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Papillary thyroid cancer: prognostic factors and risk assessment

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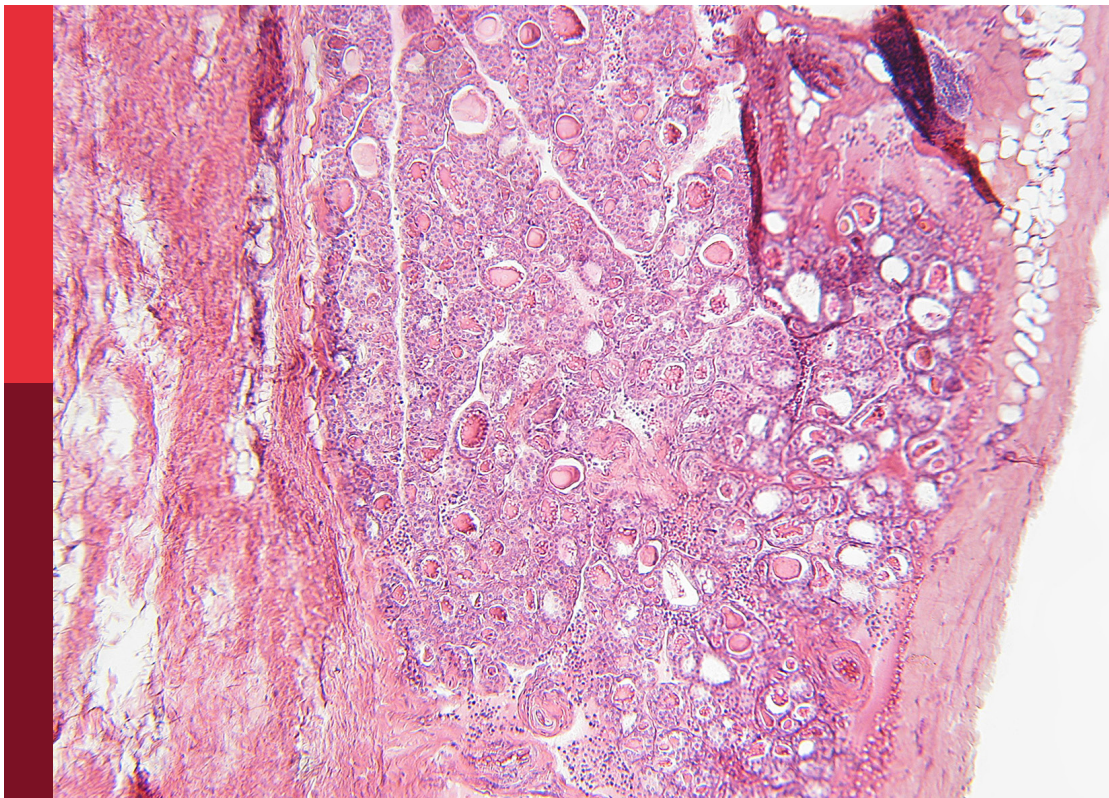

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Papillary thyroid cancer: prognostic factors and risk assessment

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Editorial: Papillary thyroid cancer: prognostic factors and risk assessment

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KEYWORDS

papillary thyroid cancer, thyroid neoplasms, thyroid nodules, prognosis, risk stratification

Editorial on the Research Topic
Papillary thyroid cancer: prognostic factors and risk assessment

Introduction

Thyroid cancer is not only the most common endocrine malignancy, but its incidence has been continuously growing during the last 40 years, being more than triplicated (1). Among thyroid malignancies, papillary thyroid cancer (PTC) is by far the most common, reaching a prevalence of about 80%, and, notably, represents the unique responsible for the increased incidence (2). Upon thyroid ablation (thyroidectomy with or without iodine-131 administration), PTC has excellent prognosis with nearly 100% 5-years disease-specific survival (3) and very low risk of disease recurrence (4). However, 25-30% of patients experience persistent structural disease/recurrence upon initial standard treatment, and a relevant portion of them (11 and 57% for those showing lymph node (LN) and distant metastases, respectively) die as related to PTC (5).

In such scenario, to identify the PTC subgroup with more aggressive behaviour and poorer outcome represents the prognostic goal.

Historically, the risk stratification was based on a limited number of static parameters (6), available at the time of initial treatment, whom prognostic significance had been mainly weighted by retrospective analyses, intrinsically carrying a relevant bias likelihood. Based on the combination of such features, death-predicting [such as the AJCC/TNM (7)] and persistence/recurrence predicting [such as that provided by the American Thyroid Association (ATA) (5)] systems were built, with the latter being the most applied in clinical practice. However, when tested into real-life, these approaches revealed suboptimal long-term risk stratification, due to the low [less than 30% (4)] proportion of variance explained (PVE) [a statistical measure analysing the capability of a staging system to predict the outcome of interest (8)], and, more importantly, to the low positive predictive value (PPV) (9), which impairs the identification of the high-risk patients.

In order to overcome these limitations, the majority of guidelines (10, 11) elaborated a prognostic dynamic model, where disease evolution, as assessed by post-ablative

biochemical and morphological data, was added to static parameters. According to such approach, long-term PTC management is determined by the so-called response to initial therapy assessment, a dynamic evaluation based on the determination of disease status starting 6-18 months after thyroid ablation, and updated at each follow-up visit. The incorporation of such parameter in the prognostic staging has demonstrated dramatic improvement of the risk stratification power (4).

However, an improvement of PTC risk stratification, as based on initial clinico-pathological features, is still required for optimizing clinical management, especially in some challenging settings, such as the heterogeneous category of subjects at intermediate risk of recurrence and the micro-PTC.

Aim of the present Research Topic was to refine the risk assessment of PTC, also focalizing on specific pathological features and PTC settings.

Overviews of the contributions

Overall, 20 articles were published within the Research Topic. One of the most relevant was the study by He et al., which was aimed at improving the initial prognostic stratification, as performed at the immediate post-operative time and therefore based on static clinico-pathological characteristics. Authors applied the decision tree methodology on a large amount of differentiated thyroid cancer patients (mainly composed of PTC) from the SEER database, in order to define a more accurate staging for the prediction of cancer-specific survival (CSS), as compared with the latest AJCC/TNM update [8th Edition (7)]. By means of such approach, a new TNM system was proposed, characterized by better metrics (higher PVE and area under the curve), as compared with the AJCC/TNM.

A number of contributions were focused on the prediction of PTC-related LN metastases (Yoon et al., Zhang et al., Sun et al., Chen et al., He et al.). This is a crucial item, as 30% of PTC patients experience LN involvement, and this event may worsen prognosis, especially in case of lateral macro-metastatic disease (12). Among the mentioned body of papers, we consider of great relevance the study by Yoon et al., which focused on a cohort of micro-PTC, typically characterized by indolent behaviour and even advisable to active surveillance (13). Authors identified a series of pre-operative ultrasonography (US) parameters (extra-thyroidal extension (ETE), multiplicity, upper lobe tumour location, and non-parallel shape) as independent predictors of lateral LN metastasis, therefore providing clinicians useful insights for choosing between surgery and surveillance. Remarkable findings were also provided by Zhang et al., who searched for risk factors of LN spread in PTC patients aged ≥ 65 years. Since age historically represents a predictor of poor survival in PTC, elderly patients have to be considered by definition a high-risk subgroup (14). The most relevant finding of the paper was the independent relationship of a series of clinico-pathological features (male gender, tumour size ≥ 1cm, age ≥ 70, and microcalcifications) with lateral LN metastases, which may allow clinicians to select "very high risk" patients in the context of a high risk category.

Two contributions (Lu et al., Xu et al.) were focused on the most challenging PTC prognostic category, namely the ATA intermediate risk of disease recurrence. This involves heterogeneous cases, from PTC with minimal ETE to those with LN metastases, and prognostics as well as clinical management, particularly attaining the indication to perform radioiodine (RAI) ablation, are not clearly codified (15). Lu et al. found that more than 5 central LN metastases and higher pre-RAI stimulated thyroglobulin (Tg) levels were independent predictors of non-excellent response (not cured disease) after complete thyroid ablation (surgery + RAI). Xu et al. focused on PTC at intermediate risk, as defined by the presence of LN metastases. They found that tumour size, multifocality, concomitant autoimmune thyroiditis, metastatic LN rate, and pre-RAI stimulated Tg were independent predictors of response to complete thyroid ablation.

Ultimately, two contributions (Wang et al., Kim et al.) dealt with pediatric differentiated thyroid carcinoma, where PTC prevalence is even higher, as compared with adults. This represents a hot-topic in thyroid oncology, due to the increasing incidence and the more advanced stage at diagnosis, as compared with adult PTC. We consider as of great relevance results from the Wang et al.'s study, where authors identified a set of independent predictors of disease cure upon complete thyroid ablation: T stage, pre-RAI stimulated Tg, and response to initial treatment [as defined by the ATA guidelines (16)].

Implications and future directions

This Research Topic provides news insights about the prediction of specific pathological features affecting PTC outcome, such as the development of LN metastases, and about the risk assessment in the context of specific clinical settings, such as elderly and pediatric PTC, micro-PTC, and PTC at intermediate risk of recurrence.

The main limit of the studies included in the Research Topic, similarly to the vast majority of publications about PTC prognostics (which represent the mainstay of the current guidelines), is the retrospective nature. Hence, there is a great need of data from prospective observational studies, in order to refine the actual impact of each clinical features on disease outcome and to improve the risk assessment tools.

Author contributions

VM: Writing – original draft, Writing – review & editing. LS: Writing – review & editing. JM: Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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The relationship between thyroid peroxidase antibody and differentiated thyroid cancer: a systematic review and meta-analysis

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Background: Thyroglobulin antibody (TgAb) has been found to be associated with the occurrence and development of differentiated thyroid cancer (DTC) for several years, but there is still controversy over whether thyroid peroxidase antibody (TPOAb) is related to differentiated thyroid cancer.

Methods: We scrutinized relevant studies published up to July 2023 across four major databases including PubMed, Embase, Cochrane Library, and Web of Science, to examine the association between TPOAb and DTC. Clinical outcome measures include the incidence of DTC, tumor size, extrathyroidal invasion, lymph node metastasis, multifocality, recurrence and bilaterality.

Results: 12 original studies were included, involving a total of 20,330 subjects. Our analysis of the included studies revealed that TPOAb+ individuals exhibited a higher risk of developing DTC (OR=1.57 [95% CI: 1.00–2.45], p=0.049) than TPOAb− individuals. Furthermore, TPOAb+ DTC patients were more prone to present with bilateral (OR=1.40 [95% CI: 1.21–1.62], p<0.00001) and multifocal (OR=1.40 [95% CI: 1.23-1.60], p<0.00001) tumors than TPOAb− patients. Sensitivity analysis indicated a high sensitivity for these three findings. No significant differences in the risk of extrathyroidal extension and lymph node metastasis, recurrence rate, tumor size, were observed between TPOAb+ and TPOAb− DTC patients.

Conclusion: The presence of TPOAb is correlated with an increase prevalence of DTC. However, its effectiveness as a prognostic marker for DTC patients warrants further investigation.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42023448824.

KEYWORDS

differentiated thyroid cancer, thyroid peroxidase antibody, prevalence, prognosis, meta analysis

Introduction

Thyroid cancer is one of the most prevalent endocrine malignancies, with its annual incidence increasing in numerous countries and regions. However, the mortality rate remains consistently low (1, 2). Differentiated thyroid cancer (DTC) is the most frequently diagnosed type, accounting for over 95% of cases (3). DTC comprises two main subtypes, with papillary thyroid cancer (PTC) account for 90% of cases and follicular thyroid cancer accounting for 7–8% (4–6). In recent years, increasing studies have reported the association of thyroid cancer with various risk factors, including radiation exposure, environmental factors, iodine intake, serum TSH levels and Hashimoto's thyroiditis (HT) (7–9). Among these factors, thyroid autoimmunity is closely linked to the development of DTC.

Thyroid peroxidase (TPO), an enzyme located in the apical membrane of thyroid follicular cells, is involved in the biosynthesis of thyroid hormone (10). Thyroid peroxidase antibody (TPOAb) is predominantly produced by lymphocytes infiltrating the thyroid gland and is one of the most common autoantibodies against the thyroid (11). It can cause thyroid cell damage through the activation of the complement system and cell cytotoxicity (12, 13). TPOAb is a hallmark thyroid autoimmune antibody in autoimmune thyroiditis (AIT) (14, 15). It is also intricately linked to several other diseases. In 1998, Smyth et al. observed significantly higher TPOAb positivity in breast cancer patients than in those with benign breast disease. Some studies have shown that TPO is expressed in breast cancer and peri-cancerous tissues, and the antigenic and biochemical properties of TPO in breast tissues are similar to those in thyroid tissues, with only minor differences in post-translational modifications (16–18). Furthermore, disease-free and overall survival were longer in TPOAb+ breast cancer patients than in their TPOAb– breast cancer counterparts (19). Numerous subsequent studies have yield similar findings (20–22). Sharma and collaborators proposed that TPOAb might cross-react with lactoperoxidase expressed in breast tissue, potentially explaining the coexistence of TPOAb and breast cancer (23). Additionally, several studies have highlighted a strong association between TPOAb and various adverse pregnancy outcomes (24–26). Furthermore, two separate fine needle aspiration cytology studies from the same center identified TPOAb as an independent risk factor for thyroid malignancy (27, 28). Nonetheless, while many studies have explored the relationship between thyroglobulin antibody (TgAb), another serum marker of AIT, and DTC, the association between TPOAb and DTC remains unclear (29–31).

Previously, a variety of diseases or molecules have been found to be associated with the prognosis of DTC, such as graves' disease, HT, thyrotropin, thyroglobulin (Tg), BRAF mutation, estrogen receptor and VEGF pathway, etc (32–38). And we aimed to conduct a comprehensive meta-analysis and systematic review to elucidate the relationship between TPOAb and DTC. By analyzing extensive large-scale research data, we expect to provide highly in-depth theoretical support for the clinical application of TPOAb in the early diagnosis, formulation of treatment strategies, and prognosis evaluation of DTC.

Methods

Registration

This systematic review was registered (CRD42023448824) in PROSPERO. We continue to update this systematic review with the latest information.

Search strategy

Our systematic literature search encompassed four databases: PubMed, Embase, Web of Science, and Cochrane Library, until July 2023. The search was conducted using the following terms: "thyroid peroxidase antibody" AND "papillary thyroid cancer" OR "follicular thyroid cancer" OR "Hürthle cell thyroid cancer" OR "differentiated thyroid cancer." Supplementary Table S1 provides a comprehensive outline of the search strategy. We selected relevant articles through the evaluation of titles, abstracts, and full texts. Two researchers independently made the selections and reviewed the abstracts and full texts. In instances where multiple original studies involving the same population were published, we selected the most recent and comprehensive study.

Inclusion and exclusion criteria

Studies that met the following criteria were included (1): prospective, retrospective, randomized controlled trial, or case-control study types (2), investigation of TPOAb levels in patients diagnosed with DTC (3), classification of patients based on their TPOAb levels (4), availability of relevant data, and (5) publication in English.

Studies that meet any of the following criteria were excluded (1): review articles, letters, comments, editorials, case reports, or laboratory-animal research (2), incomplete data or unavailability of raw data, or (3) duplication of studies originating from the same dataset.

Two researchers independently screened articles, with any disputes resolved through negotiation or with the assistance of a third author.

Data extraction

We extracted the following information from each included article (1): last name of first author (2), publication year (3), study period (4), country (5), study type (6), sample size (7), total number of TPOAb± patients (8), mean tumor sizes in TPOAb± groups (9), lymph node metastasis in TPOAb± groups (10), extrathyroidal extension in TPOAb± groups (11), tumor multifocality in TPOAb± groups (12), tumor bilaterality in TPOAb± groups, and (13) cancer recurrence in TPOAb± groups.

Quality assessment

In this meta-analysis, two reviewers used the Newcastle Ottawa quality assessment scale (NOS) to evaluate the quality of the

included studies. The NOS assesses the selection of study subjects, comparability between groups, and measurement or exposure of outcomes. Each study received a score ranging from 0 to 9 points. Studies with scores exceeding 6 were considered high quality, those with scores between 4 and 6 were considered moderate quality, and those with scores below 4 were considered low quality. Any discrepancies or inconsistencies were resolved through consensus with a third author.

Statistical analyses

We conducted statistical analyses using Review Manager 5.4 (Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration) and Stata 14 (StataCorp LP, College Station, Texas). The forest plots were generated using Review Manager 5.4. Odds ratio (OR) with a 95% confidence interval (Cl) was used to assess the strength of the association between TPOAb and DTC. Weighted mean difference and 95% Cl were calculated for continuous outcomes. In all meta-analyses, the Cochrane Q p-value and I^2 statistic were used to assess heterogeneity. A random-effect model was employed to merge results when the p-value was < 0.05 or $I^2 > 50\%$, indicating significant heterogeneity; otherwise, a fixed-effect model was used. Statistical significance was set at $p < 0.05$ was considered statistically significant. Publication bias was assessed using Egger test plots in Stata 14.

Results

Study selection

We conducted a comprehensive literature search using PubMed, Embase, Cochrane Library, and Web of Science databases as well as by examining references in relevant reviews up to July 2023. Initially, we identified 878 records. After removing 218 duplicated articles, we screened titles and abstracts, resulting in the selection of 40 studies out of 660 articles. Following a full-text review and application of inclusion and exclusion criteria, we included 12 original studies in the systematic review and meta-analysis. A visual representation of this selection process, following the PRISMA guidelines, is provided in Figure 1.

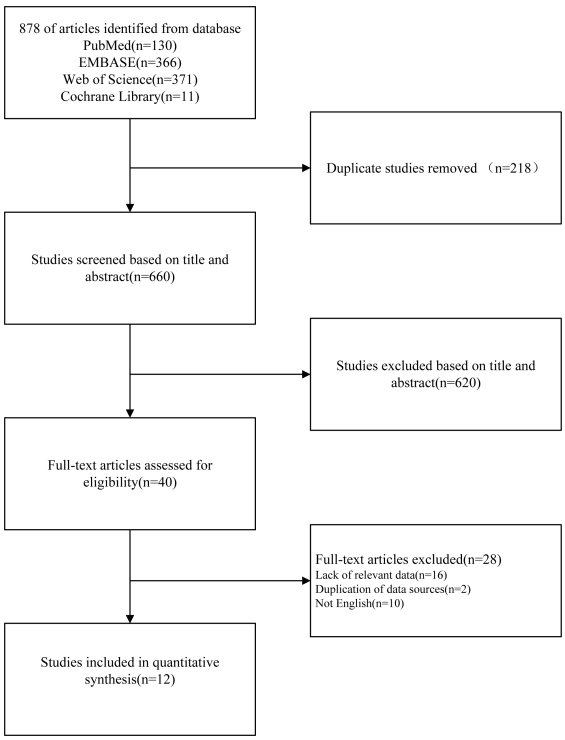

FIGURE 1
Flowchart of the inclusion or exclusion procedure.

Characteristics of included studies

The key characteristics of the 12 eligible studies are summarized in Table 1 (39–50). These 12 case-control studies encompassed 20,330 participants across the United States, China, Greece, Serbia, Korea, and Turkey. We categorized nine studies as having moderate quality and three as high quality. The sample size of the included studies ranged from 179 to 5770. We explored DTC prevalence, tumor size, extrathyroidal extension, lymph node metastasis, tumor multifocality, tumor bilaterality, and cancer recurrence between TPOAb+ and TPOAb– patients across these studies.

TPOAb positivity and DTC prevalence

To explore the association between TPOAb positivity and DTC prevalence, nine studies (39, 41–45, 48–50) were included. DTC prevalence was 62% among 2141 TPOAb+ patients and 46% among 9837 TPOAb– patients. However, no significant association between different TPOAb levels and the risk of developing DTC (OR=1.57 [95% CI: 1.00–2.45], p=0.05) was shown in the forest plot (Figure 2). As the p-value of 0.05 falls exactly on the critical threshold, repeated calculations were conducted using Stata 14, and a value of p=0.049 was ascertained. Egger's regression model did not indicate any publication bias (p=0.45), but a high level of heterogeneity was observed.

TPOAb positivity and tumor size

In our meta-analysis, two studies (42, 44) were selected to compare tumor size with various TPOAb levels. The results did not reveal a significant relationship between different TPOAb levels and tumor size (p=0.54; Figure 3A). However, the number of studies was insufficient for assessing publication bias, and a high level of heterogeneity was observed.

TABLE 1 Main characteristics of all studies included in the meta-analysis.

Study	Publication year	Study type	Study period	Country	Sample size	TPOAb + threshold	TPOAb + individuals	TPOAb− individuals	TPOAb detection time	Outcome	NOS score
Paparodis	2023	Retrospective	2000-2013 (United States) 2007-2021(Greece)	United States、Greece	1635	>34IU/mL	540	1095	Within 3 months before surgery	DTC incidence, tumor size, ETE, LNM	7
Wang	2022	Retrospective	2012-2016	China	5770	>100IU/mL	1123	4647	1 to 2 days before surgery	ETE, MF, LNM, recur, BF	6
Chen	2022	Retrospective	2014-2020	China	319	>34IU/mL	52	267	Before surgery	DTC incidence	7
Huang	2022	Retrospective	2000-2021	China	179	>9IU/mL	64	115	Before surgery	ETE, MF, LNM, recur, BF	6
Li	2021	Retrospective	2015-2018	China	3934	>5.61IU/mL	815	3119	Before surgery	DTC incidence	6
Zorić	2020	Retrospective	2008-2012	Serbia	263	N/A	33	95	NA	DTC incidence	8
Peng	2020	Retrospective	2018-2019	China	322	≥9IU/mL	134	188	Before surgery	DTC incidence	6
Song	2019	Retrospective	2007-2011	China	2070	>60IU/mL	389	1681	Within 90 days before surgery	ETE, LNM,	6
Selek	2017	Retrospective	2009-2014	Turkey	870	>9 IU/mL	228	642	Before surgery	DTC incidence	6
Zeng	2016	Retrospective	2003-2012	China	1198	>20IU/mL	121	870	Before surgery	DTC incidence	6
Qin	2015	Retrospective	2011-2013	China	1638	>5.61IU/mL	136	1502	Before surgery	DTC incidence, tumor size, ETE, LNM, MF	6
Wu	2014	Retrospective	2006-2011	China	2132	>5.61IU/mL	82	2050	NA	DTC incidence, tumor size, ETE, LNM, MF	6

TPOAb+, thyroid peroxidase antibody positive; TPOAb−, thyroid peroxidase antibody negative; DTC, differentiated thyroid cancer; ETE, extrathyroidal extension; LNM, lymph node metastasis; MF, tumor multifocality; BF, tumor bilaterality; recur, cancer recurrence; NOS, Newcastle–Ottawa scale; N/A, not applicable.

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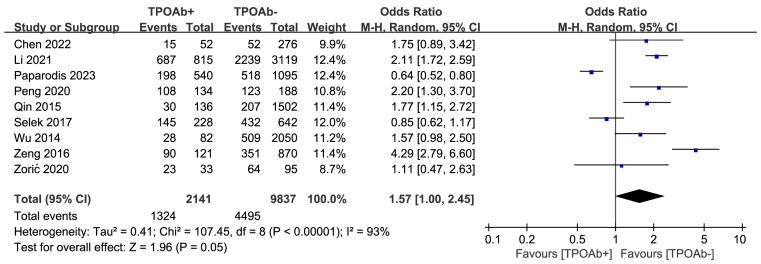

FIGURE 2
TPOAb positivity and prevalence of DTC.

TPOAb positivity and extrathyroidal extension

Our analysis focused on five studies (40, 42, 44, 46, 47) to determine whether the risk of extrathyroidal extension differs among DTC patients with various TPOAb levels. Among the 1804 TPOAb+ and 7168 TPOAb– patients, little difference in the risk of extrathyroidal extension was found, 12% and 11%, respectively. The forest plot did not indicate a significant association between different TPOAb levels and the risk of extrathyroidal extension (OR=0.95 [95% CI: 0.80–1.14], p=0.59; Figure 3B). Egger's regression model showed no publication bias (p=0.19), and a low level of heterogeneity was observed.

TPOAb positivity and lymph node metastasis

We included six studies (40, 42, 44, 46–48) to explore the relationship between TPOAb positivity in DTC patients and the risk of lymph node metastasis. Among the 1887 TPOAb+ and 7662 TPOAb– patients, little difference in the risk of lymph node

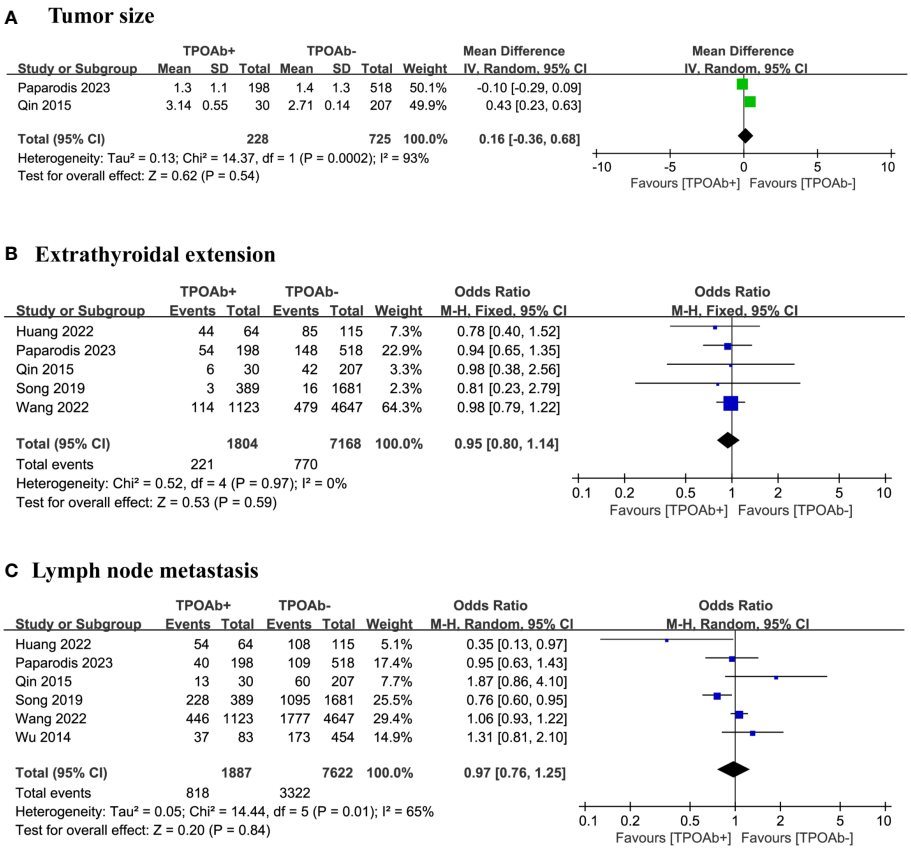

FIGURE 3
TPOAb positivity and risk of **(A)** tumor size, **(B)** extrathyroidal extension and **(C)** lymph node metastasis.

metastasis was found, 43% and 44%, respectively. The forest plot did not show a significant association between different TPOAb levels and the risk of lymph node metastasis (OR=0.97 [95%CI 0.76-1.25] p=0.84; Figure 3C). Egger's regression model indicated no publication bias (p=0.82), and a moderate level of heterogeneity was observed.

TPOAb positivity and tumor multifocality

We included three studies (40, 44, 47) to examine the association between TPOAb positivity and the risk of tumor multifocality in DTC patients. Multifocal tumors occurred in 38% of the 1217 TPOAb+ patients compared with 31% of the 4969 TPOAb– patients. The forest plot indicate the risk of tumor multifocality in TPOAb+ patients was significantly higher than that in TPOAb– patients (OR=1.40 [95% CI: 1.23–1.60], p<0.00001; Figure 4A). Egger's regression model indicated no publication bias (p=0.05), and a low level of heterogeneity was observed.

TPOAb positivity and tumor recurrence

Our analysis focused on two studies (40, 47) to evaluate the association between TPOAb positivity and the risk of tumor recurrence in DTC patients. Tumor recurrence occurred in 4% of the 925 TPOAb+ patients compared with 2% of the 3634 TPOAb– patients. The forest plot did not reveal a significant relationship between different TPOAb levels and the risk of tumor recurrence (OR=1.01 [95% CI: 0.30–3.33], p=0.99; Figure 4B). However, the number of studies was insufficient for assessing publication bias, and a high level of heterogeneity was observed.

TPOAb positivity and tumor bilaterality

We included three studies (40, 47) to evaluate the association between TPOAb positivity and the risk of tumor bilaterality in DTC patients. Of the 1187 TPOAb+ patients, 27% had bilateral tumors compared with 21% of the 4762 TPOAb– patients. The risk of tumor bilaterality in TPOAb+ patients was significantly higher than that in TPOAb– patients (OR=1.40 [95% CI: 1.21–1.62], p<0.00001; Figure 4C). However, the number of studies is insufficient for assessing publication bias, and a low level of heterogeneity was observed.

Sensitivity analysis

We conducted a sensitivity analysis to assess the stability of the results, systematically excluding each article and performing a

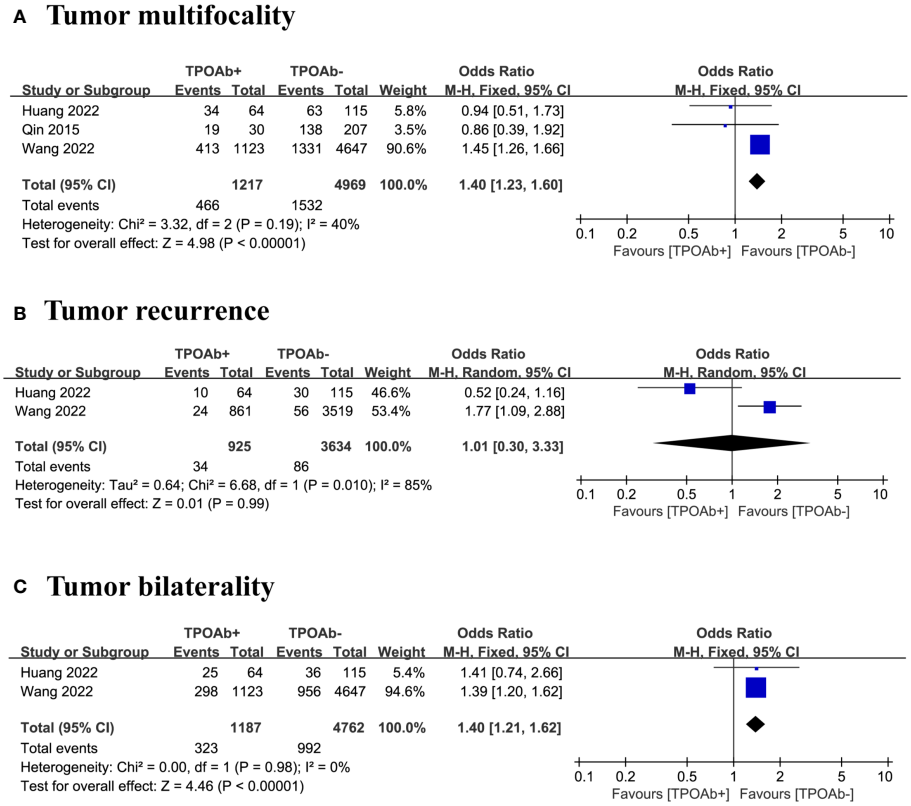

FIGURE 4
TPOAb positivity and risk of **(A)** tumor multifocality, **(B)** tumor recurrence and **(C)** tumor bilaterality.

meta-analysis on the remaining literature. Except for the high sensitivity of the results for TPOAb positivity and DTC prevalence and its association with the risk of bilateral and multifocal tumors of DTC, the remaining findings exhibited no substantial alterations, suggesting some degree of result instability.

Discussion

Our meta-analysis included 12 original studies encompassing 20,330 patients from six countries for investigating associations between TPOAb and DTC prevalence, along with various prognostic factors. Our findings reveal that TPOAb+ individuals were at a higher risk of developing DTC than TPOAb– individuals (p=0.049). Furthermore, TPOAb+ DTC patients were more likely than TPOAb– DTC patients to present with multifocal and bilateral tumors, and this difference was statistically significant. However, no significant difference in tumor size, recurrence rate, risk of extrathyroidal extension, and lymph node metastasis was observed between TPOAb+ and TPOAb– DTC patients.

We observed an association between TPOAb and DTC prevalence, but the results may be subject to controversy. Upon analysis using Review Manager, we obtained a calculated p-value of 0.05, while recalculation using Stata 14 yielded a p-value of 0.049, which was statistically significant. This discrepancy might be because Review Manager rounded the p-value, and ultimately, the p-value was determined to be 0.049. Nevertheless, both the heterogeneity and sensitivity of this result were relatively high. Several factors may account for this observed heterogeneity. First, variations in the cutoff values for defining TPOAb positivity were evident, ranging from a minimum of >5.61 IU/mL to a maximum of >100 IU/mL. Second, differences existed in the methods and instruments used for TPOAb determination. Third, differences in the study populations across diverse regions may have contributed to heterogeneity. Lastly, the presence or absence of AIT in TPOAb+ patients could have influenced the results. The available data were not sufficient for a comprehensive subgroup analysis. Furthermore, the observed sensitivity issues were likely related to ethnic and regional differences. In the nine included articles, three studies contributing to the elevated sensitivity were from joint research conducted between the United States and Greece, Serbia, and Turkey, while the remaining six studies were conducted in China. Located in Asia, China differs geographically from the other four countries primarily situated in Europe and North America. As DTC prevalence varies across regions, geographic factors might play a pivotal role (51, 52). Although the p-value was <0.05, this does not inherently guarantee result stability or high reliability. Further validation through additional independent studies is essential to establish the reliability of the results.

We initially observed that TPOAb+ DTC patients are more likely to exhibit bilateral and multifocal tumors. However, Wang's study (47) with a considerably higher weight share in both results had a significant influence. Upon exclusion of the Wang's study, we found no significant association between TPOAb and DTC multifocality (OR=0.91 [95% CI: 0.56–1.48], p=0.70) and bilaterality (OR=1.41 [95% CI: 0.74–2.66], p=0.29). Consequently, no conclusive significant association was established in this study, emphasizing the need for further exploration of the association of TPOAb positivity with DTC multifocality and bilaterality. Moreover, we found the TPOAb+ and TPOAb– DTC patients exhibited no significant differences in tumor size, recurrence rate, risk of extrathyroidal extension, and lymph node metastasis. Nevertheless, several studies have reported that TgAb+ DTC patients face a higher risk of lymph node metastasis and recurrence (53–57).

