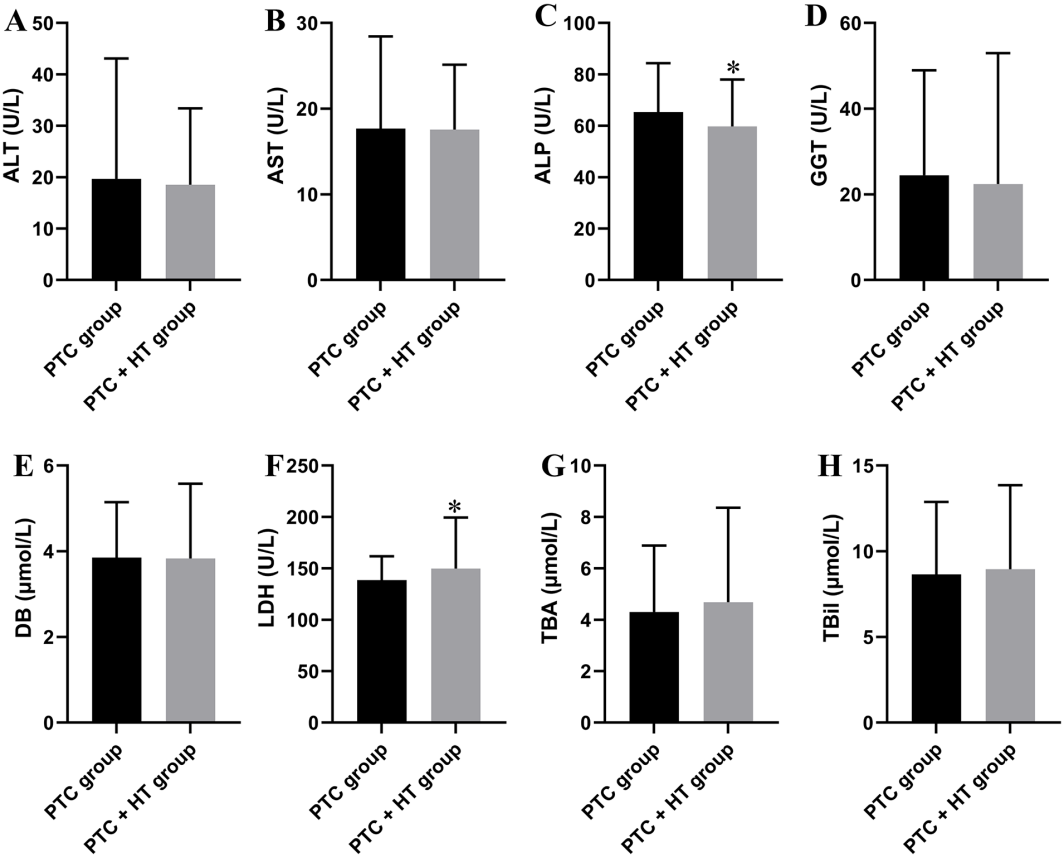

Figure 2. Comparison of characteristics of liver function indexes between papillary thyroid carcinoma (PTC) group and papillary thyroid cancer complicated with Hashimoto's thyroiditis (PTC + HT) group: (A) alanine aminotransferase (ALT), (B) aspartate aminotransferase (AST), (C) alkaline phosphatase (ALP), (D) γ-glutamyltransferase (GGT), (E) direct bilirubin (DB), (F) lactate dehydrogenase (LDH), (G) total bile acids (TBA), and (H) total bilirubin (Tbil).
The data represent the mean ± SD (n = 100) per group.
*$P < .05$, versus PTC group.