Some studies have demonstrated that persistent or recurrent thyroid cancer can induce the production of TgAb, so the time of TPOAb detection is particularly important (58, 59). Other studies have indicated an association between positive TPOAb results 7-10 years before diagnosis and thyroid cancer. However, most of the original studies included in this analysis conducted TPOAb testing prior to surgery without specifying the exact duration of TPOAb positivity before this period, potentially impacting the credibility of the results (60). Further large prospective studies are necessary for validation. Additionally, if patients were identified with thyroid cancer due to testing positive for TPOAb and subsequently included in the selection process, it could have led to an increased rate of DTC diagnosis in TPOAb+ patients, potentially introducing selection bias. Moreover, because patients with autoimmune thyroid diseases tend to be more vigilant about their thyroid function, they may detect small subclinical tumors during ongoing medical surveillance. In contrast, patients without related diseases might not undergo continuous surveillance, potentially leading to the undiagnosed status of some subclinical tumors. This discrepancy could also introduce bias into the results.

Given that TPOAb is a vital diagnostic marker of HT, considering the influence of AIT when examining the association between TPOAb and DTC is necessary. HT is known to cause substantial immune cell infiltration in the thyroid gland (61), and similar immune cell infiltration is observed around DTC (62, 63). The potential interplay between the two and its effect on DTC progression and prognosis pose intriguing questions. HT appears to be linked to an increased risk of thyroid cancer (64). When it coexists with thyroid cancer, it seems to further elevate the likelihood of thyroid cancer development (64–66). However, it may confer a protective effect against lymph node metastasis, extrathyroidal extension, and distant metastasis (64, 67, 68). Additionally, some studies have shown that immune cell infiltration surrounding PTC resulting from HT is positively correlated with a lower recurrence rate, higher overall survival, and reduced risk of extrathyroidal extension and distant metastasis (69, 70). Moreover, some studies have found that HT is associated with smaller tumor size, lower rate of aggressive PTC variants and lower risk, and DTC patients with HT have a higher clinical remission rate and longer recurrence-free survival (71, 72). However, the accuracy of "non-HT status" as a negative prognostic marker is poor, and it cannot improve the specificity of predicting prognosis. In one meta-analysis, TgAb was distinguished from HT, and TgAb+ patients with HT exhibited larger tumor sizes and a higher risk of extrathyroidal extension, tumor multifocality, lymph node metastasis, and cancer persistence than those without HT (29). Therefore, although HT can promote

the development of DTC, it seems to be a protective factor for the prognosis of DTC. However, if we consider the single effect of TgAb positivity without considering HT, it seems to become a risk factor. The studies included in our meta-analysis did not differentiate TPOAb from HT, making it challenging to determine whether our conclusions might have been confounded by HT. Further research is warranted to reach a more definitive conclusion.

Conclusions

Our analysis indicates that TPOAb positivity may be associated with an increased prevalence of DTC. However, TPOAb does not serve as a robust prognostic factor for TPOAb+ DTC patients. Our meta-analysis is based on a limited number of included studies, and we anticipate that future research will provide additional large-scale research data to further inform our understanding.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

HZ: Writing – original draft. LT: Writing – review & editing. XW: Writing – review & editing. XS: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1349041/full#supplementary-material

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Unusual coexistence: branchial cleft cyst harboring papillary thyroid carcinoma with lymph node metastasis — a rare case report and clinical insights

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Background: The simultaneous occurrence of Branchial Cleft Cyst (BCC) and Papillary Thyroid Carcinoma (PTC) represents an unusual malignant tumor, with cases featuring associated lymph node metastasis being particularly rare. This combination underscores an increased potential for metastasis, and the assessment of neck masses, particularly on the lateral aspect, may inadvertently overlook the scrutiny of the thyroid. Therefore, healthcare providers should exercise vigilance, especially in patients over the age of 40, regarding the potential for neck masses to signify metastasis from thyroid malignancies. Currently, surgical intervention stands as the primary effective curative method, while the postoperative administration of radioactive iodine therapy remains a topic of ongoing debate.

Case report: In the presented case, a 48-year-old male patient with a right neck mass underwent surgical intervention. The procedure included the excision of the right neck mass, unilateral thyroidectomy with isthmus resection, and functional neck lymph node dissection under tracheal intubation and general anesthesia. Postoperative pathology findings revealed the coexistence of a BCC with metastatic PTC in the right neck mass, as well as papillary carcinoma in the right thyroid lobe. Lymph node metastasis was observed in the central and levels III of the right neck.

Conclusion: The rare amalgamation of a BCC with PTC and concurrent lymph node metastasis underscores the invasive nature of this malignancy. Healthcare professionals should be well-acquainted with its clinical presentation, pathological characteristics, and diagnostic criteria. A multidisciplinary approach is strongly recommended to enhance patient outcomes.

KEYWORDS

papillary thyroid carcinoma, branchial cleft cyst, lymph node metastasis, case report, clinical insights

Introduction

BCC are the second most common congenital neck lesions following thyroglossal duct cysts (1). BCC and their fistulas result from abnormal development of branchial grooves or pouches during embryonic development. In the human embryo, there are four pairs of distinct branchial grooves and pouches, with the first groove forming the external auditory canal, and the second, third, and fourth grooves gradually merging and disappearing. If the fusion process of any of the first to fourth branchial grooves is abnormal, leading to incomplete closure, it can give rise to corresponding branchial cysts and fistulas. Most BCC originate from the second branchial arch, typically located in the upper third of the anterior triangle of the neck, specifically in the sternocleidomastoid muscle region, and rarely occur in other locations (2).

PTC stands as the predominant histological variant among thyroid cancers, constituting 70-80% of all cases. It commonly manifests in individuals during their third and fourth decades, with a prevalence that is twice as high in females compared to males. Occult cancers are typically smaller than 1.5 cm, not palpable, and frequently discovered incidentally. The majority of patients exhibit a painless, gradually expanding mass. This cancer variant tends to spread to the peritracheal and cervical lymphatics (3). Papillary carcinoma has a tendency for lymphatic metastasis, and metastatic lymph nodes are often detectable even when the primary tumor is not clearly apparent (4). Although uncommon, cystic lymph node metastasis in the neck can occur, and PTC may manifest as lateral neck cysts resembling BCC (5).

To enhance awareness among clinical professionals, we present the clinical data of a patient with concurrent BCC and PTC with lymph node metastasis, admitted to the Thyroid and Breast Surgery Department of Weifang People's Hospital. The details are reported below.

Case report

The patient, a 48-year-old male, presented to the Thyroid and Breast Surgery Department of Weifang People's Hospital on September 8, 2023, complaining of a right neck mass discovered six months prior, which he perceived to be progressively enlarging. Clinical examination revealed a palpable, firm, well-defined, smooth-surfaced mass measuring approximately 3*3 cm behind the sternocleidomastoid muscle, with no tenderness or local skin erythema. Thyroid ultrasound indicated a solid nodule in the right thyroid lobe categorized as ACR TI-RADS 5, a solid cystic nodule in the right thyroid lobe categorized as ACR TI-RADS 2, and a cystic solid nodule with calcification in the right neck (Figures 1A, B). A CT scan confirmed a solid-cystic lesion with calcification in the right neck, suggestive of a benign lesion, possibly of vascular origin, along with multiple small lymph nodes in bilateral neck and subclavicular regions (Figures 2A, B). Considering these findings, the patient underwent general anesthesia and tracheal intubation for the removal of the right neck mass, unilateral thyroidectomy with isthmus resection, and functional neck lymph node dissection. Postoperative pathology revealed PTC in the right thyroid lobe and isthmus, accompanied by fibrosis, with a diameter of 0.3 cm and invasion of the capsule. No definite evidence of neural invasion or intravascular tumor thrombus was observed. Lymphocytic thyroiditis was also identified. Examination of the excised lymph nodes showed metastasis (0/3 in pretracheal, 1/1 in right central, 0/2 in right level II, 1/10 in right level III, and 0/7 in right level IV). Additionally, a small amount of thyroid and skeletal muscle tissue with cancer components was found in the pretracheal specimen, while the right level II lymph node specimen contained a small amount of salivary gland tissue without cancer components. In the right neck, a cystic lesion measuring 3*2*1.8 cm was confirmed to be a BCC. Notably, calcifications and papillary-like structures were identified on the inner wall of the BCC. Pathology and immunohistochemical results revealed positive expression of TG,

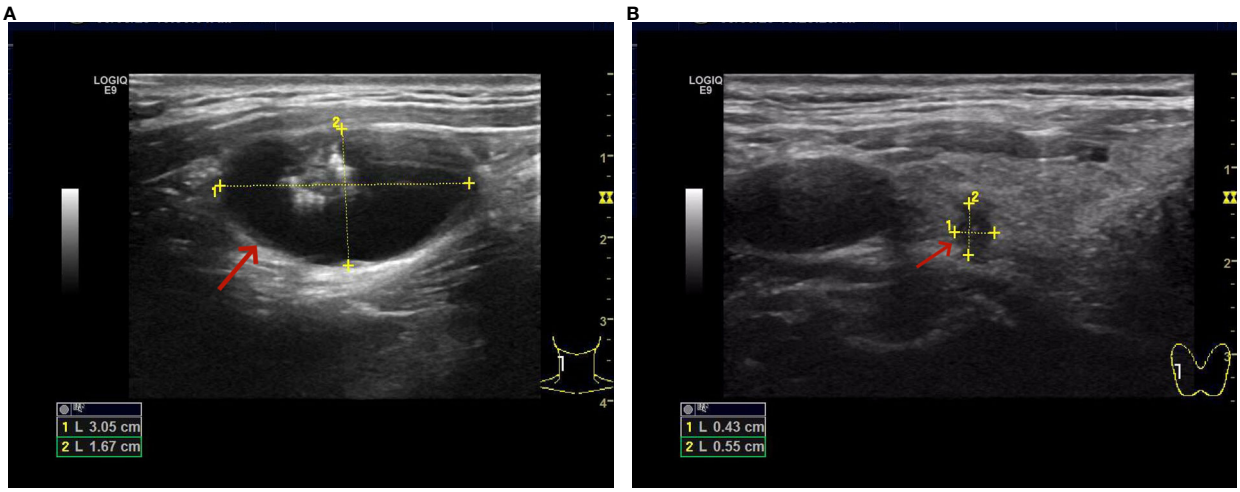

FIGURE 1
(A) Solid-cystic nodule with calcification in the right side of the neck. **(B)** There is a solid nodule in the upper pole of the right lobe of the thyroid, measuring approximately 0.4*0.6 cm.

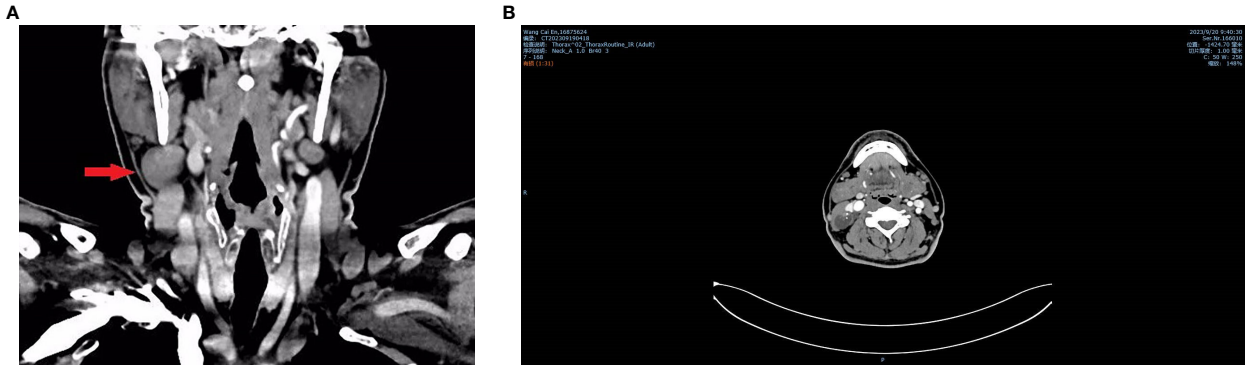

FIGURE 2
Neck CT plain scan + enhancement shows a solid-cystic mass with calcification in the right side of the neck. **(A)** Coronal view. **(B)** Horizontal view.

TTF-1, and PAX-8 in the BCC, indicating metastasis of PTC (Figures 3A, B, 4–8). The patient's postoperative recovery has been satisfactory, and regular follow-up examinations are currently ongoing.

Discussion

BCC are relatively common neck masses clinically, occurring at any age, with a higher prevalence around the age of 30, and affecting both males and females. However, the discovery of PTC within a BCC is rare. The simultaneous occurrence of PTC within a BCC with associated lymph node metastasis is exceptionally rare (1). Based on a retrospective analysis of previous cases, neck masses related to PTC can be categorized into the following four types: cystic lymph node metastasis of PTC, ectopic PTC within a BCC, BCC with concurrent PTC, and BCC with concurrent PTC and lymph node metastasis.

Differential diagnoses for lateral neck masses include inflammatory conditions such as cat scratch disease, infectious mononucleosis, sialadenitis, or other reactive lymphadenopathies; congenital anomalies such as cystic hygroma or BCC, fistulas, and abscesses; and neoplastic conditions such as lymphoma, lymphatic malformations, neurofibromas, salivary gland tumors, and various metastatic lesions. A retrospective analysis of 630 cases of neck masses in Turkey revealed that 33.49% were inflammatory, 18.9% were congenital, and 47.6% were neoplastic. However, PTC accounted for only 2% of neoplastic neck masses and 0.9% of all neck masses (6, 7).

While most lateral neck cysts are benign, metastatic lymph nodes from PTC may present as isolated neck cysts. According to investigations, the incidence of occult malignant thyroid tumors in patients with lateral neck cysts is approximately 11%, with an average age of 29 years. Therefore, consideration should be given to the possibility of occult thyroid cancer with cystic lymph node metastasis. It is noteworthy that, in our review of previous cases, reports of ectopic PTC within BCC numbered fewer than 10. Moreover, the thyroid imaging was mostly normal, and the surgical specimens from prophylactic thyroidectomy were mostly negative. PTC was only identified during postoperative pathological examinations of BCC. Cases of BCC with concurrent PTC were reported in less than 5 instances, with typical benign imaging characteristics of BCC. Only two cases displayed mild complexity in imaging features associated with BCC (wall thickening, enhancement, poorly calcified and septated development) (8). In

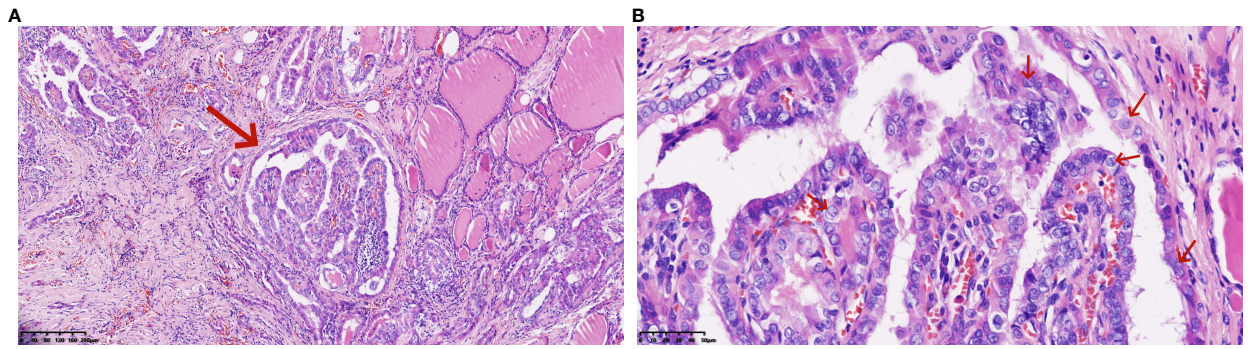

FIGURE 3
(A, B) Pathological features of right thyroid lobe carcinoma (Hematoxylin and eosin stain): The papillary carcinoma consists of tumor cells with eosinophilic cytoplasm, demonstrating typical ground-glass nuclei, overlapping nuclei, nuclear grooves, and intranuclear inclusions (*100, *400).

TABLE 1 Summary of partial cases of concurrent PTC and BCC occurrence.

Author	Year	Patient	Medical examination	pathological findings
Balasubramaniam et al. (9)	1992	34(F)	CT: 2.5cm cystic mass in the left neck (thyroid not examined).	Ectopic PTC within a BCC
Hung-Sheng Chi et al. (10)	2007	38(M)	CT: 4.5*5.5cm cystic mass in the right neck (thyroid not examined).	BCC with concurrent PTC
Juri Park et al. (11)	2010	49(M)	CT: 3.2*2.3*4.5 cm cystic mass with focal areas of high-density solid component in the right neck; no thyroid abnormalities identified.	Ectopic PTC within a BCC
Tazegul G et al. (7)	2018	22(F)	MRI: 3.5*2.0cm cystic neck mass; 0.9cm nodule in the right thyroid lobe.	BCC with concurrent PTC
Andy Cooc et al. (8)	2020	49(F)	CT: Large unenhanced cystic lesion in the right neck; heterogeneous cystic thyroid with multiple punctate calcifications.	Bcc with concurrent PTC

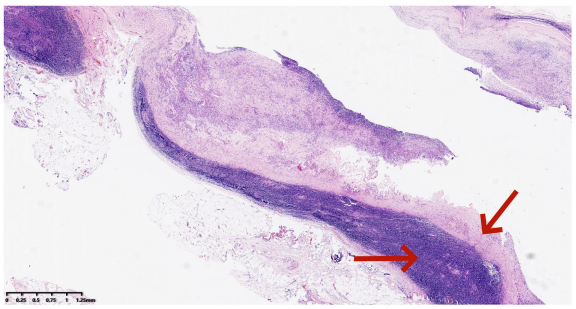

FIGURE 4
Pathological features of the right neck mass showing branchial cleft cyst (Hematoxylin and eosin stain): Lined by a single layer of epithelium, with lymphoid tissue located beneath the epithelium (*20).

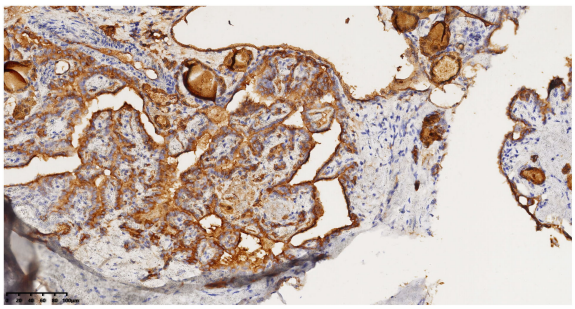

FIGURE 6
Right neck mass with positive TG staining, immunohistochemical envision (*200).

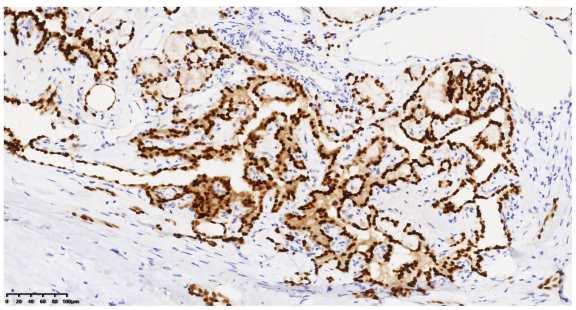

FIGURE 5
Right neck mass with positive PAX-8 staining, immunohistochemical envision (*200).

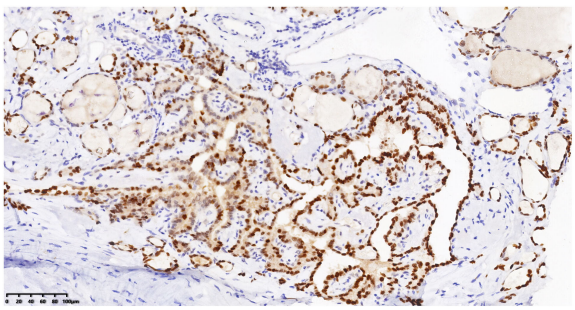

FIGURE 7
Right neck mass with positive TTF-1 staining, immunohistochemical envision (*200).

these cases (Table 1), the presence of papillary thyroid carcinoma was identified postoperatively through pathological examination of the BCC, prompting further evaluation of the thyroid, and ultimately leading to the discovery of thyroid nodules.

For patients over the age of 40, the possibility of lateral neck cysts representing metastatic lymph nodes should always be considered, and efforts should be made to identify the primary tumor before initiating neck treatment (12). Therefore, upon initially receiving this patient, we performed thyroid and cervical lymph node ultrasonography. We identified a solid nodule in the right lobe of the thyroid, measuring approximately 0.4*0.6 cm, with irregular margins and a transverse-to-longitudinal ratio greater than 1 (ACR T1-RADS 5). On neck CT examination, we observed septations, punctate, and arc-shaped calcifications within the neck mass. The solid nodule showed significant enhancement on contrast-enhanced scans. Multiple small lymph nodes were noted in bilateral neck and subclavicular regions. In

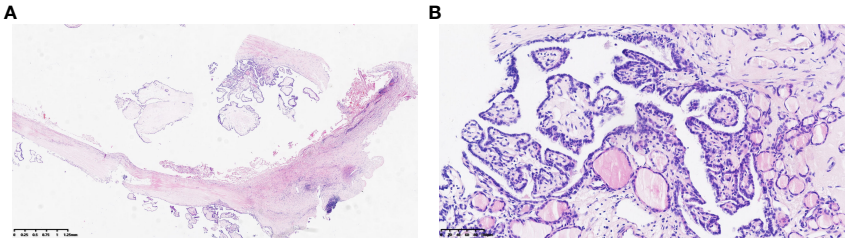

FIGURE 8
(A, B) Branchial cleft cyst with concurrent metastasis of papillary thyroid carcinoma (Hematoxylin and eosin stain) (*20, *200).

comparison to previous cases, our success lies in the timely utilization of imaging techniques to examine the patient's thyroid, identifying thyroid and cervical lymph node lesions, and promptly providing surgical treatment to the patient. To the best of our knowledge, this is the only case providing a detailed description of the occurrence of papillary thyroid carcinoma within a BCC, along with evidence of primary thyroid tumor and lymph node metastasis.

Surgery is the preferred treatment for BCC with concurrent PTC and lymph node metastasis. For BCC occurring in adults, complete excision of the entire fistula and partial thyroidectomy (if the thyroid is involved or to assist in preserving the recurrent laryngeal nerve) appears to be the optimal choice of treatment (13). For children under the age of 8, endoscopic treatment is recommended. In cases where PTC is concurrent, we suggest performing unilateral thyroidectomy with isthmus resection and functional neck lymph node dissection. In this case, the pathological diagnosis from the excisional biopsy of the mass revealed a BCC with concurrent PTC metastasis. During surgery, we performed lymph node dissection in the neck, revealing metastasis in the right central and right neck level III lymph nodes.

Conclusion

A branchial cleft cyst with concurrent papillary thyroid carcinoma and lymph node metastasis is an extremely rare malignant tumor, with almost no specific clinical and radiological presentations. Particularly for papillary thyroid carcinoma, it is prone to misdiagnosis and missed diagnosis. Therefore, we recommend timely appropriate thyroid examinations before surgery. Sufficient collection of histopathological specimens combined with immunohistochemical results can improve diagnostic accuracy. Surgery is the only effective treatment method. Whether postoperative radioactive iodine therapy should be performed remains controversial, and specific treatment standards await further research.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

W-TW: Writing – original draft, Investigation, Validation. X-HN: Conceptualization, Software, Writing – original draft. Y-XG: Writing – original draft, Validation, Visualization. RA: Supervision, Writing – original draft. C-LW: Writing – review & editing. JZ: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Score based on contrast-enhanced ultrasound predict central lymph node metastasis in papillary thyroid cancer

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Objectives: To investigate the association between contrast-enhanced ultrasound (CEUS) features of PTC and central lymph node metastasis (CLNM) and to develop a predictive model for the preoperative identification of CLNM.

Methods: This retrospective study evaluated 750 consecutive patients with PTC from August 2020 to April 2023. Conventional ultrasound and qualitative CEUS features were analyzed for the PTC with or without CLNM using univariate and multivariate logistic regression analysis. A nomogram integrating the predictors was constructed to identify CLNM in PTC. The predictive nomogram was validated using a validation cohort.

Results: A total of 684 patients were enrolled. The 495 patients in training cohort were divided into two groups according to whether they had CLNM (pCLNM, n= 191) or not (nCLNM, n= 304). There were significant differences in terms of tumor size, shape, echogenic foci, enhancement direction, peak intensity, and score based on CEUS TI-RADS between the two groups. Independent predictive US features included irregular shape, larger tumor size (≥ 1.0cm), and score. Nomogram integrating these predictive features showed good discrimination and calibration in both training and validation cohort with an AUC of 0.72 (95% CI: 0.68, 0.77) and 0.79 (95% CI: 0.72, 0.85), respectively. In the subgroup with larger tumor size, age ≤ 35 years, irregular shape, and score > 6 were independent risk factors for CLNM.

Conclusion: The score based on preoperative CEUS features of PTC may help to identify CLNM. The nomogram developed in this study provides a convenient and effective tool for clinicians to determine an optimal treatment regimen for patients with PTC.

KEYWORDS

papillary thyroid cancer, contrast-enhanced ultrasound, central lymph node, metastasis, predict, score

1 Introduction

According to the latest data, the incidence of thyroid cancer ranks the ninth among all tumors, with 10.1 cases/10 million women and 3.1 cases/10 million men, which is significantly higher than that 10 years ago (1). Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer with a high tendency of cervical lymph node metastasis. Cervical lymph node metastasis follows a sequential pattern from central cervical lymph node which are commonly referred to level VI lymph nodes including the prelaryngeal, pretracheal, left paratracheal, and right paratracheal lymph nodes, to lateral compartments (level II~IV). The presence of central lymph node metastasis (CLNM) is the most important variable in increasing the risk of locoregional recurrence and overall survival.

Ultrasound (US) is the first-line imaging modality for the preoperative evaluation of PTC and for the detection of lymph node metastases. However, the rate of cervical lymph node metastasis detection by US is unsatisfactory. A study showed that the sensitivity, specificity, and accuracy of preoperative US diagnosis for PTC patients with CLNM were 35.3%, 88.6% and 56.6%, respectively (2). A subsequent study analyzing 5768 PTC patients with 10030 lymph nodes showed that the sensitivity and specificity of US in detecting lymph node metastasis were 59% and 85%, respectively (3). Due to the lack of effective diagnosis and relatively high incidence of CLNM, dissection of the lymph node in the central region is considered necessary. However, nearly half of the PTC patients have no CLNM, and they did not benefit from the routine prophylactic central lymph node dissection but may face the potential surgical risk. Therefore, it is crucial to screen out the predictive factors of CLNM to achieve accurate diagnosis preoperatively, which is useful for surgeons to determine whether preventive central lymph node dissection is needed.

Although numerous retrospective studies have determined the value of conventional US and clinical features including age, gender, tumor size, multifocality of PTC, TgAb, microcalcifications and *BRAF* in predicting CLNM, but the results are still inconsistent. Contrast-enhanced ultrasound (CEUS) is a safe ultrasonic technique with high sensitivity for vascularity and can provide qualitative and quantitative blood perfusion information. Qualitative and quantitative CEUS features, such as hypo-enhancement at peak intensity, heterogeneous enhancement, and shorter time to peak, have been as the major characteristics of PTC (4, 5). However, the association between these PTC CEUS features and lymph node metastasis remains controversial. Both hyperenhancement, isoenhancement, and hypoenhancement at peak intensity have been reported to predict lymph node metastasis in PTC (6–9). Therefore, further studies are still needed to explore reliable CEUS features for predicting lymph node metastasis. CEUS Thyroid Imaging Reporting and Data System (TI-RADS) using qualitative nonenhanced US and CEUS features provide a simple and practical method to stratify the risk of thyroid nodule malignancy. However, it has been rarely reported whether the combination of PTC CEUS features and a score based on CEUS T1-RADS categories could classify the probability of CLNM. In this study, we aimed to determine whether conventional and enhanced US features of PTC, along with a score based on CEUS T1-RADS categories, can predict CLNM. The predictive results can help clinicians to select patients who really need central lymph node dissection and avoid the cost of another CEUS of the cervical lymph nodes.

2 Materials and methods

2.1 Patients

This retrospective study was approved by the ethics committee of Daping Hospital, and the requirement to obtain informed consent for study was waived. However, all patients undergoing CEUS and Fine needle aspiration (FNA) signed informed consent forms for these examinations or procedures. A total of 750 consecutive patients with PTC with or without CLNM were retrospectively enrolled in this study from September 2020 to April 2023.

The inclusion criteria were (a) underwent US and CEUS preoperatively at our hospital, (b) underwent primary thyroid surgery and central lymph node dissection, (c) pathologically confirmed PTC and evidence of malignancy or benign status of central lymph nodes, (d) underwent $BRAF^{V600E}$ mutation tests. The exclusion criteria were (a) other pathological types of thyroid cancer, (b) multiple nodule patients with more than one nodule confirmed as PTC, (c) previous treatment of thyroid nodules prior to ultrasonic examinations, (d) unsatisfactory of CEUS imaging, and (e) presence of other malignant tumors.

2.2 US examination

US examinations were performed by using a DC 8S ultrasound diagnostic system (Mindray Medical International Co., Ltd., Shenzhen, China) with a 12-3E MHz linear-array transducer or a Phillip EPIQ 5 system (Phillips Medical Systems, Cleveland, USA) with a L12-5 transducer for conventional US examinations and a 9L-D probe (Logiq E9, GE Healthcare, Chalfont St Giles, UK) for CEUS examinations. A second-generation US contrast agent (SonoVue; Bracco, Milan, Italy) was injected intravenously as a bolus at a dose of 1.2 mL, followed by a flush of 5 mL of 0.9% sodium chloride solution. The imaging timer was started simultaneously with the completion of the contrast agent injection. After CEUS examinations, US-guided FNA was performed. All the conventional US, CEUS and US-guided FNA were performed by one of three radiologists (L He, JY Hu, or W Chen) with 5-10 years of experience in conventional US for thyroid nodule diagnosis and at least 2 years of experience in CEUS and US-guided FNA.

2.3 US image analysis

The US features of each thyroid nodule were described and scored independently by the same radiologists (L He, JY Hu, or W Chen) who performed the US examinations and FNA, and the readers were blinded to the FNA results or final diagnosis. According to the American College of Radiology Thyroid Imaging Reporting and Data System (ACR 2017), the US characteristics, including nodule composition at conventional US (cystic, mixed solid and cystic, or solid); echogenicity (hyperechoic, isoechoic, or hypoechoic relative to adjacent thyroid tissue, very hypoechoic relative to adjacent neck musculature); orientation (wider-than-tall or taller-than-wide); shape (regular or irregular); margin (smooth, ill-defined, lobulated or irregular, or extra-thyroidal extension); echogenic foci (none or large comet-tail artifacts, macrocalcifications, peripheral calcification, or punctate echogenic foci); vascularity (poor, or rich), were recorded.

The CEUS images of each thyroid nodule were reviewed and analyzed by two radiologists (L He and JY Hu, with more than 5 years of experience in thyroid CEUS) who were blinded to the pathology results. The CEUS cine clips were analyzed with the help of time-intensity-curve (TIC) software of LOGIQ E9. The enhancement characteristics of the PTC were as follows: enhancement direction (scattered, centripetal, centrifugal), enhancement type (hyper-, iso-, hypo-, or non-enhancement, relative to adjacent thyroid tissue at peak), ring enhancement (absent, presence), composition at CEUS (solid, non-solid). According to the CEUS TI-RADS (10), each nodule was assigned a score. The point of each non-enhanced and contrast-enhanced US feature was listed in Supplementary Table 1.

2.4 Reference standard

All the patients underwent surgery within 2 weeks after the US-guided FNA, during the interval time no clinical intervention was underwent. The pathological results after surgery were used as the reference standard for the diagnosis of CLNM.

2.5 Statistical analysis

Statistical analysis was conducted using SPSS v. 24.0 (SPSS, Chicago, IL, USA) and MedCalc, v. 20.0008 (MedCalc Software, Ostend, Belgium). Qualitative data are presented as numbers and percentages and compared by Chi-Square or Fisher's exact test. Quantitative data with normal or non-normal distribution are presented as mean ± standard deviation or median (P_{25}, P_{75}) and compared using independent t-test or Mann–Whitney U test, respectively. *Bonferroni's* correction is used to adjust *p*-values for comparisons of more than one parameter. Variables with a *p*-value < 0.02 in univariate regression analysis are included in multivariate logistic regression (backward) to select optimal features for predicting CLNM. Diagnostic performance is evaluated by using the receiver operating characteristic (ROC) curve. $P<.05$ indicated a significant difference.

3 Results

3.1 Clinical characteristics of patients

A total of 684 patients with confirmed PTC were ultimately enrolled in this study, among whom 495 patients recruited between January 2022 and April 2023 were assigned to the training cohort, and 189 patients enrolled between August 2020 and December 2021 were assigned to the validation cohort. The flowchart of this study was shown in Figure 1. Among the training cohort, 367 were female, 128 were male, with a mean age of 43 ± 12 years. According to the PTC with CLNM or not, the patients were divided into two groups, pCLNM (n= 191) and nCLNM (n= 304) (abbreviation for positive and negative CLNM, respectively). There were no significant differences between the two groups in terms of age, gender, and $BRAF^{V600E}$ mutation (all $P > 0.05$). The baseline characteristics of patients was shown in Table 1. In the validation cohort, pCLNM were observed in 120 PTC and nCLNM in 69 PTC. Comparison of clinical characteristics between the training and validation cohorts is shown in Supplementary Table 2.

3.2 Comparison of conventional US and CEUS features between groups

The conventional US features of PTC with or without CLNM are summarized in Table 2, and examples of PTC with or without CLNM are shown in Figure 2. PTC in the pCLNM group had a larger tumor size than PTC in the nCLNM group, regardless of longest diameter or anteroposterior diameter (all $P < 0.00$). More PTC in the pCLNM group (104/191) had tumors ≥ 1.0cm compared to PTC in the nCLNM group (112/304) ($P = 0.00$). Compared to the nCLNM group, tumors in the pCLNM group tended to be irregular in shape ($P = 0.00$). Echogenic foci were classified into three categories: absent and large comet-tail artifacts, macrocalcifications and rim calcifications, and punctate echogenic foci (microcalcification). Although more than half of the PTC in both groups had punctate echogenic foci within the tumor, tumors in the pCLNM group (72.3%) were more likely to have microcalcification than those in the nCLNM group (57.6%; $P = 0.00$). Meanwhile, composition, internal echo, orientation, margin, extrathyroidal extension, and vascularity showed no significant difference between the two groups.

After contrast agent administration, centripetal or centrifugal enhancement was seen in 83.2% of PTC in the pCLNM group and 70.7% of PTC in the nCLNM group ($P = 0.00$). Hyper- or hypo-enhancement was shown in 82.2% of PTC in the pCLNM group and 69.7% of PTC in the nCLNM group ($P = 0.00$). However, there were no significant differences between the groups in regarding enhancing area ($P = 0.21$), ring enhancement ($P = 0.98$), and nodule composition ($P = 0.13$) on CEUS. Each nodule was assigned a score according to the CEUS TI-RADS. The mean score of PTC in the pCLNM and nCLNM groups was 7.52 and 6.89, respectively. Moreover, the difference between the two groups was significant according to the *Mann–Whitney* U test (Table 3).

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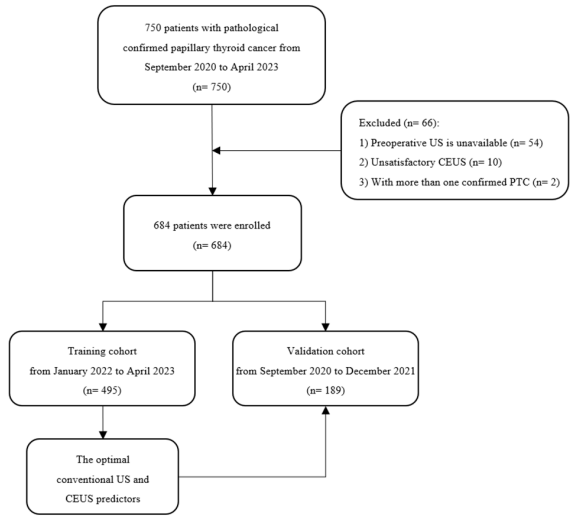

FIGURE 1
The flowchart of this study.

3.3 Construction of predictive model for PTC patients with CLNM

Based on the results of the univariate analysis, features with a *p*-value < 0.2 were included in further multivariate regression analysis. The results of multivariate regression analysis indicated that irregular shape (OR = 2.96, $P < 0.00$), score based on CEUS TI-RADS categories (OR = 1.30, $P < 0.00$), tumor size (≥ 1.0cm; OR = 2.11, $P < 0.00$) were significant predictors for PTC with CLNM (Table 4). The predictive model including irregular shape, score based on CEUS TI-RADS categories, and tumor size (≥ 1.0cm) was constructed and presented in a nomogram (Figure 3). The area under the receiver operating characteristic curve (AUC) of the model was 0.72 (95% CI: 0.68, 0.77; Figure 4), which was higher than conventional US features (0.62; 95% CI: 0.57, 0.66; P < 0.00) or score based on CEUS TI-RADS alone (0.61, 95% CI: 0.57, 0.66; P < 0.00). The predictive model also showed good performance in validation cohort, with an AUC of 0.79 (95% CI: 0.72, 0.85; Figure 4). Examples of predicting CLNM in PTC using the nomogram model were shown in Supplementary Figure 1 and Figure 2.

3.4 Clinico-ultrasonic characteristics of pCLNM in PTC with different tumor size

In the tumors ≥ 1.0cm group, there was no significant difference between the pCLNM and nCLNM groups in terms of sex, anteroposterior diameter, composition, internal echo, orientation, margin, extrathyroidal extension, enhancement area, ring enhancement, and composition on CEUS. However, age ($P = 0.009$), shape ($P = 0.000$), calcification ($P = 0.000$), peak intensity ($P = 0.036$), and score based on CEUS TI-RADS ($P = 0.000$) were associated with CLNM. Age ≤ 35 years (OR = 2.74, 95% CI: 1.46, 5.17), irregular shape (OR = 3.80, 95% CI: 1.87, 7.73), and score > 6 (OR = 1.51, 95% CI: 1.20, 1.90) were independent risk factors for CLNM. The AUC of the model constructed based on these three variables was 0.76 (95% CI: 0.69, 0.82; Figure 5).

In the tumors < 1.0cm group, shape ($P = 0.003$), enhancement direction ($P = 0.003$), peak intensity ($P = 0.031$), and score ($P = 0.026$) were correlated with CLNM. Multivariate logistic regression showed that irregular shape (OR = 2.515, 95% CI: 1.400, 4.516) and centrifugal or centripetal enhancement (OR = 2.801, 95% CI: 1.428, 5.491) were independent risk factors for CLNM.

3.5 Validation and clinical utilize of the nomogram

The predictive nomogram calibration curve demonstrated good coherence between the nomogram prediction and the actual probability (Supplementary Figure 3). Moreover, no significant difference was observed on the Hosmer-Lemeshow ($P = 0.967$), which showed a good fit.

4 Discussion

Although PTC is typically characterized by an indolent clinical course with an excellent prognosis, patients with cervical lymph node metastasis have an increased risk of local recurrence and poor outcome. Approximately 20% to 90% of PTC patients will have clinical or occult cervical lymph node involvement, with the central lymph nodes being the most common. Therefore, CLNM is highly

TABLE 1 Clinical characteristics of two groups.

Characteristics	nCLNM (n = 304)	pCLNM (n = 191)	Statistic	p-value
Age	43.72 ± 11.57	41.78 ± 11.39	t= 1.84	0.67
Gender			χ^2= 2.58	0.11
Female	233 (76.6%)	134 (70.2%)		
Male	71 (23.4%)	57 (29.8%)		
$BRAF^{V600E}$ status			χ^2= 2.3	0.13
Wild	82 (27.0%)	40 (20.9%)		
Mutation	222 (73.0%)	151 (79.1%)		

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TABLE 2 Conventional Ultrasound features between groups.

Variables	nCLNM (n = 304)	pCLNM (n = 191)	Statistic	p-value
Tumor size			χ^2= 14.79	0.00
< 1.0 cm	192 (63.2%)	87 (45.5%)		
≥ 1.0 cm	112 (36.8%)	104 (54.5%)		
LD (cm)	0.8 (0.63, 1.2)	1.0 (0.7, 1.5)	Z= 3.78	0.00
AP diameter (cm)	0.7 (0.55, 0.9)	0.8 (0.6, 1.1)	Z= 4.08	0.00
Composition			χ^2= 2.36	0.12
Cystic and solid	19 (6.3%)	6 (3.1%)		
Solid	285 (93.8%)	185 (96.9%)		
Internal echo			χ^2= 1.64	0.20
Equal echo	10 (3.3%)	2 (1.0%)		
Extremely and low	294 (96.7%)	189 (99.0%)		
Orientation			χ^2= 0.00	0.97
Wider-than-tall	103 (33.9%)	65 (34.0%)		
Taller-than-wide	201 (66.1%)	126 (66.0%)		
Shape			χ^2= 32.28	0.00
Regular	131 (43.1%)	35 (18.3%)		
Irregular	173 (56.9%)	156 (81.7%)		
Margin			χ^2= 3.83	0.05
Defined	127 (41.8%)	63 (33.0%)		
Ill-defined	177 (58.2%)	128 (67.0%)		
Extrathyroidal extension			χ^2= 0.47	0.49
Absent	285 (93.8%)	176 (92.1%)		
Present	19 (6.3%)	15 (7.9%)		
Echogenic foci			χ^2= 11.20	0.00
Absent/Large comet-tail artifacts	79 (26.0%)	35 (18.3%)		
Macrocalcifications/rim calcification	50 (16.4%)	18 (9.4%)		
Punctate echogenic foci	175 (57.6%)	138 (72.3%)		
Vascularity			χ^2= 0.14	0.71
Poor	218 (71.7%)	134 (70.2%)		
Rich	86 (28.3%)	57 (29.8%)		

related to the local recurrence, disease-free survival, and overall survival (11). Unfortunately, the preoperative detection of CLNM is unsatisfactory. US is a first-line imaging modality for diagnosing PTC and assessing lymph nodes. However, the accuracy of conventional US in CLNM detection is notably lower than that of lateral lymph node metastasis (12). CEUS provides insight into the perfusion pattern of lesions and has been reported to be an excellent imaging technology for distinguishing malignant lymph nodes from benign lymph nodes and identifying metastatic cervical lymph nodes in PTC patients (13–15). However, whether the CEUS features of PTC are effective in the prediction of CLNM is largely unknown. Thus, in this study, we retrospectively analyzed the CEUS and conventional US features of 684 PTC patients with or without CLNM to investigate the predictive value of CEUS features of PTC in identifying CLNM. Our results suggested that irregular shape, tumor size (≥ 1.0cm), and score based on CEUS TI-RADS categories may be helpful for identifying CLNM in PTC patients. In addition, in the subpopulation with larger tumor size (≥ 1.0cm), PTC patients' age ≤35 years with irregular shape on US and score more than 6 was strongly increased the risk of CLNM.

Tumor size is a crucial factor in tumor staging (eg., TNM staging classification) and prognostic risk stratification of PTC

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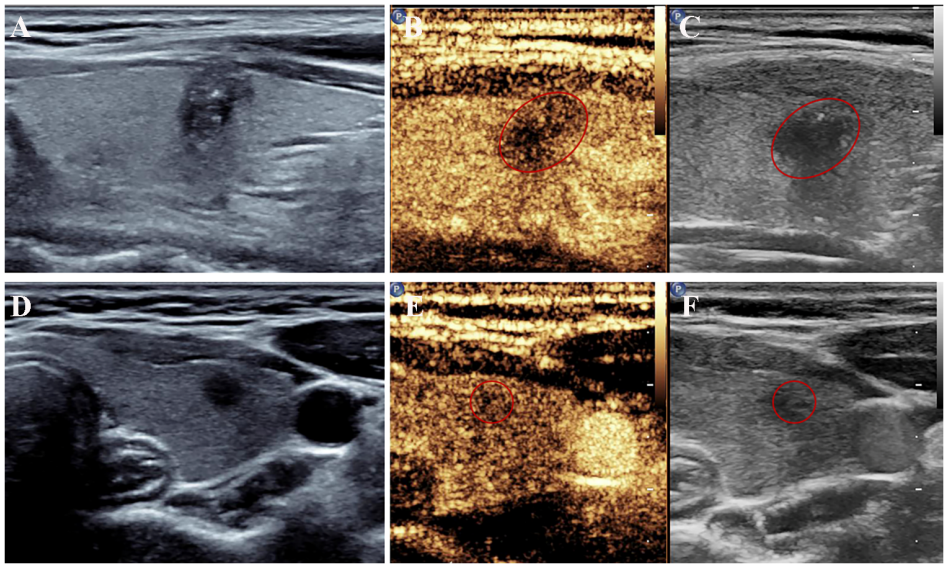

FIGURE 2
US features of papillary thyroid cancer with or without central lymph node metastasis. **(A–C)** A left thyroid nodule with tumor size > 1.0 cm showed irregular shape with microcalcifications on conventional ultrasound and hypoenhancement at peak intensity on CEUS. Metastatic central lymph nodes were confirmed surgically. **(D–F)** A left thyroid nodule showed a circular shape with a longest diameter of 0.54 cm on conventional ultrasound and mild hypoenhancement at peak intensity on CEUS. No metastatic lymph nodes were found after the surgery. CEUS, contrast-enhanced ultrasound; US, ultrasound.

patients. Tumor size has been reported to be an independent risk factor for CLNM in PTC (16–18). Consistent with the previous studies, PTC with CLNM in our study had a larger tumor size than those without CLNM regardless of axial or anteroposterior diameter. However, the tumor size threshold is inconsistent, with different studies using 0.5 cm or 1.0 cm as a cutoff. According to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system, which trialed a subdivision of T1 thyroidal tumors into T1a (<1.0 cm) and T1b (1.0-2.0 cm), we used 1.0 cm as the grouping standard in this study. We found that there were more cases measuring ≥ 1.0 cm in the pCLNM group than in the nCLNM group when tumor size was dichotomized at 1.0 cm. Subsequent multivariate regression analysis revealed that tumor size (≥ 1.0cm) was an independent risk factor for CLNM. In light of this finding,

TABLE 3 Contrast-enhanced ultrasound features between groups.

Variables	nCLNM (n = 304)	pCLNM (n = 191)	Statistic	p-value
Enhancement area			χ^2= 1.58	0.21
Equal	285 (93.8%)	184 (96.3%)		
Greater or smaller	19 (6.3%)	7 (3.7%)		
Enhancement direction			χ^2= 9.96	0.00
Scattered	89 (29.3%)	32 (16.8%)		
Centripetal or centrifugal	215 (70.7%)	159 (83.2%)		
Peak intensity			χ^2= 9.60	0.00
Iso- or nonenhancement	92 (30.3%)	34 (17.8%)		
Hyper- or hypoenhancement	212 (69.7%)	157 (82.2%)		
Ring enhancement			χ^2= 0.00	0.98
Present	11 (3.6%)	7 (3.7%)		
Absent	293 (96.4%)	184 (96.3%)		
Composition			χ^2= 2.31	0.13
Non-solid	21 (6.9%)	7 (3.7%)		
Solid	283 (93.1%)	184 (96.3%)		

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TABLE 4 Multivariate logistic regression analysis.

Variables	Beta	Z	P	OR (95%CI)
Age				
< 42years				Reference
≥ 42years	-0.34	-1.69	0.09	0.71 (0.48 - 1.05)
Score	0.26	3.08	0.002	1.30 (1.10 - 1.53)
Sex				
Female				Reference
Male	0.39	1.72	0.085	1.48 (0.95 - 2.30)
Tumor size				
< 1.0 cm				Reference
≥ 1.0 cm	0.75	3.70	<.001	2.11 (1.42 - 3.14)
Shape				
Regular				Reference
Irregular	1.08	4.64	<.001	2.96 (1.87 - 4.68)
Enhancement direction				
Scattered				Reference
Centripetal/centrifugal	0.46	1.7	0.09	1.58 (0.93 - 2.67)

we also attempted to filter out risk factors for CLNM in the larger tumor size sub-population. The results showed that a younger age (≤ 35 years), an irregular shape, and a score greater than 6 were associated with an increased risk of CLNM. Therefore, if the longest diameter is equal to or greater than 1.0cm, irregular shape is found on US, and more than 6 points are obtained on CEUS TI-RADS, further careful evaluation for CLNM is necessary.

Irregular shape means that the nodule appears poly-lobulated or spiculated appearance on US rather than being sharply delineated. Infiltration of the thyroid parenchyma with the absence of a pseudocapsule is the pathologic cause of irregular shape on US. Irregular shape increases the risk of malignancy with a sensitivity and specificity of 50 to 59% and 79 to 83%, respectively (19, 20). The more aggressive the nodule is, the more likely it is to develop lymph node metastasis. Indeed, in the present study, PTC with CLNM were more likely to have an irregular shape on US than those without CLNM. In addition, in the larger tumor size sub-population, irregular shape was also found to be associated with CLNM. These findings suggest that we should pay more attention to the suspected PTC with an irregular shape on the US.

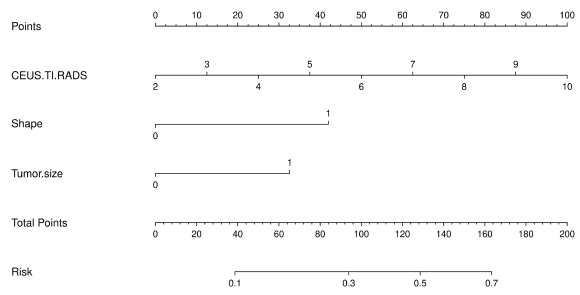

FIGURE 3
The predictive nomogram integrating conventional US features and score based on CEUS TI-RADS in the training cohort. TI-RADS, Thyroid Imaging Reporting and Data System.

CEUS can provide a wealth of information on blood perfusion and quantitative parameters for hemodynamic evaluation of pathological conditions. Using CEUS significantly improves the diagnostic accuracy in some solid tumors, including breast tumor, liver tumor, and thyroid tumors. Several studies show the potential utility of CEUS in the differential diagnosis of benign and malignant thyroid nodules and in the analysis of lymph node involvement (21). The CEUS parameters including hyper-enhancement, centripetal perfusion, and ring enhancement are related to metastatic lymph nodes (15, 22). However, few studies evaluated the association between CEUS features of PTC and lymph node metastasis. In a study of 186 PTC patients, peak intensity, capsule contact, and tumor size under CEUS were found to be the three strongest independent predictors for CLNM. However, the AUCs of these three features are only 0.586 to 0.612 (6). In line with this, Guang et al. revealed that nodule contact with the thyroid capsule ≥25% was an independent risk factor for CLNM of PTCs (23).In another study, peak of nodule interior and AUC of the peripheral ring on CEUS were independent risk factors of CLNM (24). In our study, we found a significant difference in peak intensity and enhancement direction (centripetal or centrifugal enhancement) between pCLNM and nCLNM groups. Peak intensity has been reported to be positively correlated with the p53 and Ki-67 expression in PTC (25). Since the expression levels of P53 and

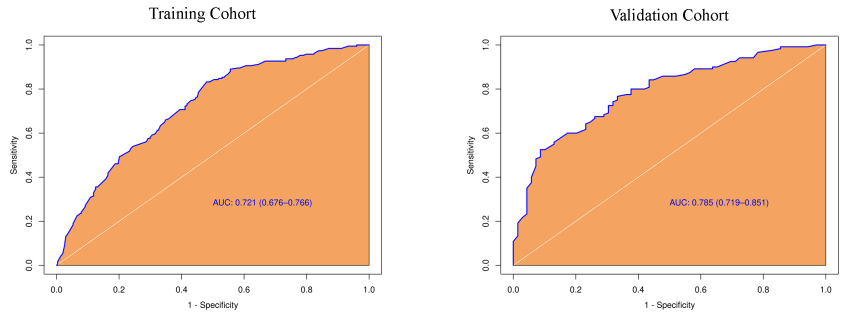

FIGURE 4
Diagnostic performance of the predictive model integrating conventional and score in both training and validation cohorts. AUC, the receiver operating characteristic curve.

Ki67 can reflect the proliferative activity of thyroid tumor cells, this may explain why there was significant difference in peak intensity between pCLNM and nCLNM groups. Generally, the tumor neovasculature is relatively dense in the tumoral periphery region and sparse in the center region. The uneven distribution of neovascularization may lead to the centripetal enhancement reflected by CEUS in most PTC (26). However, these two CEUS parameters were not associated with CLNM the final multivariate regression analysis. The discrepancy may indicate that CEUS features alone were insufficient to distinguish metastatic from benign lymph nodes.

CEUS TI-RADS, which was created with thyroid nodule malignancy risk stratification according to the regression coefficients of conventional US and qualitative features of CEUS, is practical in routine clinical practice because all US features in this stratification system are qualitative (10). In this way, a score was assigned to each thyroid nodule in our study in accordance with CEUS TI-RADS. A comparison of the mean score between the pCLNM and nCLNM groups showed a remarkable difference. Multivariate regression analysis demonstrated that the risk of CLNM increased 1.3-fold with a higher score. To our best knowledge, this was the first report to evaluate the association between CEUS TI-RADS categories and CLNM. Based on our results, discriminative features including irregular shape, tumor size, and score were used to identify PTC patients with CLNM. The predictive model, comprising these features, showed a good performance in predicting CLNM in PTC patients in both the training and validation cohorts, with an AUC of 0.72 and 0.79, respectively. This performance was superior to that of either conventional US features or scores based on CEUS TI-RADS. When the AUC >0.5, the AUC value is closer to 1, indicating a better diagnostic performance. The higher the AUC, the better the model is at distinguishing between PTC patients with and without CLNM. Our results suggest that the predictive model developed in this study is effective in predicting PTCs with CLNM. Several studies have reported the excellent performance of various artificial intelligence (AI)-based models in predicting lymph node metastasis and different metastatic patterns, achieving an AUC between 0.870 and 0.930 (27, 28). Large-scale sample size and including all cervical lymph nodes, rather than just the central lymph nodes, may lead to higher AUCs. Even so, the prediction model developed in this study is convenient as it only requires simple calculations. The AI-based model is complex, involving extensive image extractions. The calibration curve of the nomogram also shows the good agreement between the predicted outcome by the nomogram and the actual probability. Therefore, our results suggest that the predictive model developed in this study will be a convenient and valuable tool for clinicians to decide whether to proceed with central lymph node dissection.

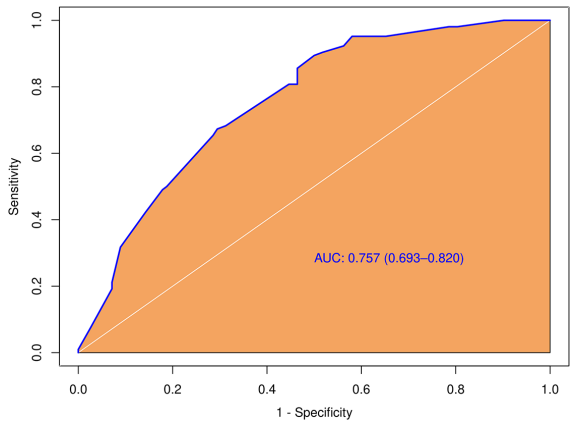

FIGURE 5
Diagnostic performance of the predictive model integrating conventional and score in the subgroup with larger tumor size (≥ 1.0cm).

There are also some limitations in our study. First, this study is a monocentric. The training and validation cohorts are from the same hospital, with no external data. The performance of the predictive nomogram is expected to increase by including more data from other hospitals or our hospitals into the training and validation cohorts. Second, because the US features that make up CEUS TI-RADS are qualitative, quantitative CEUS parameters are not included in this study. Third, this nomogram is appropriate only for PTC and not for all thyroid malignancies. Fourth, this study is retrospective, we included only patients who are pathologically confirmed PTC and metastatic status of central lymph nodes, which may have led to a selection bias in patient recruitment.

5 Conclusions

In this study, we found that US features including irregular shape, larger tumor size (≥ 1.0cm), and score based on CEUS TI-RADS categories exerted a differential role in PTC patients with CLNM. In addition, in the subpopulation with a larger tumor size, younger age (≤ 35 years), irregular shape on US, and a higher score (> 6) increased the risk of CLNM. The predictive nomogram integrating the independent predictors showed a great performance in both the training and validation cohorts. Therefore, this predictive nomogram will facilitate the individualized prediction of CLNM in PTC patients, assisting surgeons in achieving accurate CLNM for maximum patient benefit. Furthermore, the application of the nomogram is convenient as it only requires simple calculations, enabling general utility for clinicians with different specialties and levels of experience.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethics committee of Daping Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

LH: Writing – original draft, Project administration, Data curation. XC: Writing – original draft, Project administration, Data curation. JH: Writing – original draft, Investigation, Data curation. YM: Writing – original draft, Data curation. YZ: Writing – original draft, Data curation. WC: Writing – original draft, Data curation. YF: Writing – original draft, Methodology, Data curation. TL: Writing – review & editing, Supervision, Investigation. JF: Project administration, Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1336787/full#supplementary-material

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Prognostic value of postoperative anti-thyroglobulin antibody in patients with differentiated thyroid cancer

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Purpose: Postoperative thyroglobulin (Tg) generally serves as a biomarker to monitor the recurrence or persistence of differentiated thyroid cancer (DTC), whereas it constrains to interference from anti-thyroglobulin antibody (TgAb). This study aimed to determine the value of postoperative TgAb as a surrogate for monitoring tumor status in DTCs with positive TgAb after successful radioactive iodine (RAI) remnant ablation.

Methods: We retrospectively enrolled DTC patients with positive (≥40 IU/mL, Roche) postoperative TgAb measurements. An index of TgAb change (ΔTgAb) was defined to describe the TgAb decrease rate. DTC status was defined as either no evidence of disease (NED) or persistent/recurrent disease (PRD). Univariate and multivariate binary logistic analyses were used to identify the independent risk factors of PRD. Receiver operating characteristic (ROC) curves were performed to determine the optimal cutoff values of each risk factor, and DeLong's test was conducted to compare their predictive powers. Kaplan–Meier curves were used to assess the impact of different TgAb trends in the first year on progression-free survival.

Results: Of the 232 patients enrolled, the median diagnosis age was 34 years (range, 18–62 years), with a male-to-female ratio of 1:4.66 (41/191). Among them, after a median follow-up of 44 months (range, 4–128 months),183 (78.87%) patients were evaluated as NED, while the other 49 (21.12%) had either persistent (n = 25) or recurrent disease (n = 24). Multivariate regression showed that ΔTgAb ($P < 0.001$) and lymph node metastasis (LNM) rate ($P = 0.009$) were independently relevant to the presence of PRD, with optimal cutoff values of 47.0% and 35.1%, respectively. It is important to note that there is a high negative predictive value (96.93%) of ΔTgAb with the cutoff of 47.0%. DeLong's test showed that ΔTgAb alone and the combination of ΔTgAb and LNM rate were significantly greater than the isolated LNM rate (both $P < 0.001$) in predicting NED, while there was no statistical difference of the predictive power between

ΔTgAb and the combination (P = 0.203). Additionally, patients with ΔTgAb >47.0% had longer progression-free survival than those with ΔTgAb ≤47.0% (not reached vs. 50 months, P < 0.001), and those with ΔTgAb >47.0% or negative conversion within the first year after RAI ablation had longer progression-free survival.

Conclusion: Our study suggested that ΔTgAb could serve as a valuable indicator of disease status in DTC patients with positive TgAb. A ΔTgAb of >47.0% is conducive to identify those with NED and may help to obviate their overtreatment. The decrease rate and negative conversion of TgAb in the first year were good predictors of disease-free survival in patients.

KEYWORDS

differentiated thyroid cancer, anti-thyroglobulin antibody, biomarker, prognosis, persistent/recurrent disease

Introduction

Differentiated thyroid cancer (DTC) is the most prevalent endocrine malignancy, the majority of which are papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) with an excellent prognosis (1). Currently, total or near-total thyroidectomy, postoperative selective radioactive iodine (RAI/^{131}I), and long-term thyroid-stimulating hormone (TSH) suppression are commonly used as the first-line clinical treatments for patients with DTC (2). Biochemical measurements in combination with imaging examinations such as cervical ultrasound (US), chest computed tomography (CT), and radioiodine diagnostic whole-body scan (DxWBS) are considered the standard of care for the management of DTC. Thyroglobulin (Tg) is usually used as a sensitive and convenient biochemical tumor marker after initial therapy. Nevertheless, its accuracy may be interfered by anti-thyroglobulin antibody (TgAb) in up to 25% of DTC patients (3). Moreover, a dilemma emerged in such patients as to how to biochemically monitor the disease status during follow-up. In the 2015 American Thyroid Association (ATA) guidelines, measuring both serum TgAb and Tg levels simultaneously is recommended for DTCs during follow-up (4). Theoretically, after the removal of all thyroid tissue by total thyroidectomy and ^{131}I therapy in patients with DTC, Tg should be cleared, leading to a gradual decrease of TgAb until it disappears (5). Therefore, a falling TgAb trend over time often indicates the remission or improvement of the disease (6). However, as TgAb is a marker reflecting immuno-reaction, depending on the different immuno-backgrounds of patients, it remains quite illusive for us to define and expect the definite change as Tg. Several studies have demonstrated that in DTC patients with TgAb reduced slowly, long-term stable or increasing TgAb levels appear to have a varying degree of increased risk of persistent or recurrent disease (PRD) compared to those exhibiting a considerable reduction (7–13). However, so far, the dynamic changes of TgAb at postoperative follow-up and TgAb quantitative analysis in relation to the clinical outcomes of TgAb-positive DTC patients after RAI therapy remain not yet well addressed. Our objective was to evaluate the clinical value of change in TgAb as a predictor of disease status during the follow-up of patients after thyroid ablation.

Patients and methods

Study population

In this retrospective study, we screened the records of DTC patients at Peking Union Medical College Hospital between December 2009 and August 2021. The inclusion criteria were as follows: (1) the patients underwent total or near-total thyroidectomy and were pathologically diagnosed as DTC, including PTC and FTC, (2) the patients received RAI ablation, (3) detected with positive postoperative TgAb measurements, and (4) at least two TgAb measurements available during follow-up. On the other hand, individuals were excluded if they qualify under any of the following: (1) pediatric and adolescent patients aged <18 years at the time of diagnosis, (2) lack of relevant clinicopathological data such as histology and primary tumor size, and (3) lack of imaging examinations such as cervical ultrasound, computed tomography, or ^{131}I-whole body scan (WBS) during follow-up. The screening process is shown in Figure 1. In total, 232 patients were enrolled in the study. In seven cases, the TgAb levels were measured consistently above the upper limit of detection (>4,000 IU/mL) during follow-up, which could not determine TgAb change trends. Thus, 225 patients were finally included when computing ΔTgAb, which was calculated by the following

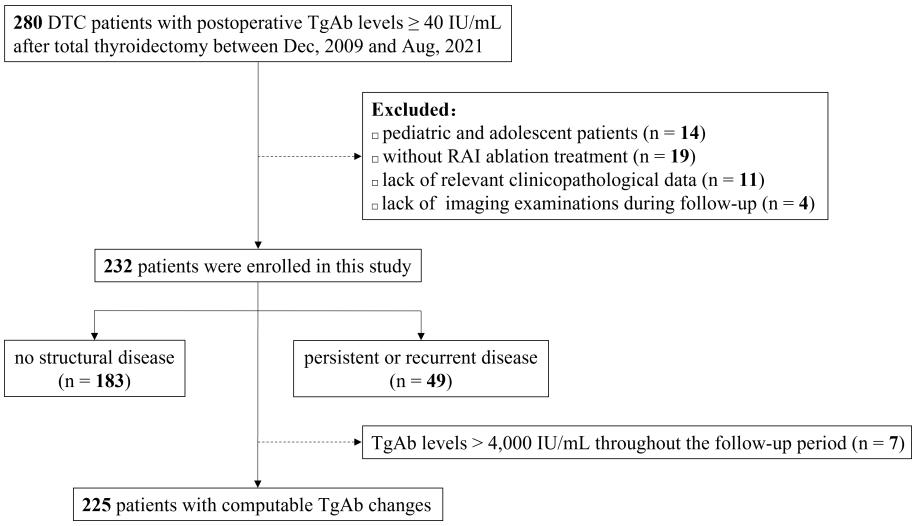

FIGURE 1
Case screening process of the study. DTC, differentiated thyroid cancer; TgAb, anti-thyroglobulin antibody; RAI, radioactive iodine.

equation: (TgAb level at initial follow-up - TgAb level at final follow-up)/(TgAb level at initial follow-up) × 100%. A positive value indicates a decrease of TgAb level at final follow-up relative to the initial, and a negative value indicates an increase.

Follow-up strategy and clinical outcome

In accordance with the ATA guidelines, all patients were given inhibitory doses of levothyroxine after surgery and iodine treatment, and then they received regular follow-up for a long term (4). The follow-up examinations included serum, ultrasound, and radiological examinations. Tg and TgAb concentrations were measured at each visit, while imaging procedures such as neck US and chest CT were performed on schedule. If a suspicious lesion is detected during follow-up, further imaging such as DxWBS and/or positron emission tomography/computed tomography (PET/CT) may be performed, and pathology would be obtained to confirm the lesion when the patient received further surgery or biopsy.

The clinical outcome of each patient was determined by a pathology report and/or imaging findings during follow-up. The patients were divided into no evidence of disease (NED, no suspicious structural/functional findings) or persistent or recurrent disease (PRD). In addition, progressive disease, including all recurrent diseases and part of a persistent disease, was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Accordingly, progression-free survival (PFS) was defined as the time interval from successful RAI remnant ablation to either disease progression or the latest visit for those with NED or non-progressive persistent disease.

The follow-up time of DTC in clinical practice is generally long and might vary tremendously between patients. Meanwhile, in order to provide a more convincing reference method for TgAb in clinical follow-up, according to Kim et al. (7), we chose the first year after RAI ablation as the time interval to stratify the decrease rate and status of TgAb to assess the impact of different TgAb decrease rates and status of negative conversion in the first year on PFS.

Laboratory studies

Serum Tg and TgAb levels were determined by electrochemiluminescence immunoassay (provided by Roche Diagnostics GmbH, Mannheim, Germany) with measurement ranges of 0. 04 to 500 ng/mL and 10 to 4,000 IU/ml, respectively. Serum TgAb titers ≥40 IU/mL were defined as positive TgAb, which might interfere with Tg measurement (14, 15). TSH was determined by chemiluminescence immunoassay (provided by Siemens Healthcare Diagnostics Inc., New York, NY, USA) with a detection range of 0.04 to 150 μIU/mL. Values above the ranges were reported as >500 ng/mL, >4,000 IU/mL, and >150 μIU/mL for Tg, TgAb, and TSH, respectively.

Statistical analysis

Continuous variables of the two groups conforming to normal distribution were represented as mean ± standard deviation (SD) and compared by Student's *t*-test, while non-normal variables were reported as median (range) and compared by Mann–Whitney *U*-test. Categorical variables were expressed as absolute numbers and percentage frequency distribution, compared by chi-square test or Fisher's exact test. Binary logistic regression analyses were conducted to identify the risk factors of PRD, and variables with $P < 0.05$ in the univariate logistic analysis were entered into a multivariate logistic analysis. For statistically significant indicators, receiver operating characteristic (ROC) analyses were conducted to evaluate the predictive values and identify the optimal cutoff values. The indicators' areas under the ROC curve (AUCs) were also compared by DeLong's test to estimate the predictive

power. Kaplan–Meier curves and log-rank tests were used to assess the impact of different TgAb trends in the first year on PFS. All hypothesis tests were two-sided with P <0.05 indicating statistically significant differences.

Results

Clinical characteristics

Of the 232 patients eventually included in this study, 227 were diagnosed as PTC and five as FTC, with a median diagnosis age of 34 years (range, 18–62 years) and a male-to-female ratio of 1:4.66 [41 (17.67%)/191 (82.33%)]. At a median follow-up of 44 months (range, 4–128 months), 183 (78.88%) patients were identified with NED, while the other 49 (21.12%) had either persistent (n = 25/49, 51.02%) or recurrent disease (n = 24/49, 48.98%) with disease progression (defined by RECIST criteria) noticed in 30. The clinical characteristics of the study population are listed in Table 1. Maximal tumor size, capsular invasion, lymph node metastasis (LNM) rate, N stage, and cumulative RAI dose were statistically different between the NED and PRD groups. The LNM rate refers to the percentage of pathologically confirmed metastatic LNs accounted for surgically removed LNs.

Predictors for persistent/recurrent disease

During follow-up, seven patients presented with continuous TgAb levels >4,000 IU/mL, of which four remained NED, one had persistent and progressive lung metastatic lesions, and two had cervical lymph node recurrences.

Among 225 patients whose ΔTgAb could be calculated, 179 presented as NED, while 46 exhibited as PRD. In the PRD group, 24 patients had a persistent disease (nine in the cervical lymph nodes, 12 in the lungs, and three in both) and 22 had a recurrent disease (16 in the cervical lymph nodes, four in the lungs, and two in both). Moreover, progressive diseases were observed in 27 cases (16 in cervical lymph nodes, nine in the lungs, and two in both). We performed binary logistic regression analyses to assess these variables' potential impact on the presence or absence of persistent/recurrent DTC (Table 2). By univariate logistic analysis, several risk factors including larger tumor size, capsular invasion, high LNM rate, advanced N stage, high cumulative RAI dose, and low ΔTgAb were significantly associated with PRD. Considering that a higher cumulative RAI dose is commonly recommended for those with a high risk of either mortality or recurrence, patients requiring high therapeutic doses are more likely to have a persistent/recurrent disease, such as lung metastases. Thus, the cumulative RAI dose was only included in the multivariate regression as a corrective variable for confounders. According to the multivariate logistic analysis, LNM rate (P = 0.009, OR = 1.044, 95% CI: 1.011–1.079) and ΔTgAb (P < 0.001, OR = 0.948, 95% CI: 0.929–0.967) were independent risk factors of PRD.