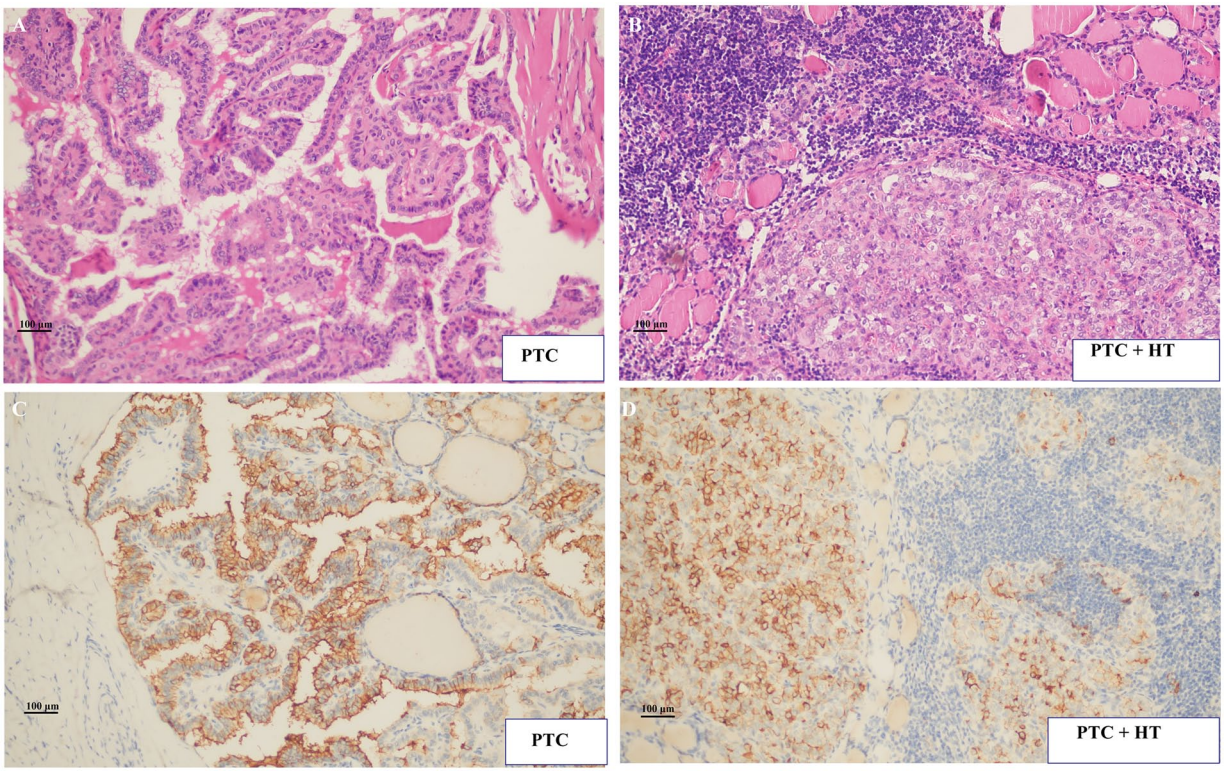

Figure 3. Representative cases of hematoxylin-eosin (HE) staining and immunohistochemistry results of papillary thyroid carcinoma (PTC) group and papillary thyroid cancer complicated with Hashimoto's thyroiditis (PTC + HT) group respectively: (A) HE staining result of PTC group, (B) HE staining result of PTC + HT group, (C) immunohistochemistry result of PTC group, and (D) immunohistochemistry result of PTC + HT group.