ROC analysis to predict persistent/recurrent disease

As shown in Figure 2, we plotted ROC curves incorporating ΔTgAb, LNM rate, and their combination. The optimal cutoffs of LNM rate and ΔTgAb in predicting PRD were 35.1% (P < 0.001, AUC = 0.745, 95% CI: 0.683–0.801) and 47.0% (P < 0.001, AUC = 0.940, 95% CI: 0.900–0.967), respectively. The AUC of the combination of both (LNM rate and ΔTgAb) was 0.950 (P < 0.001, 95% CI: 0.913–0.975). Their diagnostic performance indexes are displayed in Table 3, of which ΔTgAb >47.0% had the highest negative predictive value (NPV) of 96.93%. Furthermore, a comparison of the AUCs by DeLong's test showed that ΔTgAb alone and the combination had a significantly greater predictive power than that of LNM rate (both P < 0.001), with no statistical difference between ΔTgAb alone and the combination observed (P = 0.203) (Table 4).

Quantitative changes of TgAb levels in different disease status

Excluding seven patients whose ΔTgAb could not be calculated due to consistent TgAb levels above the upper limit of detection (>4,000 IU/mL), changes of TgAb levels during follow-up in patients with different disease status are illustrated in Figure 3. Among 179 patients with NED (Figure 3B), 176 (98.32%) demonstrated a spontaneous decrease in TgAb levels during follow-up, 158 (88.27%) had a decrease >47.0%, 130 (72.63%) had a decrease below 40 IU/mL, and only three (1.68%) showed progressively increasing TgAb levels. Among 46 patients with PRD (Figure 3C), 25 (54.35%) exhibited a gradually increasing trend of TgAb over time, 21 (45.65%) had decreasing TgAb levels, five of whom (10.87%) had TgAb levels below 40 IU/mL at the latest visit, without any significant increase in Tg.

Effects of LNM rate and different TgAb changes on progression-free survival

According to the optimal cutoff value of LNM rate, we divided the patients into two groups of LNM rate ≥35.1% and LNM rate <35.1% for further analyses. The log-rank analysis and Kaplan–Meier curve showed a significant difference of PFS between the two groups (Figure 4A): patients in the LNM rate <35.1% group had longer PFS than those in the LNM rate ≥35.1% group (P < 0.001).

Based on the optimal cutoff value of ΔTgAb, we divided the patients into two groups: ΔTgAb ≤47.0% and ΔTgAb >47.0%. During follow-up, progressive disease was found in 40.32% (25/62) of patients with ΔTgAb ≤47.0%, and only 1.22% (2/163) had ΔTgAb >47.0%. Additionally, the log-rank analysis and Kaplan–Meier curve showed that patients in the ΔTgAb >47.0% group had longer PFS than those in the ΔTgAb ≤47.0% group (not reached vs. 50 months, P < 0.001) (Figure 4B). Considering the time-dependent nature of TgAb, we grouped the decrease rate and status of TgAb by 1-year cutoff. Of the 225 patients with calculable ΔTgAb, 117 patients had a decrease >47.0% of TgAb in the first

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TABLE 1 Clinical characteristics of 232 differentiated thyroid cancer patients with positive TgAb.

Characteristics	Total (*N* = 232)	NED (*N* = 183)	PRD (*N* = 49)	*P* value
Age at diagnosis (years)				0.911
Median	34	34	33	
Range	18–62	18–61	18–62	
Gender				0.886
Male	41 (17.67%)	32 (17.49%)	9 (18.37%)	
Female	191 (82.33%)	151 (82.51%)	40 (81.63%)	
Histology				0.951
Papillary	227 (97.84%)	179 (97.81%)	48 (97.96%)	
Follicular	5 (2.16%)	4 (2.19%)	1 (2.04%)	
Maximal tumor size (cm)				0.040*
Median	1.15	1	1.4	
Range	0.2–5.0	0.2–5.0	0.2–5.0	
Bilaterality				0.763
Yes	81 (34.91%)	63 (34.43%)	18 (36.73%)	
No	151 (65.09%)	120 (65.57%)	31 (63.27%)	
Multifocality				0.233
Yes	115 (49.57%)	87 (47.54%)	28 (57.14%)	
No	117 (50.43%)	96 (52.46%)	21 (42.86%)	
Hashimoto's thyroiditis				0.900
Yes	126 (54.31%)	99 (54.10%)	27 (55.10%)	
No	106 (45.69%)	84 (45.90%)	22 (44.90%)	
Capsular invasion				0.004*
Yes	123 (53.01%)	88 (48.09%)	35 (71.43%)	
No	109 (46.98%)	95 (51.91%)	14 (28.57%)	
LNM rate (%)				<0.001*
Median	27.3	22.7	45.9	
Range	0–100	0–100	0–100	
N stage				<0.001*
N0	24 (10.34%)	23 (12.57%)	1 (2.04%)	
N1a	92 (39.66%)	84 (45.90%)	8 (16.33%)	
N1b	116 (50.00%)	76 (41.53%)	40 (81.63%)	
Cumulative RAI dose (mCi)				<0.001*
Median	100	30	150	
Range	30–800	30–270	30–800	

N stage was evaluated according to the eighth Tumor–Node–Metastasis Classification of the American Joint Committee on Cancer (16).
NED, no evidence of disease; PRD, persistent/recurrent disease; LNM, lymph node metastasis.
*P value <0.05.

year, with a median time of 7 months; the other 108 patients had a decrease ≤47.0% in the first year, and the former had a longer PFS than the latter ($P < 0.001$), as shown by the survival curve in Figure 4C. Furthermore, 135 patients achieved TgAb negative conversion (TgAb dropped to below 40 IU/mL) at final follow-up, with a median time of 8 months. Among these, 78 patients became negative during the first year, 57 became negative after the first year, and 90 patients remained positive at the end of follow-up.

TABLE 2 Univariate and multivariate logistic regression analyses for factors associated with persistent/recurrent disease.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age at diagnosis	1.004	0.973–1.037	0.797			
Gender	1.117	0.491–2.544	0.791			
Histology	0.972	0.106–8.913	0.980			
Maximal tumor size	1.407	1.021–1.939	0.037*	1.107	0.536–2.285	0.784
Bilaterality	1.032	0.522–2.038	0.928			
Multifocality	1.504	0.783–2.888	0.221			
Hashimoto's thyroiditis	1.053	0.549–2.017	0.877			
Capsular invasion	2.528	1.264–5.056	0.009*	1.245	0.320–4.844	0.751
LNM rate	1.037	1.021–1.053	<0.001*	1.044	1.011–1.079	0.009*
N stage			<0.001*			0.791
N1a vs. N0	2.190	0.260–18.422	0.470			
N1b vs. N0	11.819	1.535–90.989	0.018*			
Cumulative RAI dose	1.016	1.010–1.021	<0.001*	1.022	1.011–1.033	<0.001*
ΔTgAb	0.951	0.937–0.965	0.001*	0.948	0.929–0.967	<0.001*

ΔTgAb, decrease percentage of TgAb level; OR, odds ratio; CI, confidence interval. *P value < 0.05.

The survival curve showed that patients who turned negative in the first year had a longer PFS than those who did not turn negative in the first year ($P = 0.003$) (Figure 4D).

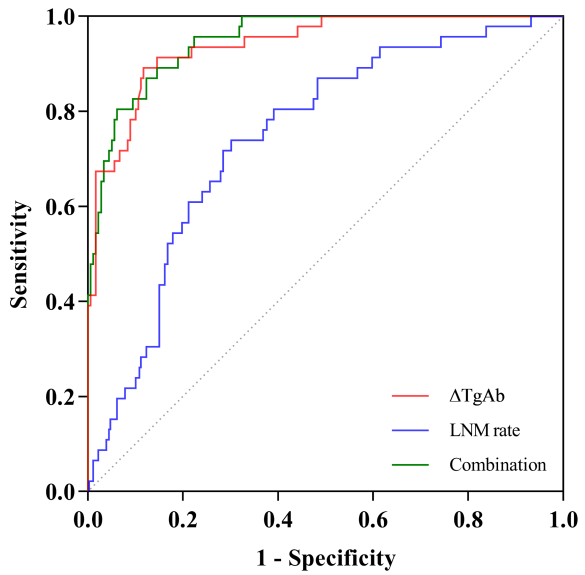

FIGURE 2
ROC curves of LNM rate, ΔTgAb, and their combination in predicting persistent/recurrent disease.

Discussion

The management of DTCs with positive TgAb has been a challenge due to its measuring interference of Tg in up to one-fourth of the patients. The focus of this study was to explore the clinical value of TgAb change during follow-up to predict different disease status in those TgAb-positive DTC patients and estimate whether it might be used as an indicator for physicians to timely adjust the follow-up management. Different from the median age at diagnosis of 51 years among thyroid cancer patients revealed by Surveillance, Epidemiology, and End Results (SEER) statistics and the male-to-female incidence ratio of approximately 1:3, in our cohort with TgAb-positive, the patients were much younger, with a median diagnosis age of 34 years old, and have a much lower male-to-female incidence ratio as 1:4.66 (41 vs. 191) (17, 18). These discrepancies may suggest that female patients are more likely to suffer autoimmune thyroiditis (AT) and a tendency of early onset of thyroid cancer derived from this immuno-inflammatory background, which are quite similar as the findings shown by others (19, 20). A recent prospective cohort study that included 9,851 patients with thyroid nodules also noted an increased risk of malignancy associated with Hashimoto's thyroiditis (HT), which suggested that thyroiditis might lead to tumor formation in a similar way that chronic inflammation of many tissues leads to cancer development (21). We thus assumed that young people and women may be more susceptible to underlying thyroid disorders (e.g., Hashimoto's thyroiditis), which might accelerate the development and lead to their earlier onset of DTC by the change of thyroid function, particularly elevated TSH and inflammatory stimulation that adversely affects normal thyroid tissue. All these may remind us that thyroiditis and TgAb-positive might be a

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TABLE 3 ROC curve analysis and diagnostic performance.

Variables	AUC (95% CI)	Optimal cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
LNM rate	0.745 (0.683–0.801)	35.1%	71.74	71.51	39.20	90.79
ΔTgAb	0.940 (0.900–0.967)	47.0%	89.13	88.27	66.12	96.93
Combination	0.950 (0.913–0.975)	18.1%	86.96	87.71	64.45	96.33

AUC, area under the ROC curve; PPV, positive predictive value; NPV, negative predictive value.

potential pre-cancerous sign which should be taken more seriously, especially in young and female patients. Studies have been performed to evaluate the tumor characteristics and prognosis of DTC patients with Hashimoto's thyroiditis. A multicenter study including 301 intrathyroidal PTC assessed the relationship between HT and disease outcome. The results showed that HT was detected in 42.5% of patients and was associated to female gender, smaller tumor size, lower incidence of aggressive PTC variants, and less frequent radio-iodine administration. Besides these, HT was associated with a significantly higher clinical remission rate, and recurrence-free survival (RFS) was significantly longer in PTCs with HT compared to non-HT tumors (22). Another multicenter study prospectively collected 4,233 DTC patients, of whom 36.7% had autoimmune thyroiditis. By comparing the clinical characteristics and outcomes of patients with or without AT at 1-year follow-up, they observed that AT patients were significantly younger and had a smaller and bilateral tumor. In addition, AT patients had more biochemical persistence disease, but there was no significant association between the presence of AT and the structural persistence disease, the potential explanation being the ability of the residual thyroid tissue of AT patients to continuously secrete TgAb, thus leading to an incomplete biochemical response (23). These results indicated that the presence of HT might only cause serological abnormalities in TgAb during clinical follow-up, but not related to the persistence or occurrence of structural disease, and might even be associated with better clinico-pathological features and prognosis. In our study, a higher percentage of 54.31% in TgAb-positive DTC patients with HT was present, illustrating that some of TgAb are probably induced by HT. We used structural persistent/recurrent disease as primary endpoint, and the result of the univariate logistic regression analysis showed no significant association between Hashimoto's thyroiditis and structural persistent/recurrent DTC in the follow-up (P = 0.877). Our study mainly predicted structural disease by serum TgAb changes, and since both suspected structural lesions and unsatisfactory biochemical levels provide evidence of disease persistence/recurrence, it is noteworthy that in the clinical follow-up of DTC we should not only monitor the occurrence of structural disease by imaging techniques but also focus on the serological changes at the same time for a more comprehensive assessment of persistent/recurrent disease.

TABLE 4 Pairwise comparisons among the AUCs of LNM rate, ΔTgAb, and the combination.

Comparisons of variables	Difference between areas (95% CI)	Z test	P value
ΔTgAb vs. LNM rate	0.194 (0.110–0.279)	4.496	<0.001*
LNM rate vs. combination	0.205 (0.130–0.280)	5.331	<0.001*
ΔTgAb vs. combination	0.011 (-0.006–0.027)	1.273	0.203

*P value < 0.05.

In cases whose thyroid tissue and Tg antigen are removed by surgery and RAI ablation without persistent or recurrent disease, TgAb concentrations have always been found to decrease over months to years and eventually disappear (24). Therefore, the normal upper limit of 115 IU/mL obviously cannot be regarded as the negative cutoff of TgAb in those with thyroid removal by surgery and RAI ablation. Thus, in this study, a cutoff value of 40 IU/mL was taken, as it has been applied in several studies to qualitatively diagnose TgAb status (positive or negative) (14, 15). Numerous studies have demonstrated that the trend of TgAb after initial treatment might serve as a surrogate predictor of a disease-free status of no residual disease (especially when TgAb is remarkably decreasing) or the presence of structural disease (especially when TgAb is *de novo* or gradually increasing) (6–11, 13, 25, 26). Meanwhile, there is still controversy concerning the association between TgAb change and DTC disease status. Studies have shown that the trends of TgAb levels could not predict the disease status of DTCs, manifested as either a similar proportion of recurrent cases in the negative trend (slope < 0) group to that in the positive (slope > 0)/no trend (slope close to 0) group based on linear regressions of TgAb values from the surgery date until the end of follow-up or no statistically significant association between *de novo* TgAb development and structural recurrence (27, 28). So far, few studies have quantitatively analyzed the dynamic changes of TgAb in adult DTCs and mostly limited to analyze its association with the efficacy of RAI ablation. Thus, in this study, TgAb changes were used and quantitatively assessed to associate with disease status in terms of recurrence/persistence or not, while the well-accepted response to therapy assessment was not used since TgAb-positive DTCs are poorly defined by such. After adjusting for other possible clinical predictors (age at diagnosis, gender, histology, maximal tumor size, bilaterality, multifocality, Hashimoto's thyroiditis, capsular invasion, N stage, and cumulative RAI dose), we obtained two independent variables including ΔTgAb and LNM rate, which could sensitively reflect DTC disease status during follow-up. ΔTgAb was identified to be negatively associated with persistent/recurrent DTC, while LNM rate was positively associated with such. Our finding suggests that ΔTgAb, an index derived from dynamic serial TgAb monitoring, could be an objective marker to sensitively reflect the disease status over time. As for LNM rate, although it reflects more about the thorough LN assessment at

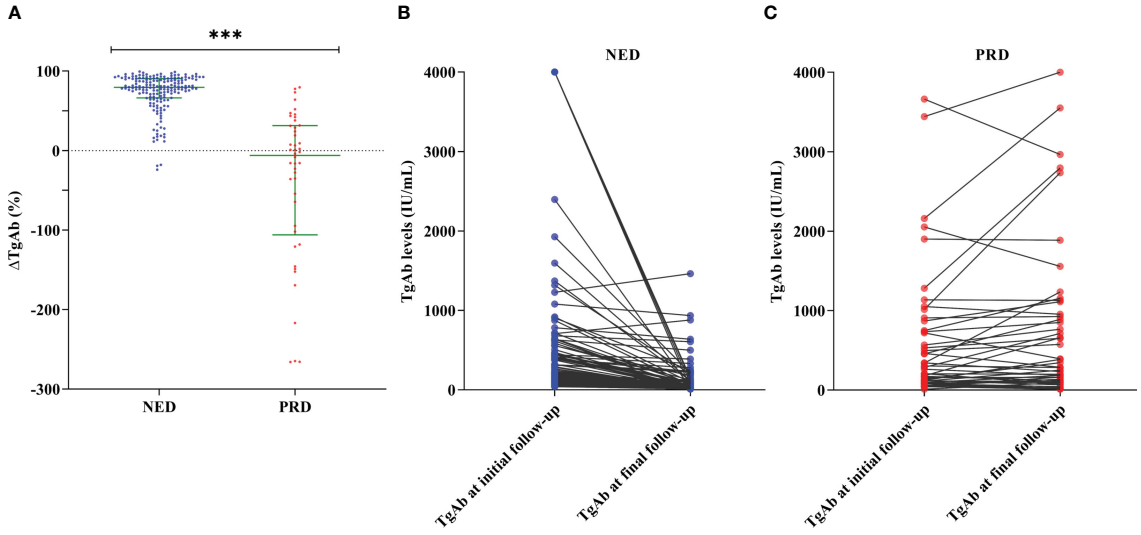

FIGURE 3
Changes of TgAb levels in patients with different disease status of differentiated thyroid cancer. **(A)** Comparison of ΔTgAb by Mann–Whitney test showed that ΔTgAb was higher in the no evidence of disease (NED) group than in the persistent/recurrent disease (PRD) group ($P < 0.001$). Trends of TgAb levels from initial to final follow-up of 179 patients with NED **(B)** and 46 patients with PRD **(C)**. Of the 28 patients with increasing TgAb levels, 25 (89.29%) were PRD and the other three remained NED. ***P value < 0.001.

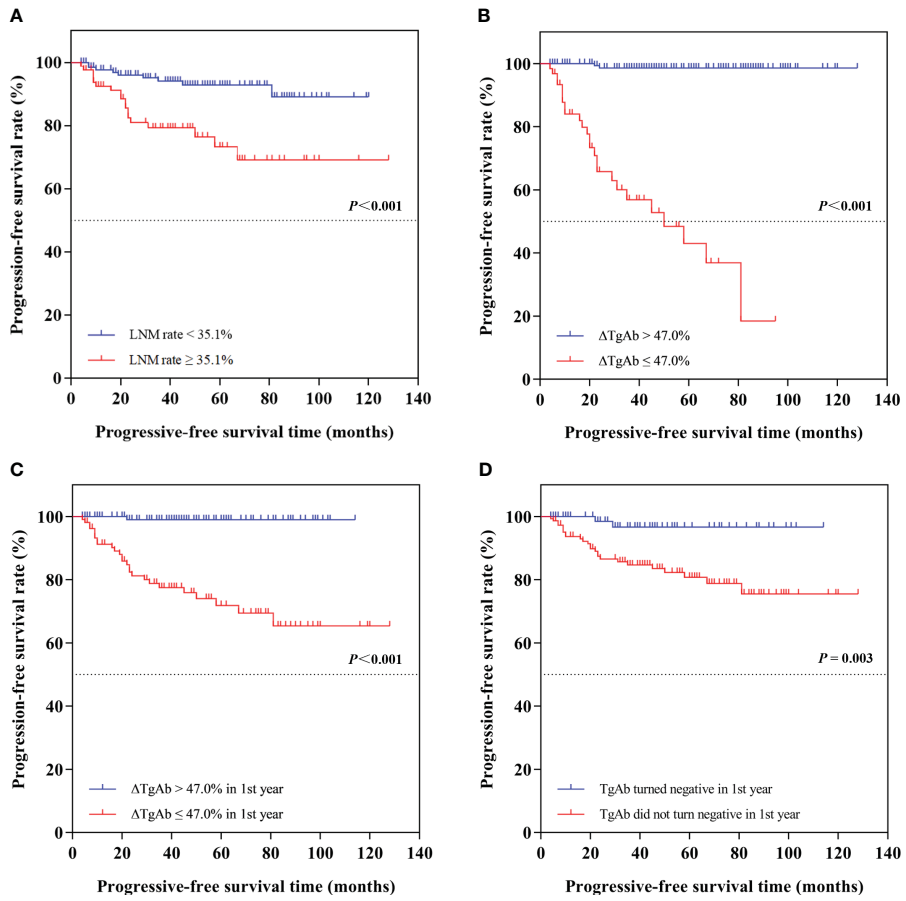

FIGURE 4
Kaplan–Meier curves of progression-free survival (PFS) in different groups of differentiated thyroid cancer patients. The log-rank analyses and Kaplan-Meier curves showed **(A)** patients in the LNM rate < 35.1% group had longer PFS than those in the LNM rate ≥ 35.1% group (P < 0.001); **(B)** patients in the ΔTgAb > 47.0% group had longer PFS than those in the ΔTgAb ≤ 47.0% group (not reached vs. 50 months, P < 0.001); **(C)** patients in ΔTgAb > 47.0% in the first year had longer PFS than those in the ΔTgAb ≤ 47.0% group (P < 0.001); **(D)** patients who turned negative in the first year had longer PFS than those who did not turn negative in the first year (P = 0.003).

surgery, it also correlates with the degree of lymph node invasion. A high LNM rate denotes that the patient has a more aggressive tumor with a large number of lymph node involvement and may be relatively susceptible to the presence of PRD during follow-up, implying that more active management such as RAI therapy should be considered in such patients. From the ROC curve analysis, a high predictive value for DTC disease status was revealed among all of the independent risk factors including ΔTgAb, LNM rate, and their combination. Though the AUC for the combination was the highest and significantly greater than that for LNM rate, there was no significant difference between the combination and ΔTgAb alone. Therefore, ΔTgAb alone could be applied as a convenient and user-friendly marker during follow-up, holding a high diagnostic value with sensitivity and specificity of 89.13% and 88.27%, respectively. It is impressive that the NPV of ΔTgAb in our study was up to 96.93%, suggesting that ΔTgAb could be used as an excellent negative indicator for disease-free status to avoid over-management in those with ΔTgAb >47.0%, which appeared more objectively than the cutoff of 50% raised arbitrarily by experience in several studies (7, 9, 10, 29, 30).

According to a retrospective study of 824 DTC patients by Kim et al. (7), serum TgAb levels measured at 6–12 months after remnant ablation could predict recurrence in TgAb-positive patients. We compared different TgAb decrease rates and status in PFS by 1 year as a boundary and found that patients with ΔTgAb >47.0% in the first year had a longer PFS than those with ΔTgAb ≤47.0%. Another result that we obtained from the survival curve was that patients who turned TgAb-negative in the first year had a longer PFS than those who did not turn negative. These results implied that the decrease rate and status of TgAb in the first year after RAI treatment could serve as early indicators for predicting disease-free survival in TgAb-positive patients. Of the 135 patients who dropped to below 40 IU/mL at final follow-up, the median time to achieve negative conversion was 8 months, which was similar to our prior study (31). For those with positive TgAb and failed to turn negative, one potential explanation might be the relatively higher level of TgAb prior to ^{131}I therapy, which may take a longer time to achieve negative conversion; thus, a longer follow-up for such patients in this study is still ongoing. For patients with rapidly rising or even consistently positive but stable TgAb, one recently published consensus warns of the risk that such patients may carry a high suspicion of PRD (32). A meta-analysis including 34 studies also reported that patients with persistent/increasing TgAb levels had a higher risk of PRD (12), which was also the case in our study. Nearly 90% (89.29%, 25/28) of the 28 patients with increasing TgAb levels were proved to be PRD. Thus, in patients with rising TgAb, more active surveillance, including both serological and imaging diagnostic procedures, is required. It is worth noting that from the Kaplan–Meier curves, we can see as long as 50 months of PFS even in patients with a slow decrease of TgAb, reminding that a more patient and longer follow-up is needed for such patients. It is noteworthy that, in the present study, the value of ΔTgAb in identifying persistent/recurrent disease of DTC seems less promising, with a PPV less than 70% (66.12%). This may be due to the indolent nature of DTC and the relatively short follow-up time of our study, which might have limited its power to identify PRD. Additionally, 21 of 46 (45.65%) PRD patients had decreasing TgAb levels, and five (10.87%) turned out TgAb-negative before the latest visit. One potential explanation is the time delay of TgAb change, with PRD occurring within a relatively short follow-up time after treatment while TgAb is still in a period of decrease. Alternatively, some PRD patients may present an iodine refractory status of tumor dedifferentiation, which reduces the capacity of the lesion to secrete Tg, resulting in TgAb maintained at a low level (33). Under this circumstance, additional imaging such as US, CT, or ^{131}I WBS and PET/CT may be more complementary in identifying those with persistence or recurrence. Besides these, in this study, patients with TgAb levels consistently above the upper limit of detection were noticed not only in the PRD group (3/7) but also in the NED group (4/7), which has also been reported by Chiovato (6). We propose that it may be due to several scenarios as follows: there may still be undetected tumor foci or related to immuno-thyroiditis background or the existence of long-lived memory cells that continue to produce TgAb in the patient's body (3). In such cases, a longer follow-up and a high-sensitivity examination for the detection of potential foci are necessary.

Several limitations in our study should be mentioned. First, the number of PRD cases was limited, which may result in a low PPV, and a larger sample size is required to confirm our findings in future studies. Second, due to ethical concerns, some of the PRD cases, particularly distant metastases, were diagnosed merely based on typical imaging features and anatomical changes in their follow-up, without having been pathologically confirmed. Additionally, the follow-up period of our study was relatively short, a more long-term follow-up is required to verify the predictive value of ΔTgAb over time.

Conclusion

In summary, our study suggested that ΔTgAb could serve as a valuable indicator of disease status in DTC patients with positive postoperative TgAb. ΔTgAb of >47.0% is conducive to identify those with NED to obviate their overtreatment. The decrease rate and negative conversion of TgAb in the first year were good predictors of disease-free survival in patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethical Committee of Peking Union Medical College (PUMC) Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from primarily isolated as part of your previous study for which ethical approval was obtained. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YZ: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. ZM: Investigation, Data curation, Writing – review & editing, Visualization, Validation, Supervision, Methodology, Formal analysis, Conceptualization. DL: Investigation, Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Data curation. TZ: Writing – review & editing, Conceptualization, Visualization, Validation, Methodology, Formal analysis, Data curation. XZ: Writing – review & editing, Supervision, Validation, Investigation, Data curation, Conceptualization. DS: Writing – review & editing, Validation, Supervision, Formal analysis, Methodology, Investigation. YS: Writing – review & editing, Supervision, Conceptualization, Methodology, Data curation. JL: Writing – review & editing, Visualization, Methodology, Validation, Supervision. YL: Methodology, Writing – review & editing, Validation, Supervision, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1354426/full#supplementary-material

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Development of a predictive nomogram for intermediate-risk differentiated thyroid cancer patients after fixed 3.7GBq (100mCi) radioiodine remnant ablation

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Objectives: The objective of this study was to develop a predictive nomogram for intermediate-risk differentiated thyroid cancer (DTC) patients after fixed 3.7GBq (100mCi) radioiodine remnant ablation (RRA).

Methods: Data from 265 patients who underwent total thyroidectomy with central lymph node dissection (CND) and received RRA treatment at a single institution between January 2018 and March 2023 were analyzed. Patients with certain exclusion criteria were excluded. Univariate and multivariate logistic regression analyses were performed to identify risk factors for a non-excellent response (non-ER) to RRA. A nomogram was developed based on the risk factors, and its performance was validated using the Bootstrap method with 1,000 resamplings. A web-based dynamic calculator was developed for convenient application of the nomogram.

Results: The study included 265 patients with intermediate-risk DTC. Significant differences were found between the ER group and the non-ER group in terms of CLNM>5, Hashimoto's thyroiditis, sTg level, TgAb level ($P < 0.05$). CLNM>5 and sTg level were identified as independent risk factors for non-ER in multivariate analysis. The nomogram showed high accuracy, with an area under the curve (AUC) of 0.833 (95% CI = 0.770–0.895). The nomogram's predicted probabilities aligned closely with actual clinical outcomes.

Conclusions: This study developed a predictive nomogram for intermediate-risk DTC patients after fixed 3.7GBq (100mCi) RRA. The nomogram incorporates

CLNM>5 and sTg levels as risk factors for a non-ER response to RRA. The nomogram and web-based calculator can assist in treatment decision-making and improve the precision of prognosis information. Further research and validation are needed.

KEYWORDS

intermediate-risk, differentiated thyroid cancer, radioiodine remnant ablation, predictive nomogram, thyroglobulin, cervical lymph node metastasis

1 Introduction

Radioactive iodine therapy (RAIT) is a pivotal treatment for differentiated thyroid carcinoma (DTC) following total thyroidectomy, categorized into three modalities based on therapeutic objectives: 1) Radioiodine remnant ablation (RRA) aims to eliminate residual thyroid tissue post-surgery; 2) Radioiodine adjuvant therapy (RAT) targets undetected metastatic or residual lesions; 3) Radioiodine treatment (RT) addresses inoperable local or distant DTC metastases (1, 2). RRA is instrumental in post-thyroidectomy DTC management, enhancing serum thyroglobulin (Tg) level stratification, patient monitoring, the sensitivity of ^{131}I whole-body scans for metastasis detection, and postoperative restaging (1, 3, 4). RAT extends beyond eliminating residual tissue to addressing latent lesions, thereby augmenting disease-free survival (DFS) rates (5, 6). Clinicians must grasp Tg level stratification in postoperative DTC patients and evaluate recurrence risk, especially in intermediate or low-risk cases, to optimize remnant ablation strategies.

The recommended ^{131}I dose for RRA varies from 1.11 to 3.70 GBq (30 to 100 mCi) (1). Research shows comparable efficacy between 1.11 and 3.70 GBq doses in low or intermediate-risk DTC patients post-surgery, with lower doses minimizing short-term adverse effects. However, higher doses are suggested for patients with substantial thyroid remnants or as adjuvant treatment. Dose determination should integrate clinical and pathological characteristics, mortality and recurrence risks, and dynamic assessment, favoring tailored approaches over standardized low (1.11 GBq) or high (3.70 GBq) doses (7). Factors influencing RRA dose escalation include larger residual thyroid tissue, elevated thyroglobulin levels, and additional risk indicators. In scenarios where patients exhibit stimulated thyroglobulin (sTg) levels above 10ng/ml and are classified as high-risk for recurrence, RAT with doses exceeding 3.70 GBq is advisable (8, 9).

Studies associate factors like tumor size, elevated serum sTg levels, lymph node capsular invasion, N1a classification, and distant metastases with increased RRA failure risk (10). A serum sTg level below 2ng/mL is a vital predictor for positive response, with higher pre-ablation sTg levels indicating a potential initial treatment inadequacy (11). Hence, sTg levels serve as a predictive measure for RRA success. Notably, prior research involving patients with sTg levels above 10, classified as high-risk, and exhibiting structural lesions, employed varying ^{131}I doses, potentially introducing biases. Therefore, a distinct risk predictive model to predict the response to fixed 3.7GBq (100mCi) RRA with intermediate-risk DTC is necessary.

The predominant staging systems for DTC are the TNM system and recurrence risk stratification. DTC typically demonstrates low disease-specific mortality. These staging systems primarily predict recurrence risk in patients rather than the efficacy of initial RRA. In contrast, nomograms, which have been developed for most cancer types, often outperform traditional staging methods (12–14). Consequently, many consider nomograms a potential alternative or new standard (15). This study aims to establish a risk nomogram utilizing clinicopathologic data from 265 intermediate-risk DTC patients who underwent a fixed dose of 3.7GBq (100mCi) RRA.

2 Patients and methods

2.1 Patients and study design

This retrospective study focused on patients who underwent thyroidectomy and RRA from January 2018 to March 2023 at the Affiliated Hospital of Guilin Medical University. Eligible participants had undergone thyroidectomy and central lymph node dissection (CND), with histopathologically confirmed DTC. They were categorized into the intermediate-risk group for recurrence and received an fixed RRA dose of 3.7GBq (100mCi). The intermediate risk group was defined in accordance with the ATA risk criteria (1). This group includes patients with the following characteristics: (1) microscopic invasion of the tumor into the perithyroidal soft tissues, (2) the presence of radioactive iodine (RAI)-avid metastatic foci in the neck as observed on the first post-treatment whole-body RAI scan, (3) aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma), (4) papillary thyroid cancer with vascular invasion, (5) clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in the largest dimension, and (6) multifocal papillary microcarcinoma with extrathyroidal extension (ETE) and BRAFV600E mutation (if known). The exclusion criteria included: sTg levels exceeding 10 ng/ml; serum thyroglobulin antibody (TgAb) positivity (>115 U/mL); evidence of cervical lymph node metastasis

(CLNM) or distant metastasis (DM) post RRA whole-body scintigraphy (Rx-WBS); being under 18 years of age; and insufficient clinicopathologic data for analysis.

2.2 RRA and follow-up

Patients underwent RRA following surgery (total thyroidectomy with central lymph node dissection [CND]). Indications for total thyroidectomy included: (a) primary tumor size exceeding 4 cm; (b) bilateral/multiple lesions; (c) extrathyroidal extension; (d) clinical evidence of lymph node or distant metastasis. Ipsilateral CND was performed for all patients, while bilateral CND was conducted in cases of bilateral carcinoma or clinically suspicious nodal disease in the contralateral central compartment. Lateral neck dissection (LND), encompassing levels II–V, was reserved for clinically or pathologically confirmed metastatic lateral neck lymph nodes.

Prior to RRA, patients adhered to a low-iodine diet for 14 days, guided by our nutrition experts, avoiding iodine-containing medications. RRA was administered post levothyroxine (LT4) withdrawal, aligned with the American Joint Committee on Cancer (AJCC) TNM staging and recurrence risk stratification, at a dose of 3.7GBq (100mCi). Pre-RRA routine biochemical (serum thyrotropin [TSH], sTg, anti-Tg antibody [TgAb]) and imaging (ultrasonography, computed tomography) examinations were conducted. Post-RRA, LT4 was prescribed for TSH suppression therapy, and Rx-WBS was performed 2–3 days later.