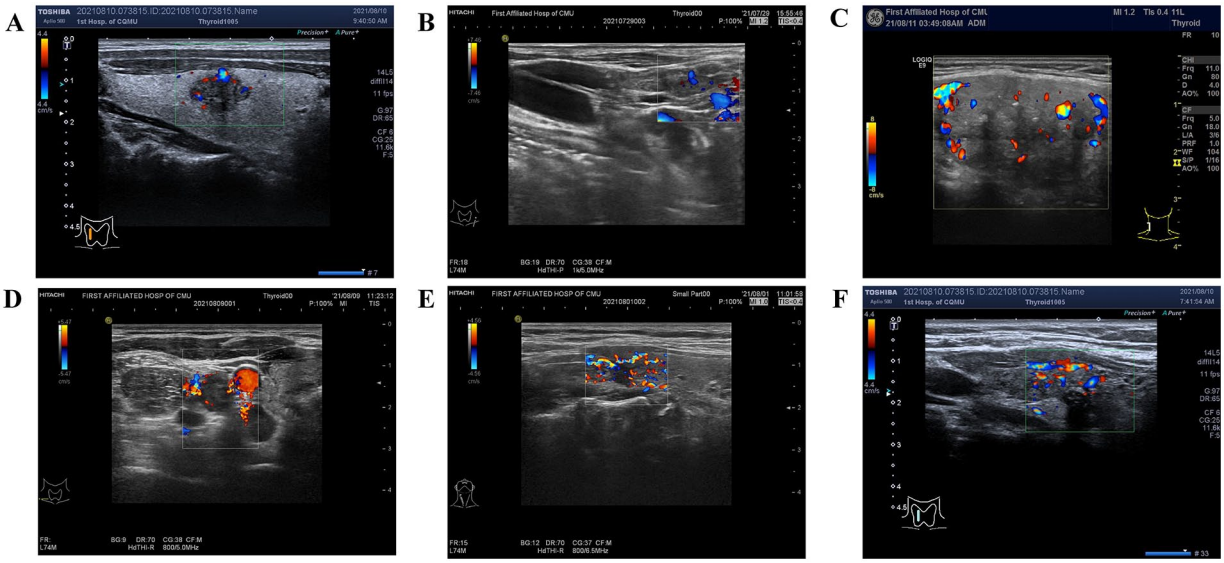

Figure 4. Ultrasound lesion feature map and ultrasound signal distribution feature map of papillary thyroid carcinoma (PTC) group and papillary thyroid cancer complicated with Hashimoto's thyroiditis (PTC + HT) group respectively: (A) substantive hypoechoic nodules, (B) irregular in shape, with indistinct borders, (C) microcalcifications, (D) abundant and tortuous blood flow signals, (E) cervical lymph node metastasis and enlargement, and (F) the boundary definition rate was lower.

headache, but lymphadenopathy is rare.[13] Papillary thyroid cancer is mostly related to the damage of radiation to the body, such as the use of related high-resolution inspection equipment may also lead to an increase in its incidence. More than 90% of PTC patients are derived from DTC.[14] Compared with other malignant tumors, PTC patients have a