Follow-up visits post-RRA included TSH-stimulated Tg level assessment and Dx-WBS at six months. Therapeutic responses were classified into four categories: Excellent Response (ER), Indeterminate Response (IDR), Biochemical Incomplete Response (BIR), and Structural Incomplete Response (SIR), with IDR, BIR, and SIR collectively termed as non-ER. ER was defined as negative imaging with suppressed Tg <0.2 ng/mL or TSH-stimulated Tg <1 ng/mL; BIR as negative imaging but suppressed Tg ≥1 ng/mL, stimulated Tg ≥10 ng/mL, or rising anti-Tg antibodies; SIR as any Tg level with structural or functional disease evidence, with or without anti-Tg antibodies; IDR as nonspecific imaging findings, faint thyroid bed uptake on RAI scanning, detectable non-stimulated Tg <1 ng/mL, stimulated Tg <10 ng/mL, or stable/declining anti-Tg antibodies without structural/functional disease. The therapeutic response assessment was conducted six months post-RAT, following the 2015 ATA guidelines (1). ER is defined as successful RRA.

2.3 Laboratory measurements

Serum TSH concentrations, sTg levels, and TgAb levels were measured by cobas e 801 analytical unit for immunoassay tests.

2.4 Post-therapy and diagnostic WBS

Rx-WBS was obtained 2–3 days after RRA using dualhead γ-cameras (Siemens Symbia T16 SPECT/CT) equipped with medium-energy collimators, set to a peak energy of 364 keV with a window width of 20%. Both anterior and posterior planar images, from the vertex to the knee, were acquired and stored in 256×1024 matrices using a scan speed of 5 to 10 cm/min. Dx-WBS was performed at 24–48 hours after oral administration of 74 to 185 MBq of ^{131}I using the same camera and protocol as for the Rx-WBS described above. A nuclear medicine physician with 14 years of experience visually analyzed WBS images. Rx-WBS findings were classified as hot uptake in the thyroid bed of the neck or not. Diagnostic WBS was used to evaluate the treatment response of RRA by classifying remaining fainted uptake lesion in the neck or not.

2.5 Data analysis

Patient clinical information was acquired through electronic medical record system, and cancer stages were determined using the eighth edition of the American Joint Committee on Cancer (AJCC) staging system. Patients were categorized into Excellent Response (ER), Biochemical Incomplete Response (BIR), Structural Incomplete Response (SIR), and Indeterminate Response (IDR) groups based on six-month Dx-WBS findings and sTg levels. This retrospective study's design received approval from the institutional review board of the Affiliated Hospital of Guilin Medical University, under approval number 19–000896. The requirement for informed consent was waived.

2.6 Statistical analysis

Statistical analyses were performed using R version 3.6.3 and Python version 3.7. In instances where baseline variables had missing values, multiple imputation analysis was conducted. The fully conditional specification discriminant function was utilized for categorical missing data, and the fully conditional specification regression was employed for continuous missing data. Continuous data are presented as means ± standard deviations (SD) for normally distributed data and medians with interquartile ranges (IQR) for non-normally distributed data. Categorical variables are expressed as frequencies and percentages. For comparisons, the chi-square test or Fisher's exact test was used for categorical variables, and analysis of variance for continuous variables with a normal distribution. Univariate and multivariate logistic regression analyses were conducted to identify risk factors for intermediate-risk DTC post-RRA. Variables in univariate analysis included gender, age, N staging, bilateral foci, multifocality, CLNM, AJCC staging, T staging, more than one operation before RRA, time from surgery to RRA exceeding one month, LND performance, primary tumor diameter, vascular invasion, thyroid capsule invasion, nodular goiter, TSH level, sTg level, TgAb level, $^{99m}TcO_4^-$ thyroid imaging, Rx-WBS, and Dx-WBS. Multivariate analysis involved forward and backward selection procedures for parameters with $P < 0.05$ in log-rank tests, reporting odds ratios (ORs) with 95% confidence intervals (CIs). A nomogram was developed using the rms6.7.1 package in R version 3.6.3 (http://www.r-project.org/). The nomogram's performance was assessed using the concordance index (C-index) and evaluated

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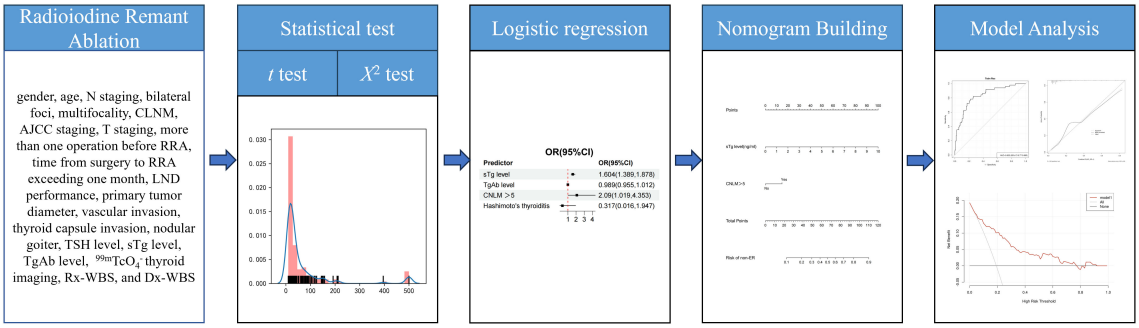

FIGURE 1
Workflow of this study. Univariate and multivariate logistic regression analyses were conducted to identify risk factors for intermediate-risk DTC post-RRA. A nomogram was developed from the result of multivariate logistic regression analyses. The nomogram's performance was assessed using the concordance index (C-index) and evaluated through calibration curves and clinical decision curves, employing the Bootstrap method with 1,000 resamplings.

through calibration curves and clinical decision curves, employing the Bootstrap method with 1,000 resamplings. The workflow was shown in Figure 1.

3 Results

3.1 Clinicopathologic characteristics of patients

In this retrospective study, we analyzed 500 consecutive patients who underwent total thyroidectomy with CND and initial RRA treatment for intermediate-risk DTC at our institution between January 2018 and March 2023. From this cohort, we excluded 128 patients with sTg levels exceeding 10 ng/ml, 35 with serum thyroglobulin antibody (TgAb) levels above 115 U/mL, 52 with CLNM or DM identified Rx-WBS, 7 with CLNM or DM detected Dx-WBS at six months, 6 who were under 18 years old, and 7 lost to follow-up. Ultimately, 265 patients were included in the study. All patients were diagnosed with papillary thyroid carcinoma (PTC). The median age was 41 years (interquartile range: 34–50 years), with 28.7% (76/265) being male. The majority had T1 stage (83.4%), with more patients presenting with N1a disease (60.4%) than N1b; all were TNM stage M0, and 83.4% were AJCC stage I. Pre-RRA, 173 patients (65.3%) displayed hot uptake in the thyroid bed on $^{99m}TcO_4^-$ thyroid imaging, reducing to 0.4% (1 patient) post-RRA. Pre-RRA, 259 patients (97.7%) showed hot uptake in the thyroid bed on Rx-WBS, decreasing to 3.4% (9 patients) post-RRA as per Dx-WBS.

Significant differences were noted between the Excellent Response (ER) group and the non-ER group in terms of CLNM>5, Hashimoto's thyroiditis, sTg level, Tg_{off} level, and TgAb level ($P < 0.05$). However, no statistically significant differences were found in gender, age, N staging, bilateral foci, multifocality, CLNM, AJCC staging, T staging, more than one operation before RRA, time from surgery to RRA exceeding one month, LND performance, primary tumor diameter, vascular invasion, thyroid capsule invasion, nodular goiter, TSH level, $^{99m}TcO_4^-$ thyroid imaging, Rx-WBS, and Dx-WBS between the two groups ($P > 0.05$). Detailed clinical characteristics of the patients are summarized in Table 1.

3.2 Development and validation of a non-ER predictive nomogram

In this study, 215 patients (81.1%) exhibited an Excellent Response (ER) upon follow-up, while 48 (18.1%) demonstrated an Indeterminate Response (IDR), and 2 (0.8%) had a Biochemical Incomplete Response (BIR). Univariate analyses identified CLNM>5, Hashimoto's thyroiditis, sTg level, and TgAb level as significant risk factors for a non-ER outcome following RRA. Factors such as gender, age, N staging, bilateral foci, multifocality, CLNM, AJCC staging, T staging, more than one operation before RRA, surgery to RRA duration exceeding one month, LND performance, primary tumor diameter, vascular invasion, thyroid capsule invasion, nodular goiter, TSH level, $^{99m}TcO_4^-$ thyroid imaging, Rx-WBS, and Dx-WBS were not significantly associated with non-ER outcomes. In multivariate analyses, CLNM>5 and sTg level emerged as independent risk factors for non-ER (Table 2). Logistic regression analysis was employed to estimate the likelihood of non-ER in patients with intermediate-risk DTC following RRA. In this model, specific point values were assigned to each predictor's observed value (Figure 2), with the cumulative points for all variables representing an individual's risk of non-ER post-RRA. The nomogram's accuracy was rigorously validated using a bootstrap method with 1000 resamples, revealing an area under the curve (AUC) of 0.833 (95% CI = 0.770–0.895) (Figure 3A). The nomogram's predicted probabilities were found to be in strong agreement with actual clinical outcomes (Figure 3B), and decision curve analysis demonstrated the model's potential clinical applicability (Figure 3C).

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TABLE 1 Demographics and clinicopathologic characteristics of patients with intermediate-risk DTC after RRA.

Demographics or Characteristics	Item	General (n=265)	ER group (n=214)	Non-ER group (n=51)	*P*
Gender, n (%)	Male	76 (28.7)	60 (28.0)	16 (31.4)	0.636
	Female	189 (71.3)	154 (72.0)	35 (68.6)	
Age, median [IQR]		41.0 [34.0,50.0]	43.0 [34.0,50.0]	37.0 [33.0,46.0]	0.093
Primary tumor diameter, median [IQR]		1.2 [0.8,2.0]	1.2 [0.8,2.0]	1.2 [0.9,2.0]	0.858
AJCC stage, n (%)	I	254 (95.8)	205 (95.8)	49 (96.1)	0.927
	II	11 (4.2)	9 (4.2)	2 (3.9)	
T stage, n (%)	T1	221 (83.4)	177 (82.7)	44 (86.3)	0.539
	T2	44 (16.6)	37 (17.3)	7 (13.7)	
N stage, n (%)	N0	31 (11.7)	28 (13.1)	3 (5.9)	0.341
	N1a	160 (60.4)	128 (59.8)	32 (62.7)	
	N1b	74 (27.9)	58 (27.1)	16 (31.4)	
Vascular infiltration, n (%)	No	254 (95.8)	204 (95.3)	50 (98.0)	0.383
	Yes	11 (4.2)	10 (4.7)	1 (2.0)	
Thyroid capsule invasion, n (%)	No	179 (67.5)	140 (65.4)	39 (76.5)	0.130
	Yes	86 (32.5)	74 (34.6)	12 (23.5)	
Multifocality, n (%)	No	148 (55.8)	122 (57.0)	26 (51.0)	0.436
	Yes	117 (44.2)	92 (43.0)	25 (49.0)	
CLNM, n (%)	No	33 (12.5)	29 (13.6)	4 (7.8)	0.267
	Yes	232 (87.5)	185 (86.4)	47 (92.2)	
CLNM>5, n (%)	No	161 (60.8)	137 (64.0)	24 (47.1)	0.026
	Yes	104 (39.2)	77 (36.0)	27 (52.9)	
Time from surgery to RRA exceeding one month, n (%)	No	248 (93.6)	200 (93.5)	48 (94.1)	0.863
	Yes	17 (6.4)	14 (6.5)	3 (5.9)	
LND, n (%)	No	169 (63.8)	136 (63.6)	33 (64.7)	0.877
	Yes	96 (36.2)	78 (36.4)	18 (35.3)	
More than one operation before RRA, n (%)	No	260 (98.1)	211 (98.6)	49 (96.1)	0.235
	Yes	5 (1.9)	3 (1.4)	2 (3.9)	
Bilateral foci, n (%)	No	186 (70.2)	154 (72.0)	32 (62.7)	0.196
	Yes	79 (29.8)	60 (28.0)	19 (37.3)	
Hashimoto's thyroiditis, n (%)	No	230 (86.8)	180 (84.1)	50 (98.0)	0.008
	Yes	35 (13.2)	34 (15.9)	1 (2.0)	
Nodular goiter, n (%)	No	167 (63.0)	137 (64.0)	30 (58.8)	0.490
	Yes	98 (37.0)	77 (36.0)	21 (41.2)	
$^{99m}TcO_4^-$ thyroid imaging, n (%)	No thyroid remnant	92 (34.7)	73 (34.1)	19 (37.3)	0.672
	Thyroid remnant	173 (65.3)	141 (65.9)	32 (62.7)	
Rx-WBS, n (%)	No thyroid remnant	6 (2.3)	5 (2.3)	1 (2.0)	0.871

(Continued)

TABLE 1 Continued

Demographics or Characteristics	Item	General (n=265)	ER group (n=214)	Non-ER group (n=51)	*P*
	Thyroid remnant	259 (97.7)	209 (97.7)	50 (98.0)	
Response to surgery, n (%)	ER	93 (35.1)	90 (42.1)	3 (5.9)	<0.001
	IDR	172 (64.9)	124 (57.9)	48 (94.1)	
Response to RRA, n (%)	BIR	2 (0.8)	0 (0.0)	2 (3.9)	0.999
	ER	214 (80.8)	214 (100.0)	0 (0.0)	
	IDR	49 (18.5)	0 (0.0)	49 (96.1)	
$^{99m}TcO_4^-$ thyroid imaging after RRA, n (%)	No thyroid remnant	264 (99.6)	214 (100.0)	50 (98.0)	0.999
	Thyroid remnant	1 (0.4)	0 (0.0)	1 (2.0)	
Dx-WBS after RRA, n (%)	No thyroid remnant	256 (96.6)	214 (100.0)	42 (82.4)	0.999
	Thyroid remnant	9 (3.4)	0 (0.0)	9 (17.6)	
TSH Level, median [IQR]		86.0 [65.7,100.0]	85.2 [61.9,100.0]	88.7 [72.8,100.0]	0.508
TgAb level, median [IQR]		12.9 [10.0,21.2]	13.2 [10.0,24.1]	11.4 [10.0,15.1]	0.013
sTg level, median [IQR]		1.5 [0.5,3.5]	1.2 [0.4,2.8]	4.5 [2.6,7.3]	<0.001
Tg_{off} level, median [IQR]		0.1 [0.0,0.7]	0.1 [0.0,0.3]	2.4 [1.5,3.9]	<0.001

3.3 Webserver development for the nomogram

For convenient application of our nomogram, we developed dynamic calculators on the basis of a user-friendly website (https://www.evidencio.com/models/show/10176), which could be used directly by researchers and clinicians. By inputting certain clinical variables, we can easily obtain the corresponding individualized predicted survival probabilities through the output data generated by the website.

4 Discussion

In this retrospective study, we found that sTg levels and CLNM>5 significantly contribute to the risk of non-ER in patients with intermediate-risk DTC following RRA. Utilizing these variables, we developed and validated a nomogram to estimate the risk of non-ER. This tool holds considerable potential importance for the primary prevention of non-ER in this patient population.

Contrary to previous research primarily centered on distinct factors influencing the prognosis of DTC post-surgery or radioactive iodine therapy, our study integrates clinicopathological characteristics and identifies that elevated sTg levels and CLNM>5 are associated with an increased risk of non-ER in patients with intermediate-risk DTC following RRA. Among these factors, elevated sTg levels were noted, corroborating findings from earlier studies (11, 16, 17). A retrospective analysis of 2,500 thyroid cancer patients established that a post-surgical thyroglobulin (ps-Tg) cutoff of ≤10.1 ng/mL predicts disease-free status with a negative predictive value of 95%. This threshold was consistently validated across all ATA risk categories. Additionally, the study revealed that a ps-Tg level of ≤10.1 ng/mL significantly reduces the likelihood of persistent or recurrent disease in patients classified as intermediate- and high-risk (18). In a prospective study of intermediate- to high-risk patients with sTg levels above 10 ng/mL, 28.4% displayed functional or structural disease following RAT. RAT, utilizing 5.55 GBq (150mCi) of

TABLE 2 Multivariate analysis result (forward and backward selection procedures).

Predictor	Estimate	SE	Z	p	Odds Ratio	Lower	Upper
sTg level	0.502	0.075	6.714	0.0	1.652	1.436	1.928
CNLM>5	0.739	0.367	2.012	0.044	2.093	1.023	4.348
TgAb level	-0.011	0.014	-0.809	0.418	0.989	0.955	1.012
Hashimoto's thyroiditis	-1.341	1.087	-1.234	0.217	0.262	0.014	1.48

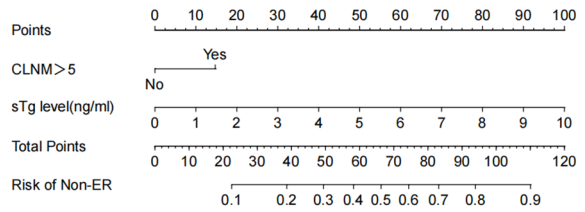

FIGURE 2
Nomogram for predicting non-ER risk. The value of each variable was scored on a point scale from 0 to 100, after which the scores for each variable were added together. That sum is located on the total points axis, which enables us to predict the probability of non-ER risk.

Iodine-131, proved effective in detecting biochemical, functional, or structural disease, and elicited a substantial therapeutic response in a significant portion of these patients. Hence, these patients are deemed appropriate candidates for RAT (5). Therefore, in patients with a high risk of recurrence and sTg levels above 10 ng/ml, RAT has been shown to effectively enhance overall survival (OS) and disease-free survival (DFS). Consequently, it can be recommended as a standard treatment approach. Research on the risk factors of RRA in intermediate-risk DTC patients with low sTg levels (<10ng/ml) is relatively scarce. Previous studies examining the efficacy of total thyroidectomy and RRA in this demographic often included low-risk DTC patients, those with sTg levels over 10ng/ml, and patients with structural lesions in both Rx-WBS and Dx-WBS (19–22). Additionally, the variation in RRA dosages used in these studies contributes to biases in the research outcomes. This study specifically focuses on intermediate-risk DTC patients with sTg levels ≤10ng/ml and no structural lesions in either Rx-WBS or Dx-WBS. Furthermore, it standardizes the RRA dosage at 3.7GBq (100mCi) to enhance the reliability of the findings.

In patients with intermediate-risk DTC, current evidence regarding the impact of RRA on disease recurrence remains inconclusive, indicating beneficial effects in some cases but showing no benefit in others (23). The 2015 ATA guidelines advise that, following total thyroidectomy in patients with low-risk thyroid cancer or intermediate-risk disease exhibiting lower risk features (such as low-volume central neck nodal metastases without additional gross residual disease or adverse features), a lower administered activity of approximately 30 mCi for RRA is generally favored over higher administered activities (1). A retrospective study evaluated the therapeutic efficacy and long-term clinical outcomes of varying doses of RRA in patients with intermediate-risk DTC. This study involved 204 intermediate-risk DTC patients, with 124 receiving a high dose (3.7 or 5.55 GBq) and 80 receiving a low dose (1.11 GBq) of radioactive iodine. The findings indicated no significant difference in treatment success rates between the high-dose (54.84%) and low-dose (45.00%) groups, regardless of whole-body scan results. According to the American Thyroid Association's reclassification system, the post-treatment response rates were as follows: ER (high-dose 54.84%, low-dose 45.00%), IDR (high-dose 34.68%, low-dose 30.00%), BIR (high-dose 4.03%, low-dose 13.75%), and SIR (high-dose 6.45%, low-dose 11.25%). Additionally, long-term follow-up showed recurrence rates of 5.65% in the high-dose group and 8.75% in the low-dose group. Consequently, the study suggests that in high-iodine intake regions of Korea, low-dose radioactive iodine therapy may be less effective for treating intermediate-risk DTC patients, potentially necessitating additional treatment in the low-dose group (19). A retrospective study evaluated the efficacy of low-dose (1110 MBq) versus high-dose (2960–3700 MBq) RRA in patients with intermediate-to-high-risk DTC. This study found no significant difference in initial success rates between the low-dose (73.5%) and high-dose (70.6%) groups, though high-dose RRA may be more effective for high-risk patients (20). Another study concluded that low-dose ^{131}I is as effective as high-dose in RRA of papillary thyroid carcinoma patients. In the intermediate-risk group, disease-free survival rates at 6 months, 1 year, and 2 years were marginally higher in the high-dose group compared to the low-dose group (24). Collectively, these studies indicate that the selection of RRA dosage for intermediate-risk DTC patients should be individualized, considering factors such as disease risk and pre-treatment thyroglobulin levels, instead of implementing a standardized dosage approach. The efficacy of low-dose RAI therapy, especially in specific patient subsets, underscores the importance of

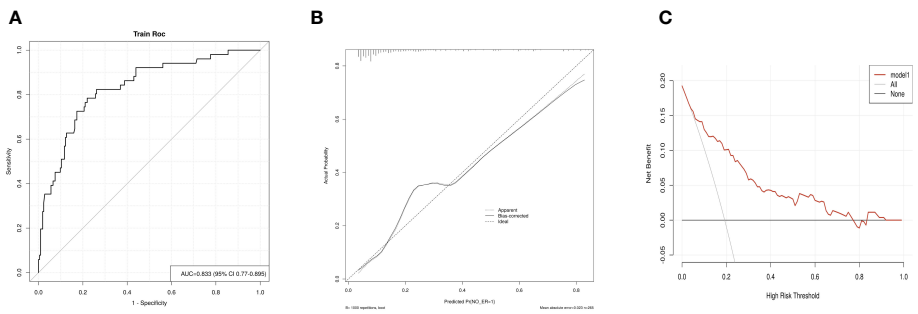

FIGURE 3
Evaluation of the nomogram model. **(A)** The Receiver Operating Characteristic (ROC) curve for the nomogram, derived using bootstrap resampling (1000 repetitions). **(B)** Calibration plot for the nomogram. The closer the performance nomogram's solid line is to the dotted line of the ideal model, the higher the prediction accuracy of the nomogram. **(C)** Decision Curve Analysis (DCA) for the prediction model. The prediction model's accuracy is represented by the red solid line, the gray line denotes the scenario where all patients exhibit non-complete response (non-ER), and the solid horizontal line implies that no patients experience non-ER. This graph illustrates the expected net benefit per patient in relation to the nomogram's prediction of non-ER risk, with increased net benefit correlating to the extension of the model curve.

meticulous patient selection and monitoring. Consequently, we performed a retrospective analysis of risk factors in patients with intermediate-risk DTC who underwent 3.7 GBq (100 mCi) RRA therapy at our center. Our evaluation suggests that these patients may face an elevated risk of recurrence and higher sTg level. We also successfully developed a predictive nomogram for intermediate-risk DTC patients undergoing RRA dosage at 3.7GBq (100mCi). Furthermore, a web-based dynamics calculator was created for use by clinicians at our center and other institutions.

The 2015 ATA guidelines introduced revised risk stratifications compared to the 2009 version (1). Under this framework, high risk is characterized by lymph node metastases larger than 3 centimeters, while intermediate risk involves either palpable disease or more than five lymph nodes (CLNM > 5), each smaller than 3 centimeters. Yun et al. (25) determined that the optimal cutoff value for lymph node metastases (LNMs) impacting RAI treatment response is five. For patients with CLNM > 5, the most effective lymph node ratio (LNR) cutoff was identified as 0.30. Factors such as CLNM > 5, gender, lymph node dissection, and ATA risk classification were found to be independent predictors of RAI response. Correspondingly, another study indicated that patients with over five metastatic lymph nodes exhibit more aggressive clinicopathological features and poorer outcomes (26). Echoing our study's results, these findings underscore the importance of both the quantity and characteristics of lymph node metastases in determining thyroid cancer prognosis. They further stress the need for precise assessment and monitoring of lymph node involvement to inform effective treatment plans and predict patient outcomes.

Recent research has advanced the development of nomograms, offering highly accurate prognostic information for thyroid cancer, surpassing traditional methods like the AJCC staging system (27–29). A study based on SEER data crafted a nomogram to predict the risk of DM and its prognostic value in female patients with DTC (30). Additionally, a nomogram has been created to forecast the cancer-specific survival (CSS) of patients with poorly differentiated thyroid carcinoma, aiding clinicians in formulating suitable treatment strategies (31). Further, specialized survival nomograms for patients with DTC and DM have been developed, enhancing prognostic understanding in this subgroup (32). Collectively, these studies represent significant advancements in predictive modeling for thyroid cancer, offering more precise and customized prognostic tools that could markedly influence patient management and treatment approaches. We aspire for our nomogram to be utilized in clinical practice, providing personalized predictions of RRA efficacy for intermediate-risk DTC patients, and facilitating individualized treatment options. We also eagerly anticipate collaborating with researchers from other centers to refine this clinical prediction model further.

This study is subject to several limitations: (1) As a retrospective analysis, it may be affected by recall bias and incomplete data, necessitating further prospective studies for confirmation of results. (2) Being a single-center study with a relatively small sample size, its findings may lack generalizability, underscoring the need for multi-center studies to verify these results. (3) The study primarily focuses on certain clinical and pathological markers as predictors, which might neglect other vital factors affecting treatment outcomes. Notably, the $BRAF^{V600E}$ mutation, demonstrated by preclinical studies to significantly diminish sodium-iodide symporter expression and reduce RAI uptake, along with its correlation with ER rates and AXL expression in DTC patients, could influence results. Regrettably, only a limited subset of our cohort underwent testing for the $BRAF^{V600E}$ mutation. Future research models should incorporate genomic data to improve prognostic accuracy for responses to RRA across a more diverse patient population. (4) The outcome selected—response to RRA—may not accurately reflect the recurrence risk and overall survival of DTC patients. Despite this, the 2015 ATA guidelines indicate that DTC patients categorized as intermediate or high risk could significantly reduce their risk of recurrent or persistent disease by achieving an ER to RRA. Additionally, in a previous study with a protracted follow-up period, no patients transitioned from an ER outcome to a non-ER outcome six months post-treatment (33). These observations highlight the utility of RRA response as an effective and practical indicator for predicting clinical outcomes concerning both recurrence and specific mortality risks, particularly in DTC, which is typically slow-growing. However, a longer follow-up period for the cohorts in this study is necessary to verify the predictive capacity of this nomogram for DFS and overall survival in DTC patients after RRA, and to identify variations in prognostic factors across different outcomes. (5) Although a nomogram and an online calculator were developed, external and clinical validations are essential before their practical implementation.

5 Conclusion

This study reveals that in intermediate-risk DTC patients, the likelihood of an non-ER to RRA is significantly linked with the presence of CLNM>5 and higher sTg levels. A predictive model incorporating these factors has been established to assess the risk of Non-ER, accompanied by the development of a network-based dynamic calculator. This model has shown high accuracy in validation, aligning closely with actual clinical outcomes. This tool not only assists in treatment decision-making but also enhances the precision of prognosis information. Nevertheless, additional research and validation are required.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the ethics committee of the Affiliated Hospital of Guilin Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

LL: Data curation, Methodology, Writing – original draft. QL: Data curation, Writing – review & editing. ZG: Formal analysis, Writing – review & editing. YL: Formal analysis, Supervision, Validation, Writing – review & editing. CL: Data curation, Writing – review & editing. JL: Data curation, Writing – review & editing. JH: Data curation, Writing – review & editing. XM: Writing – review & editing. WF: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Relationship between recurrence and age in the diffuse sclerosing variant of papillary thyroid carcinoma: clinical significance in pediatric patients

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Background: The diffuse sclerosing variant (DSV) is among the aggressive variants of papillary thyroid carcinoma (PTC) and is more prevalent in pediatric patients than in adult patients. Few studies have assessed its characteristics owing to its low incidence. We aimed to evaluate the relationship between recurrence and age in the DSV of PTC.

Methods: We retrospectively reviewed patients diagnosed with the DSV or conventional PTC (cPTC) after surgery at a medical center between May 1988 and January 2019. We compared the clinico-pathological characteristics and surgical outcomes of the DSV and cPTC groups and between adult and pediatric patients with DSV.

Results: Among the 24,626 patients, 202 had the DSV, and 24,424 were diagnosed with cPTC. The recurrence rate was significantly higher in the DSV group than in the cPTC group. In the DSV group, the recurrence rate was significantly higher in the pediatric patient group than in the adult patient group. Moreover, the association between recurrence and age group showed different patterns between the DSV and cPTC groups with restricted cubic splines (RCS). While both RCS curves showed a U-shaped distribution, the RCS curve tended to be located within the younger age group.

Conclusions: This study demonstrated that pediatric patients with DSV are at a greater risk for recurrence compared with adult patients; moreover, the pattern of recurrence risk according to age is different from that of cPTC.

KEYWORDS

thyroid neoplasm, thyroid cancer, papillary thyroid cancer, pediatrics, diffuse sclerosing variant, prognosis

1 Introduction

Papillary thyroid carcinoma (PTC) has an indolent behavior and a favorable prognosis (1, 2). However, 10–20% of PTC cases show aggressive features, resulting in frequent recurrence and sometimes higher mortality (3–5). The prognostication of DTC remains significantly constrained by low specificity (6), despite advancements in understanding the prognostic implications of tumor-specific genetic alterations (7). From the perspective of the prognostic field of thyroid cancer, there is a pressing need for prognosticators with high specificity and positive predictive value regarding the rate of recurrent disease after initial treatment.

The rare diffuse sclerosing variant (DSV) is among the representative aggressive subtypes of thyroid cancer that tends to occur in young patients (8–10), with a varying reported prevalence of 0.8–5.3% of PTC cases (11–16). DSV was first described in 1985 (17) and is characterized by aggressive clinico-pathological manifestations, including diffuse involvement of one or both thyroid lobes without a dominant mass, sclerosis, abundant psammoma bodies, prominent squamous metaplasia, extensive lymphatic permeation, and stromal fibrosis (18, 19). The outcomes and prognosis of DSV remain controversial (9, 10, 12–15, 20–22); however, in cases where preoperative sonography images show typical features of DSV, such as ill-defined margins, scattered microcalcifications with a snowstorm appearance, and varying echogenicity (23), radical treatment is pursued more frequently. This is due to the aggressive and highly recurrent nature of DSV, which distinguishes it from cases without these characteristics (24, 25).

To date, most studies have focused on the aggressiveness of the DSV by comparing it with conventional PTC (cPTC) (9, 18, 20–22). However, the recurrence pattern of the DSV itself remains unknown. Moreover, the relationship between recurrence and age in patients with DSV has not yet been investigated, although DSV is a prevalent and major variant of pediatric PTC (8).

To the best of our knowledge, this is the first study to perform a subgroup analysis of the DSV. In addition to confirming the well-known characteristics of the DSV compared with those of cPTC, we compared the characteristics of pediatric and adult patients with the DSV. In particular, we focused on the associations between age and recurrence rates in patients with DSV.

2 Materials and methods

2.1 Patient identification and data collection

We retrospectively analyzed the data of patients who were diagnosed with DSV or cPTC after undergoing surgery at a medical center in South Korea between May 1988 and January 2019. Demographic characteristics, including tumor histology, age, sex, and pathology results, were collected from electronic medical records. TNM staging was performed according to the American Joint Committee on Cancer 8th edition guidelines (25). Recognizing the varying definitions of pediatric age across countries and institutions (26), we defined the pediatric age as individuals under the age of 20 years based on the definition used in a previous publication from the same institution (8). All surgeries, including those involving pediatric patients, were performed by specialized thyroid and endocrine surgeons within the General Surgery Department's Thyroid and Endocrine Surgery Division. All patients underwent at least central compartment dissection, either therapeutically or prophylactically (27). Patients who had additional cancers, distant metastases, a history of thyroid surgery, or underwent follow-up for less than 3 years at our institution after surgery were excluded from the study. All patients received annual neck sonography for approximately 5 years from the date of surgery; after this, they underwent neck sonography at least once every 2 years. A chest CT was performed at least once within 5 years after surgery.

For each DSV case, the mutational status of the *BRAF 600E* or *TERT* genes was evaluated if the test results existed. In our institution, *BRAF 600E* and *TERT* mutational analyses have been performed routinely since 2014 and 2019, respectively. This study was conducted in accordance with the tenets of the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board (IRB) of Yonsei University (IRB number: 4–2020-1257). The requirement for informed consent was waived owing to the retrospective nature of this study.

2.2 Definition of recurrence

Recurrence was defined as structural recurrence, including local recurrence or distant metastases, which required active surgical or medical intervention. Biochemical evidence of disease without structural evidence was not considered as recurrence in this study. Recurrence-free survival (RFS) was counted from the operation date until the date of pathological confirmation of loco-regional recurrence or the date of the imaging study that provided definite evidence of distal metastases.

In cases where locoregional recurrence was suspected, fine-needle aspiration biopsy was performed, and wash-thyroglobulin levels were checked. For cases with suspected distant metastasis, treatments such as RAI ablation were actively applied. There were no cases in which the patients were solely placed under surveillance without intervention.

2.3 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows software (version 26.0; IBM, Armonk, NY). First, we determined the clinical, pathological, and treatment-related characteristics of the DSV and cPTC groups, as well as those of adult and pediatric patients. Categorical data were compared between groups using the chi-squared test; continuous numerical data with normal distribution are described as means ± standard deviations and were compared between groups using the Student's t-test. Non-normally distributed data were compared using the Wilcoxon rank sum test. RFS was examined using Kaplan–Meier

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survival curves. Univariate and multivariate Cox proportional hazards regression were used to identify factors associated with recurrence. Restricted cubic splines (RCS) were used to analyze the relationship between age and RFS (28, 29). RCS analysis provides a visual model with which to examine the relationship between a continuous parameter (age) and an outcome (recurrence) using interpolation and smoothing of data points while adjusting for other factors (tumor size). The RCS model (knot number, 3) was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) at different ages in reference to the age with the lowest HR. The number of knots was determined according to previous studies (28, 29), and knots were placed at the 10^{th}, 50^{th}, and 90^{th} percentiles of patient age. RCS models were constructed using the mgCV and rms packages in R (version 3.2.4; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

3 Results

3.1 Characteristics of patients with cPTC compared with patients with DSV

We analyzed data from 24,626 patients diagnosed with cPTC or the DSV between May 1988 and January 2019. Among them, 24,424 (99.2%) were diagnosed with cPTC, whereas 202 (0.8%) were diagnosed with the DSV. The total follow-up period was 97.9 ± 52.5 months.

The clinico-pathological characteristics of the DSV and cPTC groups were compared (Table 1). The proportion of males was significantly higher in the DSV group than in the cPTC group

TABLE 1 Clinicopathologic features of patients with conventional papillary thyroid carcinoma vs. patients with the diffuse sclerosing variant cPTC vs. DSV variant.