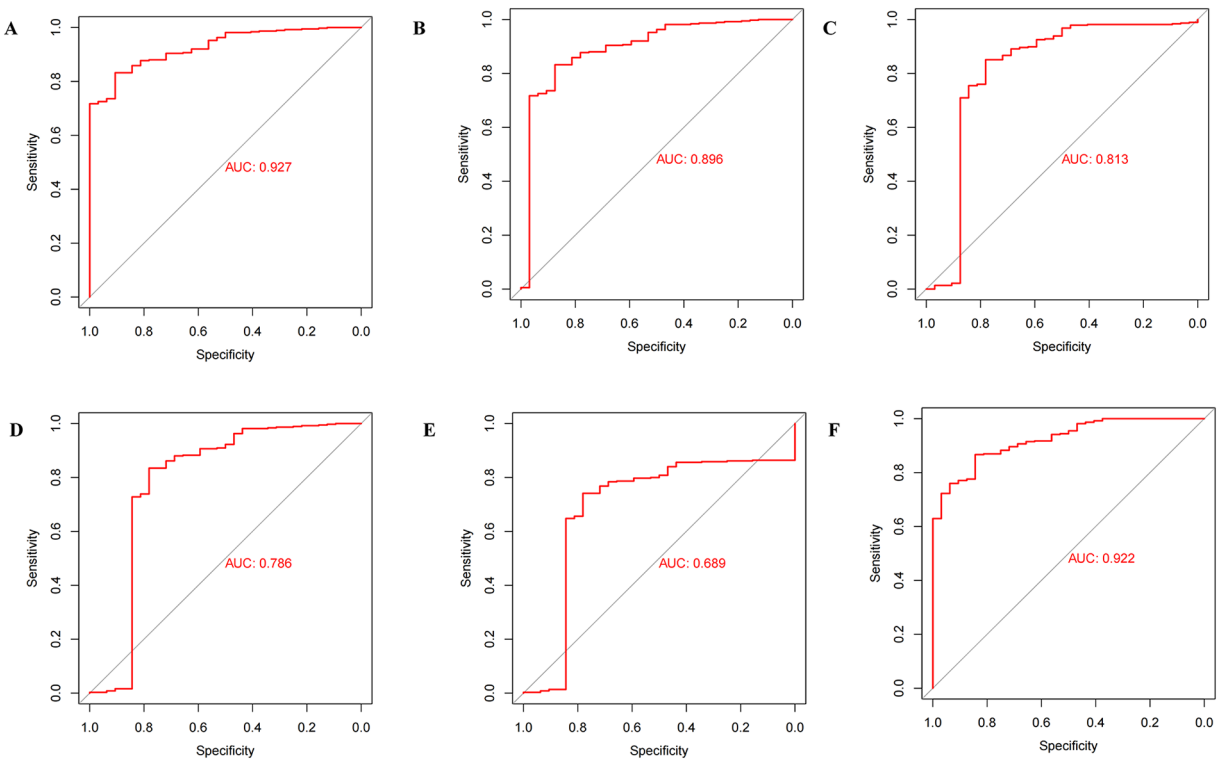

Figure 5. Receiver operating characteristic (ROC) curves for key indicators: (A) age, (B) gender, (C) central lymph node metastasis, (D) lateral cervical region metastasis, (E) number of central lymph node metastasis, and (F) number of lateral cervical region metastasis.

higher survival rate. Patients with early PTC have no obvious symptoms, and the mass can be palpated from the thyroid gland, which is generally not accompanied by pain.[15] Patients with advanced PTC have obvious symptoms, such as pharyngeal foreign body sensation, dysphagia, and hoarseness.[16] There is a certain degree of difficulty in treatment, and surgical treatment is often used, supplemented by thyroxine and related drugs. Patients who have undergone surgery need to formulate appropriate treatment plans and timely intervention for patients with postoperative recurrence.

The results of the present study showed that there were significant differences in age, gender, central lymph node metastasis rate, number of cervical lymph node metastasis, and lateral cervical lymph node metastasis rate between the PTC group and the HT + PTC group ($P < .05$). This is mainly due to the PTC patients with HT tend to be younger and more common in females. A review of relevant literature found that there is no clear conclusion on the factors that affect the recurrence of PTC patients. Previous study shows that most PTC patients have lymph node metastasis before diagnosis, and HT may have a certain protective effect on PTC.[17] The thyroid-specific antigen produced by HT will destroy the thyroid follicular cells in PTC, and thyroid follicular cells can synthesize and secretion of thyroid hormones, which can directly inhibit the proliferation, division, and metastasis of thyroid follicular cells.[18] At the same time, T cells and interleukin-1 in thyroid tissue can destroy and inhibit the metastasis of tumor cells. The prognosis of PTC patients with HT is relatively good and the recurrence rate is low.[19] The $BRAF^{V600E}$ mutation is a common driver mutation in PTC, occurring in approximately 45% of patients.[20] Some studies have demonstrated that $BRAF^{V600E}$ mutation can be used as an independent predictor of PTC recurrence and is associated with extranodal metastasis, lymph node metastasis, TNM staging, and other poor prognostic factors.[21] There are few reports on the detection of $BRAF^{V600E}$ mutation in HT. Previous studies indicated that BRAF mutations can be detected in PTC combined with HT, but the mutation rate is lower than that of PTC alone. In the present experiment, the positive rate of $BRAF^{V600E}$ protein in the PTC + HT group was similar to that in the PTC group, which may be related to the size of the sample.

Thyroid-stimulating hormone is one of the hormones secreted by the anterior pituitary, and its main function is to control and regulate the activity of the thyroid gland.[22] Elevated serum TSH is common in primary hypothyroidism, while decreased serum TSH is common in primary hyperthyroidism. Thyroid peroxidase antibody and TGAb are due to damage to thyroid cells, "peroxidase (the key enzyme for synthesizing thyroid hormone)" in the cytoplasm and "thyroid hormone."[23] The "globulin" overflows into the blood and stimulates the body to produce, which is a hallmark antibody of autoimmune thyroiditis, and its elevated level indicates that the thyroid tissue is in an active state of immune inflammation.[24] Thyroglobulin is a macromolecular glycoprotein secreted by thyroid follicular epithelial cells which is not directly secreted into the blood and a special thyroid marker. Thyroglobulin in the blood increases