Variable	cPTC (24, 424)	DSV (202)	p-value
Sex (F:M, M(%))	20,268:4,156 (20.50%)	156:46 (29.48%)	0.038
Age, years	45.0 ± 11.8	32.9 ± 12.7	<0.001
Age group, years			<0.001
- <20	148 (0.6%)	17.8%)	
- 20 ≤ age <55	18,907 (77.4%)	5.7%)	
- ≥ 55	5,369 (22.0%)	13 (6.4%)	
Tumor size, cm	0.9 ± 0.7	1.8 ± 1.1	<0.001
Capsule invasion, n (%)	12,632 (51.7%)	155 (76.7%)	<0.001
Multifocality, n (%)	2,560 (10.5%)	21 (10.4%)	<0.001
Bilaterality, n (%)	4,326 (17.7%)	99 (49.0%)	<0.001
Central node, n			
- Total	5.5 ± 4.7	11.1 ± 7.0	<0.001
- Metastatic	1.1 ± 2.2	7.0 ± 5.6	<0.001
- Lymph node ratio (metastatic/total)	0.2 ± 0.3	0.6 ± 0.3	<0.001
Lateral node, n			
- Total	33.7 ± 16.6	47.2 ± 25.2	<0.001
- Metastatic	5.6 ± 5.0	10.4 ± 6.7	<0.001
- Lymph node ratio (metastatic/total)	0.18 ± 0.23	0.23 ± 0.13	<0.001
Operative extent			<0.001
- Lobectomy	8,155 (33.4%)	19 (9.4%)	<0.001
- Lobectomy with contralateral partial	3,800 (15.6%)	6 (3.0%)	
-Total thyroidectomy	12,469 (51.1%)	177 (87.6%)	
Neck lymph node dissection			<0.001
None	385 (1.6%)	1 (0.5%)	
CCND	21,753 (89.1%)	68 (33.7%)	
MRND	2,286 (9.4%)	133 (65.8%)	
RAI-treated	10,555 (43.2%)	168 (83.2%)	<0.001
T stage			<0.001
T1	1,880 (77.3%)	116 (57.4%)	
T2	611 (2.5%)	37 (18.3%)	
T3	4,397 (18.0%)	32 (15.8%)	
T4	536 (2.2%)	17 (8.4%)	
N stage			<0.001
N0	14,914 (61.1%)	21 (10.4%)	
N1a	7,277 (29.8%)	48 (23.8%)	
N1b	2,233 (9.1%)	133 (65.8%)	
TNM stage 8^{th}			<0.001
Stage I	20,884 (85.5%)	190 (94.1%)	
Stage II	942 (3.9%)	10 (10.0%)	
Stage III	2,112 (8.6%)	2 (2.0%)	
Stage IV	486 (2.0%)	0 (0%)	
No. of recurrences	600 (2.5%)	19 (9.4%)	<0.001
No. of disease-specific deaths	76 (0.3%)	0 (0.0%)	

cPTC, conventional papillary thyroid carcinoma; DSV, diffuse sclerosing variant; CCND, central compartment neck dissection; MRND, modified radical neck dissection.

(29.48% vs. 20.50%, respectively; p=0.038). Patients in the DSV group were significantly younger than those in the cPTC group (mean age: 32.9 ± 12.7 years vs. 45.0 ± 11.8 years, respectively; p<0.001). There was an over-representation of younger patients in the DSV group (17.8%) compared with the cPTC group (0.6%) (p<0.001).

The DSV group also presented with more aggressive pathological characteristics compared with the cPTC group, including a larger tumor size, more extensive tumor capsular invasion, lymph node metastasis, a higher lymph node ratio of both central cervical and lateral neck nodes, and a more advanced T and N stages, although the TNM stage was lower (all p<0.001). Accordingly, more radical treatments were performed in patients with the DSV than in patients with cPTC, including total thyroidectomy (87.6% vs. 51.1%, respectively), modified radical neck dissection (65.8% vs. 9.4%, respectively), and RAI treatment (83.2% vs. 43.2%, respectively). The recurrence rate was significantly higher in the DSV group (9.4%) than in the cPTC group (2.5%) (p<0.001). In contrast, the disease-specific mortality rate in the DSV group was 0.0% compared with 0.3% in the cPTC group. In the Kaplan–Meier estimates of RFS, the DSV was significantly associated with a worse RFS compared with cPTC (p<0.01) (Figure 1).

3.2 Comparison of the characteristics of pediatric and adult patients in the DSV group

The demographic and clinico-pathologic characteristics of pediatric (n=35) and adult (n=167) patients with DSV were compared (Table 2). The two groups did not differ significantly in terms of sex, the presence of tumor capsular invasion, multifocality and bilaterality, node conditions, or operative extent (p<0.05). In contrast, the tumor size and T stage were significantly higher in the pediatric population (p<0.001 and p=0.001, respectively). The recurrence rate was also significantly higher in pediatric patients (22.9%) than in adult patients (6.6%) (p=0.007). The Kaplan–Meier estimates for RFS were also compared between pediatric and adult patients with the DSV, and RFS was significantly lower in pediatric patients with the DSV compared with adult patients with cPTC (p<0.01) (Figure 2).

3.3 Mutational status of patients with DSV

In this study, *BRAF* and *TERT* mutation results were only available for 65 and 21 patients, respectively. Among them, 22

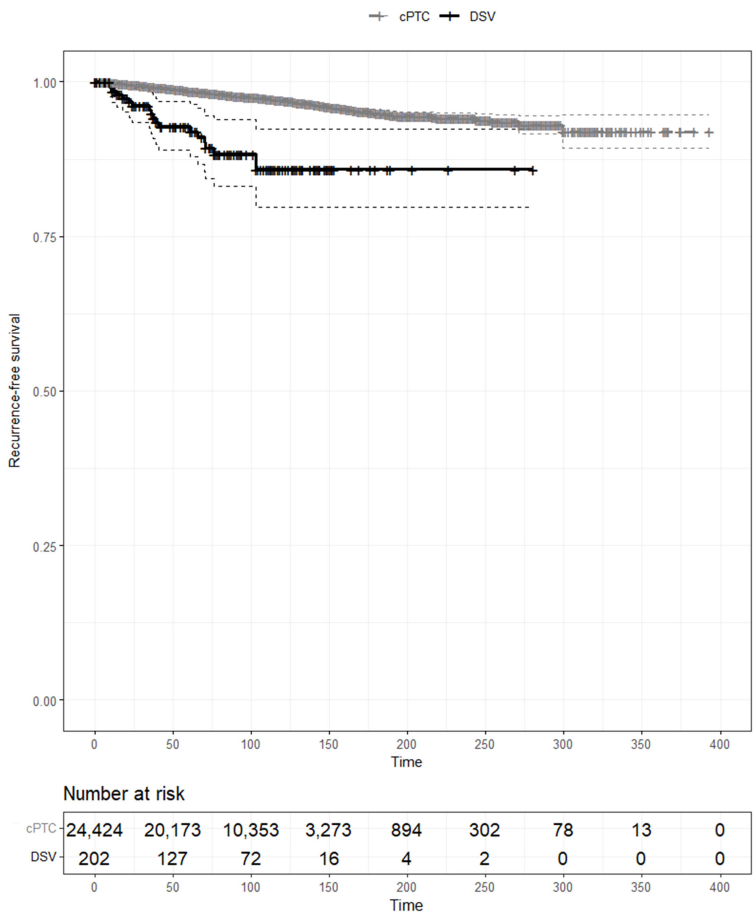

FIGURE 1
Kaplan–Meier analysis of recurrence-free survival curves of patients with conventional papillary thyroid carcinoma and those with the diffuse sclerosing variant.

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TABLE 2 Comparison of pediatric vs. adult patient characteristics.

Variable	Pediatric (N=35)	Adult (N=167)	p-value
Sex (F:M, F(%))	29:6	127:40	0.515
Age, years	15.2 ± 3.3	36.4 ± 10.4	<0.001
Tumor size, cm	2.5 ± 1.4	1.6 ± 1.0	<0.001
Capsule invasion, n (%)	28 (80.0%)	127 (76.0%)	0.777
Multifocality, n (%)	3 (8.6%)	18 (10.8%)	0.583
Bilaterality, n (%)	16 (45.7%)	83 (49.7%)	0.556
Central node, n			
- Total	11.0 ± 6.6	11.1 ± 7.1	0.862
- Metastatic	7.1 ± 5.4	7.0 ± 5.7	0.813
- Ratio	0.6 ± 0.3	0.6 ± 0.3	0.612
Operative extent			0.085
- Lobectomy	6 (17.1%)	13 (7.8%)	
- Lobectomy with contralateral partial	2 (5.7%)	4 (2.4%)	
- Total thyroidectomy	27 (77.1%)	150 (89.8%)	
Neck lymph node dissection			0.160
- None	1 (2.9%)	0 (0.0%)	
- CCND	13 (37.1%)	55 (32.9%)	
- MRND + CCND	21 (60.0%)	112 (67.1%)	
RAI-treated	26 (74.3%)	142 (85.0%)	0.122
T stage			0.001
- T1	11(31.4%)	106 (63.5%)	
- T2	12 (34.3%)	23 (13.8%)	
- T3	8 (22.9%)	26 (15.6%)	
- T4	4 (11.4%)	12 (7.2%)	
N stage			0.686
- N0	5 (14.3%)	16 (6.6%)	
- N1a	8 (22.9%)	40 (24.0%)	
- N1b	22 (62.9%)	111 (66.5%)	
TNM stage 8th			0.456
- Stage I	35 (100%)	155 (93.4%)	
- Stage II	0	10 (6.0%)	
- Stage III	0	2 (1.2%)	
- Stage IV	0	0	
No. of recurrences	8 (22.9%)	11 (6.6%)	0.007

DSV, diffuse sclerosing variant; CCND, central compartment neck dissection; MRND, modified radical neck dissection; CI, confidence interval; HR, hazard ratio.
CCND, central compartment neck dissection; MRND, modified radical neck dissection.

patients (33.8%) were *BRAF* mutation-positive, and only 1 patient (4.7%) was *TERT* mutation-positive.

3.4 Risk analysis of recurrence of the DSV

In total, 19 recurrence events were described in the DSV group. The demographic and clinico-pathological factors of interest described above were entered into a Cox proportional-hazards regression model with the recurrence rate as the dependent outcome (Table 3). The prognostic factors associated with a higher recurrence rate at the univariate level were belonging to the pediatric patient group vs. adult patient group (HR=3.17; 95% CI: 1.27–7.89; p=0.013), larger tumor size (HR=1.34; 95% CI: 1.01–1.77; p=0.042), and non-referral for total thyroidectomy (HR=0.32; 95% CI: 0.11–0.97; p=0.045). In the multivariate analysis, belonging to the pediatric patient group compared with the adult patient group was the only significant predictor of recurrence (HR=2.82; 95% CI: 1.11–7.16; p=0.047) after adjusting for tumor size.

Lastly, we used RCSs, which are more adaptive, smoother splines, to assess the relationship between age and the risk of DSV- or cPTC-specific recurrence (Figure 3). The RCS curves of both groups showed a U-shaped distribution, and the lowest HR of each group was deliberately set at 1. The lowest HR occurred at 35 years of age in the DSV group and at 47 years of age in cPTC group. The RCS curve of the DSV tended to be located within the younger age group.

4 Discussion

To the best of our knowledge, this is the first study to perform a subgroup analysis of the DSV. Treating patients with DSV is often a sobering experience for clinicians owing to the aggressive pattern of the disease and its high recurrence rate. Moreover, knowledge regarding which patient characteristics (including age, sex, maximal tumor diameter, lymph node condition, and TNM stage) should be monitored more carefully for the DSV remains largely unknown.

In the current staging system of differentiated thyroid cancer, older age is a well-established risk factor for mortality (30). Contrarily, it is also well-known that the recurrence pattern of PTC is not exactly correlated with the staging system. For instance, although pediatric patients with PTC have a relatively high recurrence rate, they also have an excellent prognosis in terms of mortality (31). Considering the low mortality rate of thyroid cancer, it is important to investigate its recurrence pattern, which is directly linked to the patients' quality of life, requiring additional active treatment such as re-operation or repetitive radioiodine ablation, especially for aggressive subtypes such as the DSV.

In this study, our data shared similar results with previous studies. First, the DSV accounted for 0.8% of PTC cases, which is similar to the results of previous studies (11–16). Second, the DSV

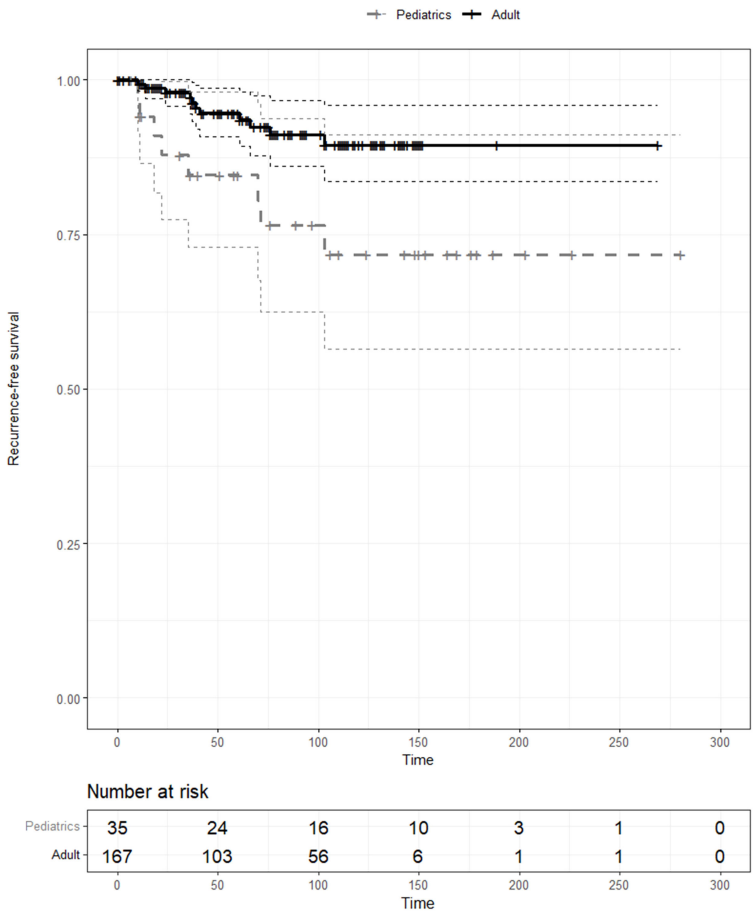

FIGURE 2
Kaplan–Meier analysis of recurrence-free survival curves of pediatric and adult patients with the diffuse sclerosing variant.

had a higher incidence in pediatric patients than in cPTC patients (8). Third, patients with the DSV had larger tumor sizes and lymph node metastases compared with patients with cPTC, resulting in more aggressive treatment (18, 19). Fourth, recurrence rates were higher in patients with the DSV compared with patients with cPTC. Fifth, despite its high recurrence rate, the DSV was associated with excellent survival rates (9, 18, 21, 22). Finally, the prevalence of *BRAF or TERT* mutations was low in patients with the DSV, which is acceptable in comparison with previous results (32–34).

Although there was a significant difference in the number of patients with cPTC (n=24,424) compared with the number of patients with DSV (n=202), no statistical matching was performed as the main purpose of this study was to perform a subgroup analysis of the DSV group.

Notably, we demonstrated that pediatric status is an independent risk factor for the recurrence of the DSV. We used only two variables for the multivariate Cox proportional hazard regression analysis owing to the limited number of events. Nevertheless, we obtained an HR of 2.82 (p=0.047) for recurrence in the pediatric patient group compared with that in the adult patient group with the DSV, even when controlling for tumor size.

It is interesting that pediatric differentiated thyroid cancer (DTC) and DSV are both known to be associated with high recurrence but with excellent survival as well. They also share similar molecular characteristics of less *BRAF 600E* or *TERT* mutations. Considering the dominance of the DSV in pediatric patients with DTC (8), we hypothesized that the reason for the distinctive characteristics of DTC in pediatric patients may be the predominance of the DSV. The present study provides an important basis for future research on this topic.

The interpretation of RCS curves requires careful attention (Figure 3). It is noteworthy that the RCS curve of both the DSV and cPTC groups showed a U-shaped distribution, with the curve of the DSV tending to be located within the younger age group. In the DSV group, the RCS curve of the population whose age was not less than 55 years was not depicted owing to the low frequency and recurrence rates. Among the 202 patients with the DSV, only 13 were aged 55 years or above, and there was only 1 patient (a 57-year-old man) with recurrence (i.e., lung metastases within 10 months of the initial total thyroidectomy). The oldest patient in the DSV group was a 70-year-old woman who did not show any signs of recurrence within 36 months after the initial surgery. Therefore, we are still

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TABLE 3 Comparison of Cox regression models between the adult and pediatric groups.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Female vs. Male						
Female						
Male	2.12	0.83–5.38	0.096			
Pediatric vs. Adult						
Adult						
Pediatric	3.17	1.27–7.89	0.013	2.82	1.11–7.16	0.047
Age	0.97	0.93–1.01	0.094			
Tumor size	1.34	1.01–1.77	0.042	1.22	0.90–1.66	0.194
Capsule invasion (+)	6.79	0.91–50.91	0.063			
Central node ratio	1.18	0.29–4.85	0.822			
Lateral node ratio	3.94	0.05–301.62	0.540			
Operative method						
- Lobectomy						
-Lobectomy with contralateral partial	0.59	0.07–5.24	0.631			
- Total thyroidectomy	0.32	0.11–0.97	0.045			
RAI						
None **Treated**	0.474	0.22-2.02	0.668			
Stage T						
T1						
T2	1.55	0.41–5.84	0.519			
T3	2.21	0.72–6.78	0.166			
T4	3.09	0.82–11.65	0.097			
Stage N						
N0						
N1a	1.34	0.27–6.63	0.722			
N1b	1.07	0.24–4.83	0.931			

uncertain whether the prognosis of patients with DSV can be predicted using the current staging system, which dichotomizes patients' age at 55 years across different types of thyroid cancer and considers older patients as having a worse prognosis.

To date, it remains unclear whether younger patients (<10–15 years of age) are at a greater risk of recurrence of DTC (31). In our study, the three youngest patients were aged <10 years (6, 7, and 9 years of age at diagnosis) and had no recurrence for at least 10 years after their initial diagnosis. The nine pediatric patients with recurrence were aged between 12 and 19 years, indicating a high recurrence rate among teenagers in the DSV group.

This study had several limitations. First, the study had a retrospective design. Second, we did not test for *RET/PTC* rearrangement, which is known as a major genetic alteration of the DSV. Third, all patients were treated at a single tertiary hospital, which may have caused selection bias. Fourth, we limited recurrence to structural recurrence. Clinicians often encounter cases of abnormal serum thyroglobin levels without structurally identifiable disease in clinical practice, indicating the need to be vigilant of biochemical recurrence; hence, this may have contributed to systematic bias in our study. Fifth, although we collected the data from 202 patients with the DSV, more independent risk factors can be obtained from a larger

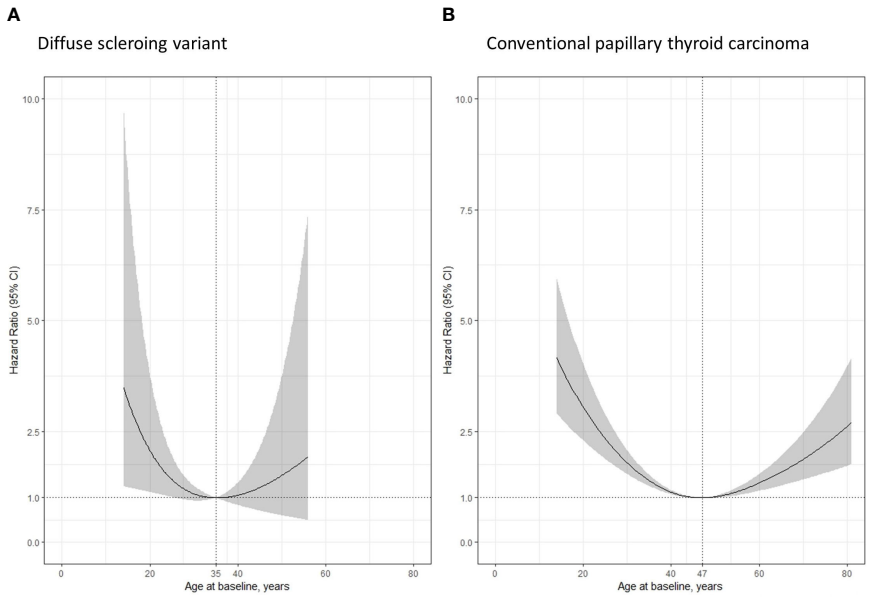

FIGURE 3
Restricted cubic spline (RCS) according to patients' age, adjusted for tumor size. **(A)** Patients with the diffuse sclerosing variant showed the lowest hazard ratio of recurrence at the age of 35 years; **(B)** Patients with conventional papillary thyroid carcinoma showed the lowest hazard ratio of recurrence at the age of 47 years.

population. Variables such as tumor size, total thyroidectomy, and extracapsular invasion were only marginally insignificant in our study.

5 Conclusions

This study demonstrated that pediatric patients with DSV are at a greater risk for recurrence compared with adult patients; moreover, the pattern of recurrence risk according to age is different from that of cPTC.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Institutional Review Board of Yonsei University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JK: Writing – original draft, Resources, Investigation, Formal analysis, Data curation. JSK: Writing – review & editing, Validation, Supervision, Software, Conceptualization. J-IB: Writing – review & editing, Validation, Supervision, Software, Formal analysis, Data curation. JKK: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. S-WK: Writing – review & editing, Validation, Supervision, Data curation. JJ: Writing – review & editing, Validation, Supervision, Data curation. K-HN: Writing – review & editing, Validation, Supervision, Data curation. WC: Writing – review & editing, Validation, Supervision, Data curation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Risk factors for cervical lymph node metastasis of papillary thyroid cancer in elderly patients aged 65 and older

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Objective: To assess the risk factors of cervical lymph node metastasis in elderly patients aged 65 years and older diagnosed with papillary thyroid cancer (PTC).

Design and method: In this retrospective analysis, we included a total of 328 elderly patients aged 65 years and older diagnosed with PTC. We thoroughly examined clinical features from these patients. Utilizing univariate and multivariate logistic regression analyses, we aimed to identify factors contributing to the risk of central and lateral lymph node metastasis (CLNM/LLNM) in this specific population of PTC patients aged 65 years and older.

Results: In the univariate analysis, CLNM was significantly associated with tumor size, multifocality, bilaterality, and microcalcification, while only tumor size ≥ 1cm (OR = 0.530, P = 0.019, 95% CI = 0.311 – 0.900) and multifocality (OR = 0.291, P < 0.001, 95% CI = 0.148 - 0.574) remained as risk factors in the multivariate analysis. LLNM was confirmed to be associated with male (OR = 0.454, P < 0.020, 95% CI = 0.233 - 0.884), tumor size ≥ 1cm (OR = 0.471, P = 0.030, 95% CI = 0.239 – 0.928), age ≥ 70 (OR = 0.489, P = 0.032, 95% CI = 0.254 – 0.941), and microcalcification (OR = 0.384, P = 0.008, 95% CI = 0.189 – 0.781) in the multivariate analysis. In elderly PTC patients with CLNM, male gender (OR = 0.350, P = 0.021, 95% CI = 0.143 – 0.855), age ≥ 70 (OR = 0.339, P = 0.015, 95% CI = 0.142 – 0.810), and bilaterality (OR = 0.320, P = 0.012, 95% CI = 0.131 – 0.779) were closely associated with concomitant LLNM in both univariate and multivariate analyses.

Conclusion: For elderly PTC patients aged 65 and older, tumor size ≥ 1cm and multifocality are significant risk factors for CLNM. Meanwhile, male, tumor size ≥ 1cm, age ≥ 70, and microcalcification are crucial predictors for LLNM. In patients already diagnosed with CLNM, male, age ≥ 70, and bilaterality increase the risk of LLNM.

KEYWORDS

papillary thyroid cancer, elderly, central lymph node metastasis, lateral lymph node metastasis, aging

Introduction

Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, and its incidence has been increasing worldwide. While PTC is generally associated with a favorable prognosis and low malignancy, up to 50% of PTC patients present with clinically evident regional lymph node metastasis (LNM) at diagnosis (1, 2). The high incidence of lymph node metastasis in PTC is widely regarded as a significant factor contributing to cancer recurrence and poor prognosis (3, 4). The prevailing view currently is that for PTC patients, lymph node dissection should only be performed in cases where there is clear evidence of lymph node metastasis, such as confirmed by biopsy (5). Therefore, it is particularly important to thoroughly assess the risk of lymph node metastasis in patients preoperatively and guide treatment accordingly.

Current research suggests that lymph node metastasis in PTC patients is associated with several potential risk factors, including male gender, larger tumor size, multifocal tumors, extrathyroidal extension, and other factors (6–8). Central lymph node metastasis (CLNM) is highly prevalent among PTC patients. Surgical intervention of central lymph node dissection (CLND) is considered appropriate based on the recommendation of the American Thyroid Association, which advises cervical node dissection for patients presenting with clinically involved (cN1) cervical lymph nodes (5). Lateral lymph node metastasis (LLNM) usually follows the occurrence of CLNM, a sequence facilitated by the lymphatic drainage system. In certain cases of PTC, metastasis to the lateral neck lymph nodes (LLNs) can occur without involvement of the central lymph nodes. This may be attributed to the thyroid papillary carcinoma metastasizing to the LLNs via the superior thyroid artery, rather than through the classical lymphatic drainage system (9, 10).

It is widely recognized that age is a crucial factor influencing the prognosis of thyroid cancer patients. The 8th edition of the American Joint Committee on Cancer guidelines indicates that elderly patients have a lower disease-free survival rate (11). The aging population is increasing in many countries globally, elderly individuals with papillary thyroid cancer are not uncommon in clinical practice. Peri et al. proposed that elderly and young patients with thyroid cancer may have different pathogenic mechanisms (12). Studies have also indicated that the malignancy degree of thyroid nodules in individuals over 65 years old is closely associated with age (13, 14). The study by Zhou et al. demonstrated that active surgical treatment is beneficial for PTC patients under the age of 85 (15). Further investigation into elderly patients with papillary thyroid cancer, particularly the characteristics of neck lymph node metastasis in this subgroup, holds significant clinical significance.

This study analyzed the clinicopathological data of patients aged 65 and older with PTC, assessing risk factors associated with lymph node metastasis. The findings of this study can assist surgeons in evaluating cervical lymph nodes and making appropriate clinical decisions in elderly patients with papillary thyroid cancer preoperatively.

Methods

The medical records of 519 patients aged 65 years and older who underwent partial or total thyroidectomy at Fudan University Shanghai Cancer Center (FUSCC) from January 2019 to December 2020 were reviewed. The study was approved by the Ethics Committee of FUSCC (050432–4-2307E), and informed consent was obtained from all patients.

Diagnostic evaluations and surgical management were conducted in accordance with the guidelines of the American Thyroid Association (ATA). Patients were included based on the following criteria: 1) Confirmation of PTC through surgical pathology, 2) Pathological confirmation of the presence or absence of LNM, 3) Availability of complete clinical data, and 4) Age ≥65 years for all 519 patients. A total of 191 patients were excluded based on the following criteria: 1) Benign final pathological findings, 2) Pathological diagnosis of thyroid malignancies other than PTC, 3) Incomplete clinical data, 4) History of prior thyroid surgery, 5) Presence of other extrathyroidal malignancies, and 6) History of head and neck radiation therapy. Ultimately, 328 patients were included in this study. All participants included in the study underwent ultrasound-guided fine-needle aspiration biopsy (UG-FNAB) several weeks prior to surgery. Tumor morphology-related ultrasound data, including microcalcifications, were obtained by ultrasonography examination performed by two experienced radiologists specializing in thyroid pathology. Following surgery, diagnosis confirmation and corresponding histopathological features were assessed by two experienced thyroid tumor pathologists.

Clinical and pathological characteristics data were collected, including age, sex, tumor size, capsular invasion, tumor location, unifocality/multifocality, unilateral/bilateral involvement, presence of Hashimoto's thyroiditis, presence of nodular goiter, tumor margin smoothness, presence of microcalcifications, central compartment lymph node metastasis, and lateral compartment lymph node metastasis.

Data management and statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp.). Continuous variables such as age and tumor size were summarized using means and variances, with group comparisons conducted through chi-square or non-parametric U tests. Categorical variables were described using frequency percentages, and group comparisons were made using the Chi-square test. Initial analyses involved univariate assessment using either the chi-squared test or Fisher's exact test. Variables with a significance level of $p < 0.05$ underwent subsequent multivariate analyses utilizing binary logistic regression. The data evaluating the influence of potential risk factors are reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

Results

Patient characteristics

In our study, 328 patients aged 65 years and older diagnosed with papillary thyroid cancer (PTC) were included. The mean age (± standard deviation) was 68.4 ± 3.2 years (range, 65–80 years), with 75.3% of the patients being female (247 females and 81 males). Among all 328 elderly PTC patients, central neck lymph node metastasis (CLNM) occurred in 109 patients, lateral neck lymph node metastasis (LLNM) occurred in 60 patients, and among the

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109 patients with CLNM, 46 patients developed LLNM. Tables 1, 2 show the clinical and ultrasonic factors of the patients.

Association of CLNM/LLNM and clinical characteristics of elder PTC patients aged 65 years and older

In the univariate analysis of CLNM with clinical/ultrasound features in all elderly PTC patients (see Table 1), CLNM was found to be significantly associated with tumor size (P < 0.001), multifocality (P < 0.001), bilaterality (P = 0.003), and ultrasound-detected microcalcifications (P = 0.006). However, no significant association was observed between CLNM and other clinical factors such as Gender (P = 0.098), HT (P = 0.065), etc.

In the univariate analysis of LLNM with clinical/ultrasound features in all elderly PTC patients (see Table 3), LLNM was significantly associated with Gender (P = 0.017), tumor size (P < 0.001), age (P = 0.011), tumor location (P = 0.003), multifocality (P < 0.001), bilaterality (P < 0.001), and microcalcifications (P < 0.001). However, no significant association was observed between LLNM and other clinical factors such as ETE (P = 0.131), HT (P = 0.600), NG (P = 0.054), etc.

For elderly PTC already with CLNM (see Table 2), the univariate analysis revealed significant associations between LLNM and Gender (P = 0.032), age (P = 0.017), and bilaterality (P = 0.010). Nevertheless, no significant relationship was found between LLNM and other clinical factors including multifocality (P = 0.126), microcalcifications (P = 0.117), NG (P = 0.071), among others.

Multivariate logistic regression analysis

In the multivariate analysis, CLNM in elderly PTC patients was significantly associated with tumor size ≥ 1cm (OR = 0.530, P = 0.019, 95% CI = 0.311 – 0.900) and multifocality (OR = 0.291, P <0.001, 95% CI = 0.148 - 0.574), as shown in Table 4. Regarding LLNM, male gender (OR = 0.454, P <0.020, 95% CI = 0.233 - 0.884), tumor size ≥ 1cm (OR = 0.471, P = 0.030, 95% CI = 0.239 – 0.928), age ≥ 70 (OR = 0.489, P = 0.032, 95% CI = 0.254 – 0.941), and microcalcifications (OR = 0.384, P = 0.008, 95% CI = 0.189 – 0.781) were identified as closely associated risk factors in elderly PTC patients, as shown in Table 5. For elderly PTC patients with CLNM, male gender (OR = 0.350, P = 0.021, 95% CI = 0.143 – 0.855), age ≥ 70 (OR = 0.339, P = 0.015, 95% CI = 0.142 – 0.810) and bilaterality (OR = 0.320, P = 0.012, 95% CI = 0.131 – 0.779) were found to be closely associated risk factors for concomitant LLNM, as shown in Table 6.

TABLE 1 Association between CLNM and clinical characteristics of elder PTC patients.

Variables	CLNM(%)		P value
	- (N=219)	+ (N=109)	
Gender			0.098
Female	171 (69.28)	76 (30.72)	
Male	48 (59.26)	33 (40.74)	
Tumor size (cm)			0.001
<1	117 (75.99)	37 (24.01)	
≥1	102 (58.62)	72 (41.38)	
Age			0.185
65≤age<70	162 (68.92)	73 (31.08)	
age≥70	57 (61.95)	36 (38.05)	
Location			0.431
Upper	61 (64.91)	33 (35.09)	
Middle	82 (66.67)	41 (33.33)	
Lower	69 (71.15)	28 (28.85)	
Full	7 (50.00)	7 (50.00)	
Multifocality			0.001
Yes	58 (50.43)	57 (49.57)	
No	161 (75.59)	52 (24.41)	
Coexistent HT			0.065
Yes	56 (75.68)	18 (24.32)	
No	163 (64.14)	91 (35.86)	
Coexistent NG			0.287
Yes	102 (69.84)	44 (30.16)	
No	117 (64.28)	65 (35.71)	
ETE			0.121
Yes	23 (56.10)	18 (43.90)	
No	196 (68.30)	91 (31.70)	
Bilateral			0.003
Yes	35 (51.52)	33 (48.48)	
No	184 (70.78)	76 (29.22)	
T			0.064
T1–2	180 (69.23)	80 (30.77)	
T3–4	39 (57.35)	29 (42.65)	
Margin			0.492
Smooth	60 (69.77)	26 (30.23)	
Ill-defined	159 (65.69)	83 (34.31)	
Microcalcification			0.006
Yes	114 (60.67)	74 (39.33)	
No	105 (75.00)	35 (25.00)	

CLNM, central lymph node metastasis; PTC, papillary thyroid cancer; HT, Hashimoto's thyroiditis; NG, Nodular Goiter; ETE, Extrathyroidal Extension.

Discussion

In this study focusing on elderly PTC patients aged 65 years and older, we demonstrated that tumor size larger than 1cm and multifocality were risk factors for CLNM. Additionally, male gender, Tumor size ≥ 1cm, age ≥ 70, and microcalcifications were closely associated with LLNM. For patients who already presented with CLNM, male gender, age ≥ 70, and bilaterality significantly increased the risk of further LLNM.

The current research holds that age is closely associated with the prognosis of PTC patients. In the previous edition of the AJCC

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TABLE 2 Association between LLNM and clinical characteristics of elder PTC patients with central lymph node metastasis.

Variables	LLNM in CLNM(%)		P value
	- (N=63)	+ (N=46)	
Gender			0.032
Female	49 (64.53)	27 (35.47)	
Male	14 (42.42)	19 (57.58)	
Tumor size (cm)			0.284
<1	24 (64.86)	13 (35.14)	
≥1	39 (54.17)	33 (45.83)	
Age			0.017
65≤age<70	48 (65.75)	25 (34.25)	
age≥70	15 (41.67)	21 (58.33)	
Location			0.134
Upper	16 (48.48)	17 (51.52)	
Middle	28 (68.29)	13 (31.71)	
Lower	17 (60.71)	11 (39.29)	
Full	2 (28.57)	5 (71.43)	
Multifocality			0.126
Yes	29 (50.88)	28 (49.12)	
No	34 (65.38)	18 (34.62)	
Coexistent HT			0.463
Yes	9 (50.00)	9 (50.00)	
No	54 (59.34)	37 (40.66)	
Coexistent NG			0.071
Yes	30 (68.18)	14 (31.82)	
No	33 (50.78)	32 (49.22)	
ETE			0.833
Yes	10 (55.56)	8 (44.44)	
No	53 (58.26)	38 (41.74)	
Bilateral			0.010
Yes	13 (39.39)	20 (60.61)	
No	50 (65.79)	26 (34.21)	
T			0.917
T1–2	46 (57.54)	34 (42.46)	
T3–4	17 (58.62)	12 (41.38)	
Margin			0.356
Smooth	13 (50.00)	13 (50.00)	
Ill-defined	50 (60.24)	33 (39.76)	
Microcalcification			0.117
Yes	39 (52.70)	35 (47.30)	
No	24 (68.57)	11 (31.43)	

CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; PTC, papillary thyroid cancer; HT, Hashimoto's thyroiditis; NG, Nodular Goiter; ETE, Extrathyroidal Extension.