when thyroid damage, thyroid cancer, or an overactive thyroid occurs.[25] It was revealed that long-term oral administration of thyroxine tablets in HT patients, low levels of levothyroxine tablets (<0.90 μg/kg) can stimulate the progression of HT to thyroid cancer, and high levels of TPOAb have an effect on the combined HT.[26] Progression of PTC patients may have a protective effect, and TPOAb-negative or low-level TPOAb patients have a 1.59-fold increased risk compared with high-level TPOAb patients.[27] Kim et al reported that TGAb status was associated with an increased risk of PTC. It has demonstrated that high levels of TPOAb have a protective effect on patients with PTC combined with HT.[28] Its protective effect is mainly reflected in the tumor progression effect of TGAb may be offset by the protective effect of TPOAb on tumor, and the lymph node metastasis rate of TPOAb-positive PTC patients is lower, and distant metastasis is less common. The results of our study showed that the TSH, TPOAb, and TGAb levels in the PTC + HT group were significantly increased compared with the PTC group, while the TG value was significantly decreased which is consistent with the previous study.

Dailey et al[29] first reported the existence of a link between HT and PTC, and subsequent studies have gradually found that there is a common immune mechanism in the occurrence of the two in 1955. Some scholars believed that HT may also promote the occurrence of PTC.[30] Some studies have shown that HT is a protective factor for PTC. It is believed that lymphocyte infiltration in HT patients will reduce the invasiveness of tumors, and cytokines produced by lymphocytes will inhibit tumor proliferation.[31] However, there are few studies on the effect of HT on the progression of PTC disease and the results are controversial. Marotta et al[32] found that compared with pure PTC (without HT), PTC patients with HT had smaller primary tumor diameter, lower TNM stage, and higher clinical remission rate. Mazokopakis et al[33] also believed that in thyroid tumors, the lymph node metastasis rate and recurrence rate of HT patients are lower than those of simple PTC, and the prognosis is better. In the present study, we focused on the relationship between HT and PTC and analyzed various indexes of the PTC group and the PTC + HT group. Patients with HT and PTC + HT had several different pathological and biological features, respectively. The results showed that the females of the patients in the HT + PTC group were predominant compared with the PTC group ($P < .05$). The central lymph node metastasis rate, the number of cervical lymph node metastases and the lateral cervical lymph node metastasis rate were significantly decreased ($P < .05$). Thyroid peroxidase antibody, TSH and TGAb in the thyroid function index were significantly increased, while the TG value was significantly decreased ($P < .05$). The ALP level in the liver function index was significantly decreased, while the LDH level was significantly increased ($P < .05$). In the pathological examination, lymphocytes can be seen infiltrated by a large number of mononuclear cells in the follicular stroma. In the B-ultrasound examination, the boundary definition rate is lower.

There are still some limitations in the manuscript. First, the study is a retrospective analysis, limited by the content, accuracy, and availability of the clinical records used. Second, the enrolled cases in this study were all patients from the local area, with a small number included. At the same time, the research was limited to existing clinical and pathological data, and due to the tumor characteristics and time constraints of PTC, it was not possible to determine whether there was a clear causal relationship between HT and PTC. In addition, due to the small sample size and limited follow-up time included in this study, there may be some bias in the conclusions drawn. In the future, large-scale and deeper research is needed.

Conclusion

In conclusion, women may be more susceptible to PTC or PTC and HT than men. Patients under 55 years old accounted for a larger proportion in PTC + HT than PTC. The present study revealed that HT may play an inhibitory role in the occurrence of PTC. The thyroid-specific antigen produced by HT may destroy the thyroid follicular cells in PTC; therefore, the existence of HT may be a protective factor for PTC. On this basis, more effective drugs may be developed to enhance the clinical efficacy of HT combined with PTC and improve the prognosis of patients.

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Author Contributions

KZ and JXM conceived and designed the project. JXM and KZ finished the experiment and wrote the article. JXM and KZ conducted analysis on the present study. All authors have read and approved the manuscript.

Data Availability

The raw data supporting the conclusions of this article will be made available by the corresponding author, without undue reservation.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (106312024-008). Written informed consent was obtained from each patient.

Patient Consent

Written informed consent was obtained from the patients for their information to be published in the manuscript.

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