TABLE 3 Association between LLNM and clinical characteristics of elder PTC patients.

Variables	LLNM (%)		P value
	- (N=268)	+ (N=60)	
Gender			0.017
Female	209 (84.60)	38 (15.40)	
Male	59 (72.83)	22 (27.17)	
Tumor size (cm)			0.001
<1	138 (89.66)	16 (10.34)	
≥1	130 (74.70)	44 (25.30)	
Age			0.011
65≤age<70	200 (85.11)	35 (14.89)	
age≥70	68 (73.00)	25 (27.00)	
Location			0.003
Upper	72 (76.60)	22 (23.40)	
Middle	105 (85.42)	18 (14.58)	
Lower	84 (86.57)	13 (13.43)	
Full	7 (50.00)	7 (50.00)	
Multifocality			0.001
Yes	81 (70.45)	34 (29.55)	
No	187 (87.80)	26 (12.20)	
Coexistent HT			0.600
Yes	62 (83.78)	12 (16.22)	
No	206 (81.14)	48 (18.86)	
Coexistent NG			0.054
Yes	126 (86.84)	20 (13.16)	
No	142 (78.02)	40 (21.98)	
ETE			0.131
Yes	30 (73.17)	11 (26.83)	
No	238 (82.92)	49 (17.08)	
Bilateral			0.001
Yes	42 (61.76)	26 (38.24)	
No	226 (86.92)	34 (13.08)	
T			0.108
T1–2	217 (83.46)	43 (16.54)	
T3–4	51 (75.00)	17 (25.00)	
Margin			0.574
Smooth	72 (83.72)	14 (16.28)	
Ill-defined	196 (81.00)	46 (19.00)	
Microcalcification			0.001
Yes	142 (75.54)	46 (24.46)	
No	126 (90.00)	14 (10.00)	

LLNM, lateral lymph node metastasis; PTC, papillary thyroid cancer; HT, Hashimoto's thyroiditis; NG, Nodular Goiter; ETE, Extrathyroidal Extension.

system, forty-five serves as a significant age threshold for prognostic risk assessment (16). For patients with differentiated thyroid cancer under the age of 45, even with distant metastasis, they are still classified as stage II. However, recent studies have raised doubts about the use of age 45 as a cutoff to upstage patients (17, 18). One significant factor influencing the designation of 45 years as a prognostic risk threshold for thyroid cancer patients may be the significant impact of lymph node metastasis on prognosis (19). Therefore, for PTC patients, age and lymph node metastasis are risk factors that need to be considered comprehensively. Recently, in the

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TABLE 4 Multivariate logistic regression analyses of factors contributing to central lymph node metastasis in elder PTC patients.

Characteristics	OR	P Value	95% CI for OR	
			Lower	Upper
Size ≥ 1	0.530	0.019	0.311	0.900
Multifocality	0.291	<0.001	0.148	0.574

CI, confidence interval; OR, Odds ratio.

eighth edition of the AJCC TNM classification system, the age cutoff for PTC was adjusted from 45 to 55 years, following analysis of several population-based studies (20, 21). According to this revision, the age cutoff of 55 years is more robust, leading to better predictability for cancer-specific survival (22, 23).

The World Health Organization (WHO) typically defines individuals aged 65 and above as elderly. With the increasing size of the aging population, the potential PTC patients aged 65 and above cannot be ignored. Prioritizing the risk of lymph node metastasis in elderly PTC patients is particularly important for prognosis management in this demographic group. In this study, we found that for CLNM, age in elderly patients is not a significant risk factor. However, for LLNM, including cases where CLNM already exists, older age is a key factor in promoting LLNM occurrence. This aligns with current research perspectives, as noted by Wang et al., who indicated that the protective effect of age on cervical LNM diminishes gradually and increasingly with age, particularly for lateral LNM (24). Elderly patients frequently exhibit poorer health conditions compared to younger patients, often accompanied by multiple underlying diseases. Once cervical lymph node metastasis occurs, elder patients face increased treatment-related risks and poorer prognosis, hence requiring particular attention.

According to previous studies, male gender, larger tumor size, multifocality, and extrathyroidal extension are the main risk factors for lymph node metastasis in PTC (25–28). This study yielded similar results. In elderly thyroid cancer patients, larger tumor size and multifocality are closely associated with an increased risk of CLNM occurrence. Tumor size is a critical component in TNM staging, with lesions larger than 1 cm demonstrating increased invasiveness as they grow in size (29). In some elderly patients, irregular medical examinations may lead to a longer potential growth period of the tumor, resulting in a larger tumor size at diagnosis. As for multifocality, reported rates of its occurrence in PTC range from 20.0% to 36.1% (30). In our study, multifocality was observed in 35.1% of elderly patients. This relatively high

TABLE 5 Multivariate logistic regression analyses of factors contributing to lateral lymph node metastasis in elder PTC patients.

Characteristics	OR	P Value	95% CI for OR	
			Lower	Upper
Male	0.454	0.020	0.233	0.884
Size ≥1	0.471	0.030	0.239	0.928
Age ≥70	0.489	0.032	0.254	0.941
Microcalcification	0.384	0.008	0.189	0.781

CI, confidence interval; OR, Odds ratio.

TABLE 6 Multivariate logistic regression analyses of factors contributing to lateral lymph node metastasis in elder PTC patients with central lymph node metastasis.

Characteristics	OR	P Value	95% CI for OR	
			Lower	Upper
Male	0.350	0.021	0.143	0.855
Age ≥ 70	0.339	0.015	0.142	0.810
Bilateral	0.320	0.012	0.131	0.779

CI, confidence interval; OR, Odds ratio.

incidence underscores the significance of not missing potential multifocal lesions during preoperative assessment.

In elderly male PTC patients, the risk of LLNM is significantly higher. Male patients often exhibit advanced stage disease and aggressive histopathology (31). Furthermore, male patients with PTC tend to have worse prognoses than females diagnosed under the age of 55 years (32). In our study, LLNM incidence among elderly male PTC patients was 27.2%, nearly twice that of female patients. This underscores the importance of paying special attention to the potential risk of LLNM in elderly male PTC patients. Additionally, preoperative ultrasound findings indicating tumor microcalcification should also be given attention for potential LLNM risk. Microcalcification is a highly specific indicator and significant sonographic feature suggestive of malignant nodules and may increase the risk of cervical lymph node metastasis (33). In this study, elderly PTC patients with microcalcifications had a LLNM incidence of 24.5%, significantly higher than those without this risk feature. For elderly PTC patients with existing CLNM, bilateral lesions are a significant LLNM risk factor that should not be overlooked, consistent with findings from multiple studies (34, 35). In this study, 14 elderly PTC patients developed LLNM in the absence of CLNM, which accounts for nearly 25% of LLNM cases, aligning with previous research findings ranging from 5% to 25% (36, 37), this underscores the importance of preoperative assessment and warrants further investigation into the necessity of central compartment dissection in this subgroup.

In this study, capsule invasion did not correlate with the risk of lymph node metastasis. One possible explanation for this phenomenon is that lesions remained stable over time, even in the presence of capsule invasion, which may significantly increase the risk of tumor progression. Additionally, in our study, we found that patients with coexisting Hashimoto's thyroiditis had a lower probability of lymph node metastasis, although not statistically significant, which is consistent with the current research findings (7, 38). There are differences in the occurrence of LLNM based on tumor location, particularly with tumors located in the upper pole of the thyroid gland showing a higher rate of lateral cervical lymph node metastasis. This finding aligns with the conclusions drawn from the present study (9, 39).

Our study is subject to certain limitations. Firstly, its retrospective design restricted the adjustment for certain confounding factors. Secondly, being a single-center analysis, a multicenter approach would be required for a more comprehensive understanding of this issue. At the same time, we did not incorporate molecular pathological features such as BRAF

mutations, mainly due to the significant number of patients referred from external institutions already diagnosed through fine-needle aspiration, where BRAF testing was not universally conducted. Currently, we have placed considerable emphasis on collecting molecular pathological data for admitted patients. Additionally, with the increasing importance placed on molecular pathology, most medical institutions in the region now include testing for gene mutations such as BRAF when diagnosing PTC through fine-needle aspiration. In further studies, we will thoroughly incorporate molecular pathological information including BRAF mutations.

Conclusion

This study, based on PTC patients aged 65 and older treated at our center, revealed several significant risk factors for CLNM, including tumor size ≥ 1cm and multifocality. Meanwhile, for LLNM, male gender, tumor size ≥ 1cm, age ≥ 70, and microcalcification on ultrasound are important risk factors. In patients who already have CLNM, male gender, age ≥ 70, and bilaterality are risk factors for LLNM.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of Fudan University Shanghai Cancer Center (050432-4-2307E). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YZ: Data curation, Formal analysis, Writing – original draft. XJ: Conceptualization, Investigation, Methodology, Software, Writing – review & editing. ZY: Funding acquisition, Investigation, Project administration, Visualization, Writing – review & editing. YW: Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Predictors of lateral lymph node metastasis and skip metastasis in patients with papillary thyroid microcarcinoma

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Background: Papillary thyroid microcarcinoma (PTMC) is characterized by its favorable prognosis and potential for active surveillance (AS) as a management option. However, the presence of cervical lymph node (LN) metastasis, especially lateral LN metastasis, significantly impacts management and prognosis. Previous studies have focused on post-surgery risk factors for cervical LN metastasis. This study aims to identify predictors of lateral LN metastasis by analyzing pre-operative ultrasonographic findings alongside clinicopathological factors.

Methods: A retrospective review of medical records was conducted for patients with PTMC who underwent surgery at Chonnam National University Hwasun Hospital between 2004 and 2013. This is a case–control study that compares patients with lateral LN metastasis (N1b) to age- and sex-matched patients without LN metastasis (N0). Subgroup analysis was performed to evaluate risk factors of skip metastasis.

Results: The study included 90 patients with PTMC with lateral LN metastasis (N1b) and 268 age- and sex-matched patients without LN metastasis (N0). The mean age was 49.3 years, and female patients were dominant in both groups. Structural recurrences of 4.4% (4/90) were observed only in the N1b group. The N1b group exhibited a higher frequency of upper lobe tumor location compared to the N0 group (38.9% vs. 16.0%, $p < 0.001$). There was no significant difference in the locations with the presence of invasion to adjacent organs. A higher proportion of non-parallel shape was observed in the N1b group than the N0 group (80.0% vs. 66.0%, $p = 0.013$). There were no differences in echogenicity, sonographic feature, margin, and AP diameter of the thyroid gland between the two groups. In multivariate analysis, independent risk factors for lateral LN metastasis included extrathyroidal extension, multiplicity, upper lobe tumor location, and non-parallel shape. Skip metastasis in patients with PTMC was associated with upper lobe tumor location.

Conclusion: Detailed ultrasound examinations, evaluating tumor location, number, orientation, and the presence of ETE, are crucial in accurately predicting lateral LN metastasis especially when primary tumor was in the upper lobe to avoid missing skip metastasis. These evaluations can help guide the decision between AS and immediate surgery in patients with PTMC.

KEYWORDS

papillary thyroid microcarcinoma (PTMC), lymph node (LN), extra-thyroidal extension (ETE), upper lobe, non-parallel shape, multifocality

1 Introduction

The indolent nature and excellent prognosis of papillary thyroid microcarcinoma (PTMC) have contributed to the emergence of active surveillance (AS) as a viable treatment approach for low-risk thyroid cancer (1). AS for low-risk PTMC was introduced in Japan, and the American Thyroid Association guideline also recommended AS as an applicable management strategy in selected cases of low-risk thyroid cancer (2). A Korean study revealed a good prognosis, including 1.5% recurrence rate during a median follow-up of 7.7 years and 0.1% distant metastasis rate among 8,808 patients with PTMC (3). However, physician- and patient-related barriers to accepting AS in patients with PTMC still exist, and one of the main barriers is the fear of cancer progression, even though the risk of disease progression is low. Therefore, appropriate candidate identification for AS, especially the exclusion of cases with high risks of disease progression, is important.

Many studies have evaluated the prognostic factors of PTMC, including old age, male gender, larger tumor size, extrathyroidal extension (ETE), lymph node (LN) metastasis, multifocality, BRAF mutation, and coexistence of chronic thyroiditis, with varying or inconclusive results (4–8). The majority of prognostic factors can be ascertained through postoperative pathological results, which makes their utilization challenging for patients under consideration for AS. However, all patients diagnosed with PTMC undergo ultrasonography (US) before the AS decision to identify high-risk features, such as invasion and LN metastasis. Distant metastasis in patients with PTMC was rarely observed, but it could be fatal and all patients with PTMC with distant metastasis had synchronous cervical LN metastasis at the time of the first diagnosis (3). In particular, lateral LN metastasis is a prognostic factor of recurrence in patients with PTMC (9). Most of the lateral LN metastases in patients with PTMC progress sequentially from the initial central LN metastasis to the ipsilateral lateral LN metastasis (10). However, skip metastasis with a discontinuous lymphatic spread pattern has been reported in up to 21.8% of cases and PTMC (less than 1 cm) is a risk factor of skip metastasis among patients with papillary thyroid carcinoma (PTC) (11, 12).

Hence, the primary objective of this study is to assess potential risk factors associated with the development of lateral LN metastasis in patients with PTMC. This will be achieved by analyzing US findings in conjunction with clinicopathological factors among patients with lateral LN metastasis (N1b) and comparing them to age- and sex-matched patients without LN metastasis (N0). Additionally, we analyzed risk factors for skip metastasis in patients with PTMC with lateral LN metastasis.

2 Materials and methods

2.1 Patient population

This study is a retrospective, age- and sex-matched case–control cohort study where we reviewed medical records of patients diagnosed with PTMC who underwent surgery at Chonnam National University Hwasun Hospital between 2004 and 2013. The eligibility criteria included patients with PTMC with lateral LN metastasis (N1b) at the first surgery, resulting in the identification of 95 patients. Propensity score matching (PSM) analysis was used to match patients with PTMC with lateral LN metastasis (N1b) and those without LN metastasis (N0) based on age and sex as a confounding factor, with a matching ratio of 1:3. We utilized the "Matchit" package in R software (version 3.3.3) for PSM analysis, and 285 patients were enrolled as controls. Among the 95 patients with lateral LN metastasis, we excluded three patients who had no preoperative US and poor US quality, as well as two patients with insufficient follow-up periods of less than 6 months. In the control group without LN metastasis, we excluded 6 patients with no preoperative US and poor US quality, and 11 patients with insufficient follow-up periods of less than 6 months. Finally, we included and analyzed 90 patients with lateral LN metastasis (N1b) and 268 patients without LN metastasis (N0) to

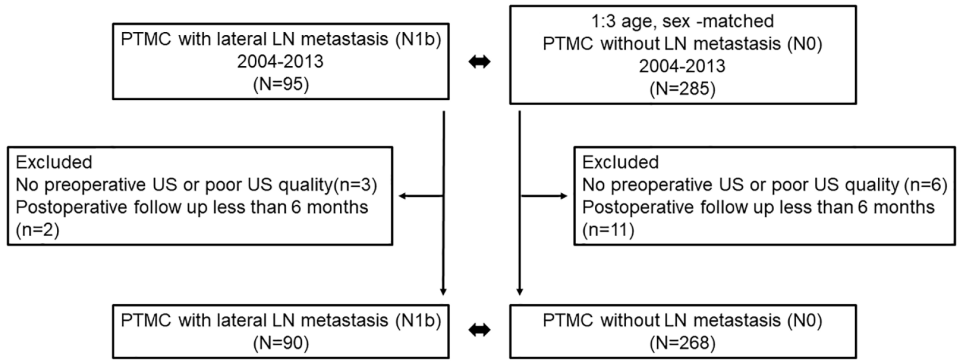

FIGURE 1
Flow chart of study population.

identify risk factors for lateral LN metastasis in patients with PTMC (Figure 1).

Informed consent was waived due to the retrospective nature of the study, and the Institutional Review Board of Chonnam National University Hwasun Hospital (No. CNUHH-2020–271) approved this study.

2.2 Evaluation of clinical and histopathological factors

To assess risk factors for lateral LN metastasis, we collected and analyzed baseline clinical characteristics and pathologic results. ETE included both minimal and gross invasion in pathologic results. Skip metastasis and stepwise metastasis were defined as lateral LN metastasis without central LN metastasis and lateral LN metastasis with central LN metastasis, respectively. Thyroid-stimulating hormone (TSH) levels were measured using Elecsys and Cobase analyzer kits (Roche Diagnostics, GmbH, Mannheim, Germany), with laboratory reference ranges of 0.4–4.48 mIU/L. At the last follow-up point, structural recurrence was defined as evidence of structural or functional disease, regardless of serum thyroglobulin (Tg) level or anti-Tg antibody (2).

2.3 Evaluation of preoperative thyroid image findings

Preoperatively, thyroid US was performed to assess the thyroid gland and neck. Gray-scale static US images of the thyroid and nodules were acquired using either the Logiq9 system (GE Medical System, Milwaukee, WI, USA) or ACUSON Antares system (Siemens Medical Solutions, Malvern, PA, USA) with a linear high-frequency probe (5–13 MHz). Two expert endocrinologists (K.C.H. and K.H.K.) conducted the US imaging. Following a training session with randomly selected US images, consensus criteria for the US images were defined, and one endocrinologist (P.J.Y.) reviewed the images. In cases where multiple suspicious nodules were present, the dominant nodule was determined, based on its aggressive nature as determined by the pathologic result, or if aggressiveness was not discernible, the largest nodule was selected as the dominant nodule.

2.4 US for thyroid nodule (main thyroid tumor)

Each nodule was evaluated using at least two US images, including the transverse and longitudinal planes. Tumor location was classified into upper, mid, and lower categories (13). For the assessment of invasion, tumor location 2 was categorized into various groups, including intra-thyroidal, adjacent to the anterolateral capsule, adjacent to the post-capsule, adjacent to the trachea, gross ETE to the strap muscle, gross ETE to the recurrent laryngeal nerve (RLN), or gross ETE to the trachea (14). The trachea invasion risk stratification (tumor location 3) was divided into three categories based on the angles between the tumor and the trachea: acute angle, right angle, or obtuse angle (15). Nodule composition was categorized as solid, partially cystic, partially solid, or cystic based on the ACR TI-RADS (American College of Radiology Thyroid Imaging, Reporting, and Data System) (16, 17). Nodular echogenicity was classified as marked hypoechoic, mild hypoechoic, isoechoic, or hyperechoic compared to the echogenicity of anterior neck muscles and normal thyroid parenchyma as reference (18). Nodular margin was divided into three categories: smooth, irregular, or ill-defined (16). Nodular orientation was categorized as either parallel or non-parallel (taller than wide shape). Finally, calcifications were divided into four categories: no calcification, punctate echogenic foci, macrocalcification, or rim (peripheral) calcification (16).

2.5 US for the thyroid gland (diffuse thyroid disease)

To assess the presence of diffuse thyroid disease (DTD), US findings of the thyroid were evaluated, including echogenicity (normal versus decreased), echotexture (fine or coarse/micronodular), margin (smooth, microlobulated, or

macrolobulated), and the anteroposterior (AP) diameter of the thyroid gland (considering 1–2 cm as the normal reference, decreased, or increased) (19, 20). The vascularity of the thyroid was not analyzed in this study due to the lack of available data.

2.6 US for lymph nodes

Among patients with lateral LN metastasis, preoperative US findings of suspicious LNs were collected. The LNs were evaluated based on size, cystic change, calcifications, and echogenicity (particularly abnormal hyperechogenicity) (21).

2.7 Statistical analysis

The data are presented as mean ± standard deviation or as *n* (%). Continuous variables were analyzed using Student's *t*-test, while categorical variables were analyzed using the Chi-square test and Mann–Whitney test. Kaplan-Meier analysis with the log-rank test was used to compare recurrence-free survival between the lateral LN metastasis group and the no-LN metastasis group. Clinical response data were dichotomized based on the presence of structural recurrence. Binary logistic regression models were employed to evaluate predictive risk factors for lateral LN metastasis in patients with PTMC. All statistical analyses were conducted using SPSS Statistics, version 28 (IBM, Armonk, NY), and a *p*-value <0.05 was considered statistically significant.

3 Results

3.1 Clinical and histopathological characteristics between lateral LN metastasis and no-LN metastasis

The study included a total of 90 patients with PTMC with lateral LN metastasis (N1b) and 268 patients without LN metastasis (N0) (Table 1). The mean age in both groups was 49.3 years (48.8 years in N1b group and 49.4 years in N0 group, respectively). All patients in the N1b group underwent total thyroidectomy with central neck dissection and therapeutic lateral cervical neck dissection. Sixty-one patients (67.8%) in the N1b group were underwent therapeutic central neck dissection due to central LN metastasis (N1a).

Except for one patient who opted not to receive RAI therapy due to personal preference, RAI therapy was performed in the N1b group. In the N0 group, 59.0% underwent total thyroidectomy and 23.3% received RAI therapy. Classic PTC was the most common subtype in both groups, and there was no significant difference in PTC subtypes between the two groups.

The N1b group showed a larger tumor size (0.7 ± 0.4 cm vs. 0.6 ± 0.3 cm, $p = 0.009$) and more aggressive pathological features, including bilaterality (26.7% vs. 8.6%, $p < 0.001$), multiplicity (44.4% vs. 14.2%, $p < 0.001$), and ETE (25.6% vs. 4.5%, $p < 0.001$) compared to the N0 group. There were no significant differences in capsular invasion, lymphovascular invasion, strap muscle invasion, or concurrent chronic thyroiditis [Hashimoto's thyroiditis (HT)] between the two groups. The N1b group had ipsilateral LN metastasis, except for two cases with contralateral LN metastasis originating from the primary tumor.

Only one case of metachronous distant metastasis at 82 months after the first surgery was observed in the N1b group. Patients in the N0 group had better structural recurrence-free survival compared to those in the N1b group ($p = 0.002$) (Figure 2). Structural recurrence was observed in 4.4% (4/90) of the N1b group. The

TABLE 1 Comparison of clinicopathological findings.

	PTMC with lateral LN metastasis [N1b] (*n* = 90)	PTMC without lateral LN metastasis [N0] (*n* = 268)	*p*-value
Age (years)	48.8 ± 11.8	49.4 ± 10.6	0.226
Sex (female, %)	67 (74.4)	200 (74.6)	0.973
Preoperative TSH level (mIU/L)	1.87 ± 1.23	1.99 ± 1.46	0.101
Surgical extent (%)			<0.001
Total thyroidectomy	90 (100.0)	158 (59.0)	
Lobectomy	0 (0.0)	110 (41.0)	
RAI (%)	89[a] (98.9)	21 (23.3)	**<0.001**
Mean dose of RAI (mCi)	173.2 ± 75.9	56.2 ± 55.1	**<0.001**
Pathologic results			
Cancer type			0.654
Classic	88 (97.8)	262 (97.8)	
Follicular variant	2 (2.2)	4 (1.5)	
Tall-cell variant	0 (0.0)	0 (0.0)	
Cribriform morular variant	0 (0.0)	1 (0.4)	
Oncocytic variant	0 (0.0)	1 (0.4)	
Tumor size (cm)	0.7 ± 0.4	0.6 ± 0.3	**0.009**
Bilaterality (%)	24 (26.7)	23 (8.6)	**<0.001**
Multifocality (%)	40 (44.4)	38 (14.2)	**<0.001**
Extrathyroidal extension (%)	23 (25.6)	12 (4.5)	**<0.001**
Lymphovascular invasion (%)	1 (1.1)	0 (0.0)	0.084
Concurrent chronic thyroiditis (%)	30 (33.3)	97 (36.2)	0.624
Distant metastasis	1 (1.1)	0 (0.0)	0.084
Follow-up months	112.4 ± 41.5	94.6 ± 48.5	**<0.001**

PTMC, papillary thyroid microcarcinoma; LN, lymph node; TSH, thyroid-stimulating hormone; RAI, radioactive iodine.
Data are expressed as mean ± standard deviation (SD) or n (%).
[a]One patient did not receive RAI therapy.
Compared with PTMC without lateral LN metastasis (N0), P<0.05.

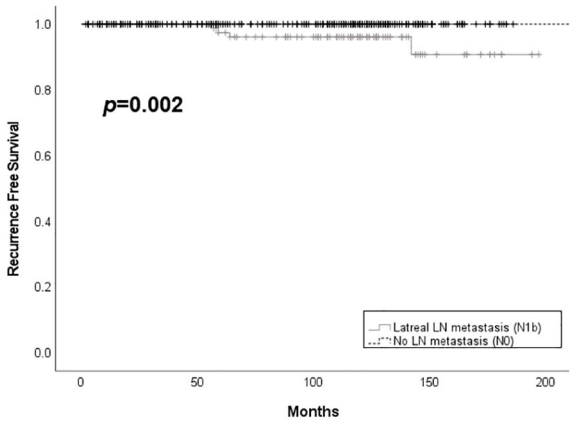

FIGURE 2
Structural recurrence free survival according to the presence of lateral lymph node metastasis among patients with PTMC. LN, lymph node.

N1b group had a longer follow-up duration than the N0 group (112.4 ± 41.5 months vs. 94.6 ± 48.5 months, $p < 0.001$).

3.2 Ultrasonographic findings according to the presence of lateral LN metastasis

3.2.1 US for dominant thyroid tumor

The tumor locations addressed by US are summarized in Table 2. The N1b group showed more frequently upper lobe tumor location compared to the N0 group (38.9% vs. 16.0%, $p < 0.001$). There was no significant difference of the locations with the presence of invasion to adjacent organs including capsule, muscle, trachea, and RLN between N1b and N0 groups. US features of the main thyroid tumor are summarized in Table 3. Echogenicity, composition, and margin showed no differences between N1b and N0 groups. Macrocalcification was more frequently observed in the N1b group compared to the N0 group, but the difference was not significant ($p = 0.053$). The N1b group had a higher percentage of non-parallel shape compared to the N0 group (80.0% vs. 66.0%, $p = 0.013$).

3.2.2 US for the thyroid gland and suspicious lymph node

US findings of background thyroid gland is summarized in Supplementary Table 1. There were no differences in echogenicity, sonographic feature, margin, and AP diameter between the two groups. US features for suspicious LN are summarized in Supplementary Table 2. Among patients with PTMC with lateral LN metastasis, the rate of suspicious LNs observed on both sides of the neck was 3.3%. The most frequently observed US feature of suspicious LN was echogenic foci (calcification), followed by cortical hyperechogenicity (55.6% and 24.4%, respectively). Cystic changes were observed in 12.2% of a total of 90 patients, and all of them showed no malignant cells on FNA and all of them showed no malignant cells on FNA. Washout fluid Tg was obtained and evaluated in all suspicious LN with cystic change and the range for washout fluid Tg was 9.70–659.0 ng/ml.

TABLE 2 Comparison of tumor locations on ultrasonographic images.

	PTMC with lateral LN metastasis [N1b] (n = 90)	PTMC without lateral LN metastasis [N0] (n = 268)	p-value
Tumor location 1			<0.001
Upper	35 (38.9)	43 (16.0)	
Mid	46 (51.1)	177 (66.0)	
Lower	9 (10.0)	48 (17.9)	
Tumor location 2			0.944
Intra-thyroidal	38 (42.2)	103 (38.4)	
Adjacent to anterolateral capsule	23 (25.6)	67 (25.0)	
Adjacent to post capsule	17 (18.9)	60 (22.4)	
Adjacent to trachea (medial capsule)	9 (10.0)	29 (10.8)	
Gross ETE to strap muscle	2 (2.2)	7 (2.6)	
Gross ETE to RLN	1 (1.1)	1 (0.4)	
Gross ETE to trachea	0 (0.0)	1 (0.4)	
Tumor location 3 (trachea)			0.929
Not adjacent to trachea	81 (90.0)	237 (88.4)	
Acute angle	8 (8.9)	27 (10.1)	
Right angle	0 (0.0)	1 (0.4)	
Obtuse angle	1 (1.1)	3 (1.1)	

PTMC, papillary thyroid microcarcinoma; LN, lymph node; ETE, extra-thyroidal extension; RLN, recurrent laryngeal nerve.
Data are expressed as n (%).
- Tumor location 1 was classified into upper, mid, and lower categories [13].
- Tumor location 2 was assessed for the invasion [14].
- Tumor location 3 was divided into three categories according to the angles between the tumor and the trachea for the trachea invasion risk stratification [15].

TABLE 3 Differences in ultrasonographic characteristics of the primary thyroid tumor.

	PTMC with lateral LN metastasis [N1b] (*n* = 90)	PTMC without lateral LN metastasis [N0] (*n* = 268)	*p*-value
Echogenicity			0.913
Marked hypoechoic	82 (91.1)	246 (91.8)	
Mild hypoechoic	7 (7.8)	18 (6.7)	
Isoechoic	1 (1.1)	4 (1.5)	
Hyperechoic	0 (0.0)	0 (0.0)	
Composition			0.180
Cystic	0 (0.0)	0 (0.0)	
Predominantly cystic	2 (2.2)	1 (0.4)	
Predominantly solid	1 (1.1)	7 (2.6)	
Solid	87 (96.7)	260 (97.0)	
Margin			0.087
Smooth	14 (15.6)	60 (22.4)	
Irregular	71 (78.9)	203 (75.7)	
Ill-defined	5 (5.5)	5 (1.9)	
Orientation			0.013
Parallel	18 (20.0)	91 (34.0)	
Non-parallel	72 (80.0)	177 (66.0)	
Calcification			0.053
No	6 (6.7)	19 (7.1)	
Punctate echogenic foci (microcalcification)	61 (67.8)	212 (79.1)	
Macrocalcification	22 (24.4)	33 (12.3)	
Rim calcification	1 (1.1)	4 (1.5)	
TIRAD			0.608
3 (low suspicion)	0 (0.0)	2 (0.8)	
4 (intermediate suspicion)	3 (3.3)	6 (2.2)	
5 (high suspicion)	87 (96.7)	260 (97.0)	

PTMC, papillary thyroid microcarcinoma; LN, lymph node; TIRAD, Thyroid Imaging Reporting and Data System.
Data are expressed as n (%).
Ultrasonographic findings of main thyroid tumor (echogenecity, composition, margin, orientation, and calcification) were evaluated based on the ACR TI-RADS [16-18].

3.3 Predictors for lateral LN metastasis

Multivariate regression analysis was performed for both pathological and sonographic variables exhibiting significant differences. ETE, multifocality, upper lobe tumor location, and non-parallel shape were independent risk factors for lateral LN metastasis in patients with PTMC (Table 4).

3.4 Subgroup analysis to evaluate risk factors for skip metastasis in patients with lateral LN metastasis from PTMC

Among a total of 90 patients with lateral LN metastasis, 29 cases (32.2%) had skip metastasis (Table 5). There were no significant differences between skip metastasis and stepwise metastasis in age, sex, ETE, and the location of LN metastasis. However, a higher frequency of upper lobe tumor location was observed in skip metastasis compared to stepwise metastasis (55.2% vs. 31.1%, p = 0.029). Conversely, bilaterality and multifocality were more frequently found in the stepwise metastasis group (6.9% vs. 36.1%, p = 0.003, 24.1% vs. 54.1%, p = 0.008, respectively) and a greater number of metastatic LNs were observed in the stepwise metastasis group (2.9 ± 2.6 vs. 7.9 ± 4.7, $p < 0.001$).

4 Discussion

This study focused on identifying risk factors for lateral LN metastasis in patients with PTMC. We evaluated clinicopathologic features and US findings not only in the main thyroid tumor but also in the background thyroid gland. Additionally, this study aimed to evaluate predictors of skip metastasis in patients with PTMC. The results revealed that ETE, tumor multifocality, upper lobe tumor location, and non-parallel tumor shape were independent predictors for lateral LN metastasis in patients with PTMC. Importantly, all these predictors can be assessed non-invasively using US, making it a valuable tool for risk stratification before the decision of AS.

PTC, the most common type of differentiated thyroid cancer, has seen a significant increase in incidence over the last few decades (22), resulting in considerable economic and emotional burden. As a result, AS is increasingly recommended as a suitable management option for low-risk PTC, particularly PTMC, given its favorable prognosis (23). The most important part of AS is to find appropriate criteria for AS, which could reduce the possibility of disease progression during observation. The definition of disease progression under AS is divided into two sections: tumor size growth and the emergence of new LN metastasis (14). The lower frequency of LN metastasis and the lack of significant benefit from prophylactic central LN dissection have supported lobectomy and even AS strategies in patients with PTMC. However, the presence of lateral LN metastasis can alter the treatment approach, with reported rates of up to 39.5% when prophylactic LN dissection is performed (24). This distinction can significantly impact the management strategy choice between AS and immediate surgery (IS) for patients with low-risk PTC. Moreover, LN metastasis has been linked to distant metastasis and recurrence in PTC patients, further emphasizing the importance of detecting and addressing LN involvement in the disease management (3, 25, 26). Our study demonstrated that patients with PTMC without LN metastasis (N0) at diagnosis showed no structural recurrence during an average follow-up period of 94.6 months, which could be safe candidates for AS.

TABLE 4 Risk factors for lateral LN metastasis in patients with papillary thyroid microcarcinoma.

	β	SE	OR (95% CI)	*p*-value
Tumor size	0.942	0.560	2.566 [0.856–7.697]	0.093
Extrathyroidal extension	1.599	0.436	4.948 [2.106–11.622]	**<0.001**
Multifocality	1.410	0.327	4.096 [2.160–7.768]	**<0.001**
Bilaterality	0.479	0.402	1.615 [0.735–3.550]	0.233
Location (upper)	1.165	0.309	3.207 [1.750–5.877]	**<0.001**
Orientation (nonparallel)	0.738	0.336	2.091[1.082–4.042]	**0.028**

LN, lymph node; SE, standard error; OR, odds ratio; CI, confidence interval.
The correlation with lateral LN metastasis in patients with papillary thyroid microcarcinoma, p<0.05.

In a Korean study analyzing 5,656 patients with PTMC, male gender was identified as one of the independent predictors for lateral LN metastasis, with the difference of loco-regional recurrence according to nodal stage (27). Similarly, a Japanese AS cohort study revealed that young age (<40 years) was an independent risk factor for newly developed LN metastasis among low-risk patients with PTMC (28). Young age and male gender are well-known predictors in patients with PTC; however, a Korean study demonstrated higher recurrence rates and mortality in male patients compared to female patients with PTC, but male gender was not an independent prognostic factor for recurrence in propensity score-matched patients with PTMC (29). In this study, we performed the PSM for age and sex among patients with PTMC; thus, the age and sex variables for the risk of LN metastasis could not be analyzed. Nevertheless, special attention is warranted to identify lateral LN metastasis in patients with young age and male gender.

TABLE 5 Clinicopathological findings between skip metastasis and stepwise metastasis in papillary thyroid microcarcinoma patients with lateral lymph node metastasis.

	Skip metastasis (*n* = 29)	Stepwise metastasis (*n* = 61)	*p*-value
Age (year)	47.5 ± 10.4	49.5 ± 12.5	0.447
Sex (female, %)	22 (75.9)	45 (73.8)	0.832
Tumor size (cm)	0.6 ± 0.2	0.7 ± 0.5	0.260
Tumor location (upper)	16 (55.2)	19 (31.1)	**0.029**
Bilaterality (%)	2 (6.9)	22 (36.1)	**0.003**
Multifocality (%)	7 (24.1)	33 (54.1)	**0.008**
Extrathyroidal extension (%)	7 (24.1)	16 (26.2)	0.832
Number of the involved LNs	2.9 ± 2.6	7.9 ± 4.7	**<0.001**
Location of LN metastasis[a]			
II (%)	13 (44.8)	28 (45.9)	0.706
III (%)	21 (72.4)	48 (78.7)	0.194
IV (%)	17 (58.6)	35 (57.3)	0.803

LN, lymph node.
[a]multiple LN metastasis was observed in the same patient.
Compared to stepwise metastasis, p<0.05.
The location of lateral LN metastasis was classified as belonging to level II (the upper jugular group), III (the middle jugular group), and IV(the lower jugular and medial supraclavicular group).

In a Korean study analyzing 3,578 patients with PTMC, central LN metastasis, ETE, and multifocality were identified as significant risk factors for lateral LN metastasis (30). Our study also found similar trends, with multifocality and ETE being related to lateral LN metastasis, although central LN metastasis could not be evaluated due to the study's design comparing N1b with N0. Many studies have shown that multifocality is a risk factor for LN metastasis in PTC and patients with PTMC (7, 31, 32), and there are still controversies regarding its relationship with prognosis. A recent study suggested that minimal ETE is linked to lateral LN metastasis (33), but there is no association between minimal ETE and recurrence among patients with PTMC (34). A future prospective study could explain the relationship between multifocality and clinical outcome in patients with PTMC.

At the time of the decision for AS in low-risk patients with PTMC, many histopathological risk factors are not readily available. However, tumor size, ETE, and multifocality can be evaluated by US with some limitations. For instance, capsular invasion on US can be defined as the percentage of the tumor perimeter in contact with the thyroid capsule, and PTC patients with >50% capsular invasion on US show a higher frequency of lateral LN metastasis (35). Loss of the echogenic capsule has been identified as a reliable US value for evaluating capsular invasion in PTC patients, with 75% sensitivity and 65% specificity, but a false discovery rate of 57.1% (36). US may have some limitations in accurately assessing multifocality due to the possibility of occult tumors with small size, and three patients were excluded because tumor was not observed in preoperative US of our study. Despite these challenges, our study showed the association of ETE and multifocality with lateral LN metastasis; thus, careful US evaluation of ETE and tumor number can provide valuable clues for the risk of lateral LN metastasis.

US findings play a critical role in predicting disease progression, especially lateral LN metastasis, in patients with PTMC considering AS because US should be performed in all patients before the decision of AS. Despite its importance, only a few studies have focused on US features for PTMC. A Chinese study highlighted that US features, such as central LN metastasis in the presence of concurrent HT, upper lobe tumor location, lack of a well-defined margin, and the presence of calcifications, were significantly associated with lateral LN metastasis in patients with PTMC (37). Another study identified upper lobe tumor

location, microcalcification, and subcapsular lesions (defined as nodules abutting the thyroid capsule without intervening thyroid tissue) as factors associated with lateral LN metastasis (38). In the present study, we found that upper lobe tumor location and a non-parallel shape of the main thyroid tumor were independent predictors for lateral LN metastasis in patients with PTMC. The association between upper lobe tumor location and lateral LN metastasis has been consistently demonstrated in most studies focusing on patients with PTMC (39). Consequently, meticulous US follow-up is essential with a specific focus on detecting lateral LN metastasis in patients with PTMC with tumors located in the upper lobe. The upper lobe tumor location and PTMC were risk factors of skip metastasis (40, 41). This study evaluated risk factors of skip metastasis in patients with PTMC, and upper lobe tumor location was identified as a risk factor. Furthermore, skip metastasis could suddenly occur without other progressive signs including bilaterality, multifocality, and the expansion of metastatic LNs.

Apart from the main characteristics of the thyroid tumor, the background of the thyroid itself could also influence LN metastasis. The association between DTD and PTC has primarily been evaluated in the context of HT. Previous reports have indicated a higher prevalence of PTC in patients with HT compared to those without HT, and some studies have suggested a potential protective effect of HT in terms of recurrence and disease-related mortality of PTC (42). However, controversies still exist regarding this association. In our study, we found that coexisting HT, as determined by pathological results and US findings, showed no association with lateral LN metastasis in patients with PTMC. Similarly, other studies have shown no significant association between HT and LN metastasis or recurrence rate in patients with PTMC when HT was defined based on thyroid autoantibodies or pathology (43). Furthermore, a meta-analysis reported that there was no relationship between HT and LN metastasis in patients with PTMC and that HT had a negative association with LN metastasis in PTC cases larger than 1 cm (44).

This study has several limitations that need to be acknowledged. Firstly, the retrospective design of the study may introduce selection bias and limit the generalizability of the findings. Secondly, the evaluation of vascularity using Doppler US was not conducted due to the lack of data, which could have provided valuable information on the vascularity of the thyroid tumor and gland. Thirdly, age- and sex-matched data were used as controls (N0 group), which means that the effects of age and sex as potential risk factors were not specifically evaluated in this study. Despite these limitations, this study is valuable as it assessed and analyzed US findings of both the main tumor and the thyroid gland, allowing for the identification of potential candidates for AS without relying solely on pathological findings.

In conclusion, factors including upper lobe tumor location and non-parallel shape, along with ETE and multifocality, were identified as independent risk factors for lateral LN metastasis in patients with PTMC, and skip metastasis is also more commonly observed in tumors of the upper lobe. Therefore, meticulous US examinations to predict LN metastasis that include an assessment of tumor location, number, orientation shape, and the presence of ETE beyond mere detection of LN metastasis are necessary in the decision-making process for AS in especially when primary tumor was found in upper lobe.

Data availability statement

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

Ethics statement

The Institutional Review Board of Chonnam National University Hwasun Hospital (No. CNUHH-2020-271) approved this study. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JY: Data curation, Formal analysis, Investigation, Writing – original draft. JP: Data curation, Methodology, Writing – original draft. AH: Investigation, Software, Writing – review & editing. HK: Supervision, Validation, Writing – review & editing. H-CK: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1392247/full#supplementary-material

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Improving the diagnostic performance of inexperienced readers for thyroid nodules through digital self-learning and artificial intelligence assistance

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Background: Data-driven digital learning could improve the diagnostic performance of novice students for thyroid nodules.

Objective: To evaluate the efficacy of digital self-learning and artificial intelligence-based computer-assisted diagnosis (AI-CAD) for inexperienced readers to diagnose thyroid nodules.

Methods: Between February and August 2023, a total of 26 readers (less than 1 year of experience in thyroid US from various departments) from 6 hospitals participated in this study. Readers completed an online learning session comprising 3,000 thyroid nodules annotated as benign or malignant independently. They were asked to assess a test set consisting of 120 thyroid nodules with known surgical pathology before and after a learning session. Then, they referred to AI-CAD and made their final decisions on the thyroid nodules. Diagnostic performances before and after self-training and with AI-CAD assistance were evaluated and compared between radiology residents and readers from different specialties.

Results: AUC (area under the receiver operating characteristic curve) improved after the self-learning session, and it improved further after radiologists referred to AI-CAD (0.679 vs 0.713 vs 0.758, $p<0.05$). Although the 18 radiology residents showed improved AUC (0.7 to 0.743, $p=0.016$) and accuracy (69.9% to 74.2%, $p=0.013$) after self-learning, the readers from other departments did not. With AI-CAD assistance, sensitivity (radiology 70.3% to 74.9%, others 67.9% to 82.3%, all $p<0.05$) and accuracy (radiology 74.2% to 77.1%, others 64.4% to 72.8%, all $p<0.05$) improved in all readers.

Conclusion: While AI-CAD assistance helps improve the diagnostic performance of all inexperienced readers for thyroid nodules, self-learning was only effective for radiology residents with more background knowledge of ultrasonography.

Clinical Impact: Online self-learning, along with AI-CAD assistance, can effectively enhance the diagnostic performance of radiology residents in thyroid cancer.

KEYWORDS

thyroid cancer, artificial intelligence, ultrasound, learning, digital learning

Highlights

- **Key-finding:** Online self-learning with 3,000 cases improved the diagnostic performance of 26 inexperienced readers (0.679 vs 0.713, p=0.027). Results from an artificial intelligence-based computer-assisted diagnosis program improved it even more (0.713 vs 0.758, p=0.001)
- **Importance:** Online self-learning can improve the diagnostic performance of inexperienced readers from variable backgrounds, and performance can be further enhanced with artificial intelligence-based computer-assisted diagnosis software.

Introduction

The primary tool for diagnosing thyroid cancer is ultrasonography (US) (1–5). While US exhibits a high diagnostic accuracy, it is inherently operator-dependent and this necessitates appropriate training of related personnel to maintain the quality of examinations. Traditionally, US training isconducted through textbooks, lectures, or one-on-one education sessions between an educator and trainee. While the latter method has been effective, it also has notable disadvantages, such as putting a significant burden on educators and resources and an inability to guarantee a consistent quality of education (6).

Considerable experience is required to make accurate diagnoses with US, and the skill of examiners is known to correlate with the number of scans they have performed (7, 8). Thus, trainees need sufficient practice before performing examinations on people; not only is foundational knowledge of scan techniques or anatomy required but also preparation for actual "diagnosis" or "decision-making" is required. The diagnostic performance of inexperienced readers is known to improve through one-on-one training or structured training in the radiology department (9–11). Considering the pattern-based diagnosis of thyroid nodules in US, simple training with a large number of image examples combined with answers can be helpful when learning how to differentiate benign and malignant thyroid nodules. In a past study, deep learning software achieved similar diagnostic performance to expert radiologists based on 13,560 images (12), and in another, meaningful improvements in diagnostic performance were also observed in college students who had no previous experience in thyroid US, who went through learning sessions using a large training input of image-pathology sets (13).

With the development and commercialization of artificial intelligence-based computer-assisted diagnosis (AI-CAD) in thyroid imaging, potential improvements have been reported in diagnostic performance, particularly among readers with relatively limited experience (14–16). Thyroid Imaging Reporting and Data System (TI-RADS) is commonly used in the evaluation of thyroid nodules, and one study showed that an AI algorithm trained on TI-RADS characteristics outperformed another trained solely on distinguishing benign from malignant nodules (17). Furthermore, another study reported that an AI-proposed new TI-RADS criteria demonstrated superior specificity compared to the established American College of Radiology (ACR) TI-RADS (18). This underscores the potential of AI to enhance diagnostic protocols by leveraging structured reporting systems like TI-RADS. These advancements in AI-CAD not only support diagnostic precision but also provide crucial feedback during the learning phase, directly assisting beginner radiologists. We hypothesize that AI assistance can further aid beginner radiologists in diagnosing thyroid nodules after they undergo a self-learning process, ensuring more consistent and reliable diagnostic outcomes.

In this study, we investigated the value of self-learning and AI-CAD assistance in inexperienced readers.

Materials and methods

This study was approved by the Institutional Review Board of Severance Hospital and informed consent was obtained from all participants (No. 4–2022-1562).

Abbreviations: AI-CAD, artificial intelligence-based computer-assisted diagnosis; K-TIRADS, Korean Thyroid Imaging Reporting and Data System; AUC, area under the receiver operating characteristic curve; ICC, intraclass correlation coefficients.

Study design

Between February and August 2023, we recruited 26 inexperienced readers (less than 1 year of experience in thyroid US) from 6 hospitals. These participants were medical residents or fellows specializing in various departments including radiology, internal medicine, surgery, and family medicine. At first, readers were asked to watch a 5-minute online lecture (available via https://youtu.be/pnF5vUaIovI, Korean only) on K-TIRADS (Korean Thyroid Imaging Reporting and Data System classification (19) and perform a pretest consisting of 120 US images to make binary decisions (benign vs malignant) and assess K-TIRADS categories. Next, readers learned with a training set of 3,000 US images using an online platform, designed to consecutively display single nodule images, each accompanied by a binary diagnosis of benign or malignant. The platform allowed readers to adjust the playback speed according to their preferences. After completing the learning session, readers immediately repeated the same test as the pretest. Lastly, they underwent the test again, this time with AI assistance, using the SERA (SEveRance Artificial intelligence) program described in the following section. They were asked to complete training and testing within two weeks, and while the pace of online learning was adjusted to each individual, the readers had to record the time taken to study all 3,000 cases and the time spent on testing (Table 1).

Learning and test sets

We selected 3,000 images from 13,560 image sets utilized in a previous study (13). Images that demonstrated the most significant mean accuracy enhancement compared to earlier data points were selected, and these images made up Set 3 in the preceding study (13). The mean age of patients from whom the US images were derived for the learning set was 48.2 ± 13.8 years, and 81% of the patients were women. The mean size of the nodules was 20.0 ± 11.0 mm, with 49% being benign and 51% malignant, the latter of which 98.8% were identified as papillary thyroid carcinoma.

The test set, which was not included in the learning set, included 120 surgically confirmed thyroid nodules. The sample size for the test set was determined through estimations of the effect size, non-centrality parameters, denominator degrees of freedom, and power calculations. The mean age of patients from whom the US images were obtained for the test set was 43.7 ± 12.4 years, and 78.3% of the patients were women. The mean size of the nodules was 20.1 ± 9.4 mm. In terms of pathology, 48% of the nodules were benign and 52% were malignant, with a vast majority (93.5%) of the malignant nodules being classified as papillary thyroid carcinoma.

The standard reference of the test set for K-TIRADS assessment was consensus among the three experienced readers (5, 13, 23 years of experience in thyroid imaging). For reference, their intraclass correlation coefficient (ICC) was 0.908 (95% CI 0.876–0.933).

AI-CAD application

SERA is an online deep learning-based computer-aided diagnosis program trained with 13,560 US images of thyroid nodules that were surgically confirmed or cytologically proven as benign (category II) or malignant (category VI) on the Bethesda system and larger than 1cm in size (12). When users upload an US image cropped around the focal thyroid lesion according to user preference, SERA provides continuous numbers between 0 and 100, which correspond to the probability of the given test image being malignant (Figure 1). Since SERA presents results that are dependent on how images are cropped and which images are uploaded, the SERA scores are impacted by the initial judgments of users. In prior research, SERA showed comparable diagnostic performance to expert radiologists in an external validation set for diagnosing thyroid nodules (12).

Statistical analysis

Sensitivity, specificity, accuracy and area under the receiver operating characteristic curve (AUC) were used to assess the diagnostic performance of each inexperienced reader. Interobserver agreement was quantified by the ICC. A two-sample t-test was used to detect differences between groups, specifically readers of radiology against readers of other specialties. The paired t-test was used to assess changes in diagnostic performance within the same group throughout the training program.

All statistical analyses were performed using SPSS (version 26.0) and MedCalc 22.009 (MedCalc Software, Oostende, Belgium). A p-value of 0.05 or less was considered statistically significant.

TABLE 1 General information on the 26 inexperienced readers from 6 hospitals.

	Total (%)	Radiology department (n=18)	Other departments (n=8)	p-value
Department				
Radiology	18 (69.2)			
Internal medicine	2 (7.7)			
Surgery	2 (7.7)			
Family medicine	4 (15.4)			
Duration of previous thyroid US (month, SD)	2.3 ± 3.0	2.4 ± 2.6	2.4 ± 4.1	0.969
Time required for self-learning (min, SD)	222 ± 120	247 ± 140	165 ± 42	0.122
Time required for test with AI assistance (min, SD)	83 ± 59	83 ± 68	83 ± 41	0.990

Min, minute; SD, standard deviation; AI, artificial intelligence.

FIGURE 1
Image of the working process of the SERA program. When an US image is uploaded and cropped by the user, SERA presents the binary result (benign or malignant) with a malignant probability score. SERA, SEveRance Artificial intelligence program.

Results

Among 26 participants, 18 readers were radiology residents (1st and 2nd year), and the other 8 were 4 fellows in endocrinology and surgery and 4 residents in family medicine (3rd year). All 26 readers had none to little experience with thyroid US (range 0–10 months). The learning process for the 3,000 sets took an average of 222 minutes, and the test for the 120 sets utilizing AI assistance was completed in an average of 85 minutes (Table 1). There was no statistical difference in the duration of exposure between radiology residents and readers of other specialties (Table 1).

Changes in diagnostic performance after self-learning

After self-learning with 3,000 cases, 26 readers improved accuracy (68.0% vs 71.2%, p=0.037) and AUC (0.679 vs 0.713, p=0.027) compared to their pretest performance (Table 2).

We separated 18 readers of radiology residency from the remaining 8 readers, and the pretest results of the radiology residents showed higher specificity (73.8% vs 47.4%, p=0.04) (Table 3). After self-learning, the radiology residents improved accuracy (69.9% to 74.2%, p=0.013) and AUC (0.7 to 0.743, p=0.016), but readers of other departments did not. Also,

TABLE 2 Changes in the mean diagnostic performance of 26 readers during the learning program.

	Pretest	Posttest*	P-value†	AI-assistance	P-value‡
Sensitivity (%)	70.2 ± 15.7	69.6 ± 13.4	0.857	77.2 ± 8.7	0.002
Specificity (%)	65.7 ± 24.7	73.1 ± 20.0	0.126	74.3 ± 18.0	0.584
Accuracy (%)	68.0 ± 6.6	71.2 ± 6.4	0.037	75.8 ± 5.1	0.001
AUC	0.679 ± 0.07	0.713 ± 0.07	0.027	0.758 ± 0.06	0.001
ICC	0.575 ± 0.12	0.601 ± 0.13	0.104	0.590 ± 0.12	0.608

AI, artificial intelligence.
AUC, area under the receiver operating characteristic curve; ICC, intraclass correlation coefficients.
* after self-learning.
† Comparison between pretest and posttest.
‡ Comparison between posttest and test with AI assistance.

radiology residents showed better accuracy (74.2% vs 64.4%, p<0.001) and AUC (0.743 vs 0.647, p<0.001) than readers from other departments (Table 3, Figure 2).

Changes in diagnostic performance with AI assistance

For all readers, diagnostic performance improved more with AI assistance compared to posttest; sensitivity (69.6% vs 77.2%, p=0.002), accuracy (71.2% vs 75.8%, p=0.001) and AUC (0.713 vs 0.758, p=0.001) all improved (Table 2). In the radiology group, sensitivity increased from 70.3% to 74.9% (p=0.023), and accuracy from 74.2% to 77.1% (p=0.046). In the other departments group, sensitivity increased from 67.9% to 82.3% (p=0.024), accuracy from 62.4% to 72.8% (p=0.007), and AUC from 0.647 to 0.725 (p=0.006). Final sensitivity, specificity, accuracy and AUC were not statistically different between the two groups (Table 3, Figure 2).

Changes in K-TIRADS assessment

When we calculated the ICC for K-TIRADS assessment in consensus with the three staff radiologists, the overall ICC for K-TIRADS assessment did not significantly change during self-learning (0.575 vs 0.601). In the subgroup analysis, the ICC of radiology residents was higher than the other department readers in the pretest (0.615 vs 0.485, p=0.002). However, the ICC of readers from other departments increased after self-learning, The ICC showed no statistical difference between the two groups after self-learning (0.621 vs 0.557, p=0.203) (Table 3). The ICC value for each reader before and after self-learning is shown in Supplementary Table 1.

Discussion

In this study, we investigated the effectiveness of online-based self-learning for diagnosing thyroid cancer in 26 inexperienced readers from six different hospitals from diverse specialties.

TABLE 3 Changes in the mean diagnostic performance of 26 readers during the learning program compared between radiology residents and readers of other specialties.

	Pretest	Posttest*	P-value†	AI-assistance	P-value‡
Sensitivity (%)					
Radiology	66.1 ± 14.4	70.3 ± 9.1	0.125	74.9 ± 7.8	0.023
Other	79.2 ± 18.3	67.9 ± 20.9	0.145	82.3 ± 9.0	0.024
P-value§	0.067	0.763		0.069	
Specificity (%)					
Radiology	73.9 ± 18.3	78.3 ± 14.4	0.323	79.5 ± 13.4	0.637
Other	47.4 ± 28.6	61.4 ± 26.5	0.273	62.7 ± 22.4	0.795
P-value§	0.04	0.129		0.08	
Accuracy (%)					
Radiology	69.9 ± 5.4	74.2 ± 4.9	0.013	77.1 ± 3.9	0.046
Other	63.9 ± 7.4	64.4 ± 3.7	0.862	72.8 ± 6.5	0.007
P-value§	0.066	<0.001		0.115	
AUC					
Radiology	0.7 ± 0.06	0.743 ± 0.51	0.016	0.772 ± 0.04	0.053
Other	0.633 ± 0.08	0.647 ± 0.38	0.671	0.725 ± 0.07	0.006
P-value§	0.059	<0.001		0.111	
ICC					
Radiology	0.615 ± 0.11	0.621 ± 0.14	0.771		
Other	0.485 ± 0.07	0.557 ± 0.1	0.008		
P-value§	0.002	0.203			

AI, artificial intelligence.
AUC, area under the receiver operating characteristic curve; ICC, intraclass correlation coefficients.
* after self-learning.
† Comparison between pretest vs. posttest.
‡ Comparison between posttest vs. with AI assistance.
§ Comparison between residents in radiology vs. readers of other specialties.

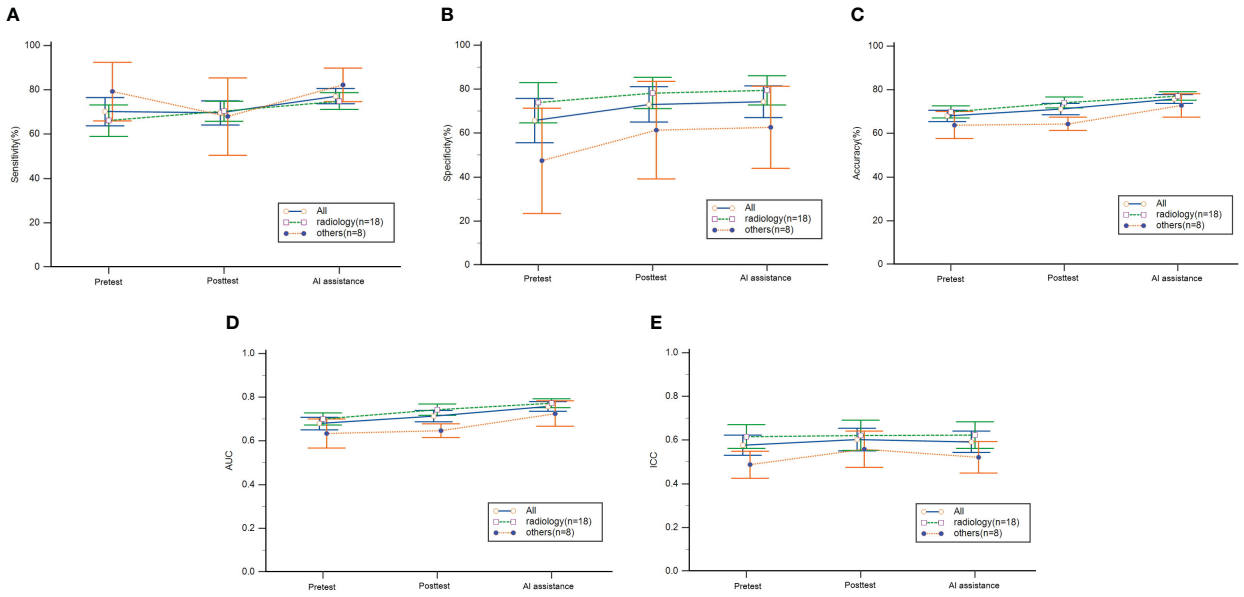

FIGURE 2
Mean diagnostic performance of readers during the learning program. **(A)** sensitivity, **(B)** specificity, **(C)** accuracy, **(D)** AUC and **(E)** ICC with 95% confidence intervals. The pretest was performed before self-learning and the posttest was performed after self-learning. AI, artificial intelligence; AUC, area under the receiver operating characteristic, ICC, intraclass correlation coefficients.

Furthermore, we examined the impact of AI assistance on their diagnostic performance for thyroid nodules. After training with a set of 3,000 images, both AUC and accuracy improved for all readers on average, and AI assistance further enhanced these metrics.

Previously, a similar method of self-learning was proposed with 13,560 images being learned by six college freshmen (13). The six freshmen also showed improved sensitivity, specificity, accuracy, and AUC. However, it took an average of 30 hours for these freshmen to learn with 13,560 images (13), and viewing 13,560 images at a specific learning location for this amount of time poses considerable challenges in real life. In this study, we provided 3,000 images and all training was executed via an online platform, enabling participants to learn in their personal space at their convenience and record their results subsequently. In our study, we trained individuals with little to no experience in thyroid US but found that those more likely to benefit from training were radiology residents, family medicine residents, endocrinology fellows, and surgery fellows. On average, our participants took a mean of 222 minutes to learn from the 3,000 images, and this training led to increase in accuracy and AUC.

When we performed a subgroup analysis according to the medical department, the benefit of digital self-learning was only significant in radiology residents. Although there was no statistical difference in the recorded duration of exposure in the learning session between the radiology and other department groups, radiology residents are continuously exposed to images and cases through lectures and conferences during their training. This aspect of learning is likely to differentiate them from readers from other medical specialties. For groups less familiar or exposed to US images or radiological diagnostics, self-learning with 3,000 images may simply not be enough to achieve significant increase in diagnostic accuracy. Given the variation in outcomes across different specialties, incorporating detailed explanations for correct or incorrect answers during the self-learning phase could potentially enhance understanding and retention, particularly for those less familiar with ultrasound imaging. This method could mirror more interactive learning approaches found in question banks, which have been shown to improve diagnostic skills by reinforcing learning points through immediate feedback.

After the self-learning process, the final test performance with AI-CAD assistance showed additional increases in sensitivity, AUC, and accuracy. Previous research has well-documented the increased advantage that AI-CAD offers to beginners in US (12, 20–24). AI-CAD appears to supplement self-learning by offering direct assistance on specific cases, rather than just amplifying the learning effect. Unlike digital self-learning, AI-CAD assistance was effective for all readers, regardless of whether they were from the radiology department or others.

Additionally, as K-TIRADS is predominantly used for image interpretation in Korea, we also sought to ascertain whether the self-learning program had an impact on K-TIRADS assessment. Although the overall ICC for K-TIRADS assessment did not improve with self-learning, the ICC of readers from other specialties increased to the ICC of radiology residents. While such categorical assessments are known to have high interobserver variability (25), if we take into consideration that our standard reference group of experienced readers had an ICC of 0.908, we can assume that K-TIRADS assessments by inexperienced readers need further calibration. The challenges of these assessments appear hard to overcome with image-diagnosis set training.

Our study was conducted entirely on an online platform, enabling participants to learn at their own pace and schedule.

This approach facilitated the recruitment of participants from hospitals located in diverse regions. One major advantage of online learning is its ability to reduce the burden on instructors, offer flexibility in terms of time and location, and provide consistent education to a broad audience (26). The proliferation of online learning, especially post-COVID, means that learners today have a strong propensity for web- and social media-based curricula (27, 28). However, US education isn't just about gaining knowledge; it encompasses the development of psychomotor skills, visual perception for image acquisition, interpretation, and integration into medical decision-making (29). While our online self-learning can address some of these aspects, we anticipate it being particularly effective as a preparatory step to enhance diagnostic performance and boost confidence before trainees handle real clinical situations.

Similarly, AI-based diagnostic augmentation has shown comparable trends in improving diagnostic performance across other medical fields such as dermatology, cardiology, and oncology, where it enhances accuracy and aids less experienced practitioners. The success of these applications suggests that the learning methods employed in our study could potentially be adapted to these fields. In line with expanding our understanding of AI's utility in medical training, further research could involve testing readers of different experience levels, including senior radiology residents, fellows, and junior faculty. Such studies would help ascertain if even more senior readers can benefit from AI, potentially broadening the scope of AI tools in supporting ongoing professional development and decision-making processes across various stages of a medical career.

There are some limitations to our study. First, since our approach was entirely based on online learning and testing, we had limited control over the learning process. Although we restricted the learning period to two weeks, outcomes might differ between participants who studied intensively and those who learned sporadically. Second, we assessed the overall effects on 26 learners from various medical departments, but the standard deviation of performance due to their different specialty backgrounds was substantial, especially for readers from other specialties than radiology. This variability makes it challenging to achieve statistical significance. Third, we evaluated performance based on binary diagnoses, which may seem overly simplistic. Finally, although we provided a set of 3000 cases for the one-time self-learning session, repetitive training might change the results.

In conclusion, In conclusion, our study demonstrated that while AI-CAD assists all inexperienced readers in improving diagnostic performance for thyroid nodules, the effectiveness of self-learning appears more pronounced in radiology residents, likely due to their prior ultrasonography knowledge. Further studies could explore its impact on other non-radiologist groups.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethical Review Board of Severance Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SL: Data curation, Methodology, Writing – original draft, Writing – review & editing. HK: Data curation, Methodology, Writing – review & editing. HJ: Data curation, Writing – review & editing. JJ: Data curation, Writing – review & editing. JJ: Data curation, Writing – review & editing. JL: Data curation, Writing – review & editing. HH: Methodology, Visualization, Writing – review & editing. EL: Formal analysis, Software, Writing – review & editing. DK: Formal analysis, Software, Writing – review & editing. JK: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1372397/full#supplementary-material

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Development of a novel dynamic nomogram for predicting overall survival in anaplastic thyroid cancer patients with distant metastasis: a population-based study based on the SEER database

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Background: Anaplastic thyroid cancer (ATC) is highly invasive, prone to distant metastasis (DM), and has a very poor prognosis. This study aims to construct an accurate survival prediction model for ATC patients with DM, providing reference for comprehensive assessment and treatment planning.

Methods: We extracted data of ATC patients with DM diagnosed between 2004 and 2019 from the SEER database, randomly dividing them into a training set and a validation set in a ratio of 7:3. Univariate and multivariate Cox regression analyses were sequentially performed on the training set to identify independent prognostic factors for overall survival (OS) and construct nomograms for 3-month, 6-month, and 8-month OS for ATC patients with DM based on all identified independent prognostic factors. Receiver operating characteristic (ROC) curve analysis, decision curve analysis (DCA) curve analysis, and calibration curves were separately plotted on the training and validation sets to demonstrate the model's performance. Furthermore, patients were stratified into high- and low-risk groups based on their risk scores, and the Kaplan-Meier (KM) survival curves were used to illustrate the survival differences between the two groups.

Results: A total of 322 patients were included in this study. Univariate and multivariate Cox regression analyses identified five independent prognostic factors for OS in ATC patients with DM: surgery, tumor size, age, chemotherapy, and radiotherapy. Nomograms for 3-month, 6-month, and 8-month OS were established based on these factors. The training set AUC values (3-month AUC: 0.767, 6-month AUC: 0.789, 8-month AUC: 0.795) and validation set AUC values (3-month AUC: 0.753, 6-month AUC: 0.798, 8-month AUC: 0.806) as well as the calibration curves demonstrated excellent applicability and accuracy of the model. Additionally, the DCA curves indicated substantial clinical net benefit of the model. The KM curves also confirmed the model's excellent stratification ability for patient OS.

Conclusion: The nomogram developed in this study accurately predicts OS for ATC patients with DM. It can assist clinicians in formulating appropriate treatment strategies for these patients.

KEYWORDS

anaplastic thyroid cancer, distant metastasis, SEER, overall survival, nomogram

1 Introduction

Anaplastic thyroid cancer (ATC) is a rare but highly aggressive malignancy (1). Although it accounts for less than 2% of all types of thyroid cancer, it contributes to more than 50% of the annual mortality rate associated with thyroid cancer (2, 3). The median survival time for ATC is approximately four months (4), and the disease-specific mortality rate ranges from 98% to 99% (5, 6). The most notable clinical feature of ATC is its high invasiveness, which leads to local infiltration and metastasis to regional lymph nodes or distant organs (7). Around 50% of ATC patients are diagnosed with distant metastasis (DM) at the time of diagnosis (8, 9), resulting in a significantly worse prognosis. Current treatment options for ATC patients with DM mainly include surgery, radiotherapy, and chemotherapy (10). The selection of precise treatment strategies for individual patients relies on their comprehensive systemic evaluation and survival prediction. Given the highly malignant nature and rapid disease progression of this condition, it is crucial to develop appropriate assessment tools for ATC patients with DM to facilitate accurate management planning.

Although previous studies have contributed some practical clinical prediction tools (11–13), these tools encompassed all ATC patients. However, patients with ATC and DM often exhibit distinct clinical characteristics and biological behaviors compared to the overall population, representing a significant proportion of all ATC patients. Therefore, there is an urgent need to establish a precise clinical prediction tool specifically tailored to ATC patients with DM.

In this study, we included multicenter patient data from the Surveillance, Epidemiology, and End Results (SEER) database to evaluate independent prognostic factors influencing overall survival (OS) in ATC patients with DM. We constructed a nomogram to predict OS for this patient population and confirmed the excellent performance of the model through a series of evaluation metrics.

2 Materials and methods

2.1 Data source

The patient cohort for this study was derived from ATC patients with DM diagnosed between 2004 and 2019 in the SEER database. The clinical information of all patients was extracted from the SEER Cancer Database (http://www.seer.cancer.gov) using SEER*Stat software (https://seer.cancer.gov/seerstat/, version 8.4.2). As patient data in the SEER database is de-identified, local ethical review was not required for this study.

2.2 Patient selection criteria

The inclusion criteria for the patient cohort in this study were as follows: (1) primary tumor site in the thyroid; (2) histological diagnosis codes according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) as 8020/3 and 8021/3; (3) presence of distant metastasis, classified as stage IVC according to the eighth edition of the AJCC. Patients meeting any of the following criteria were excluded from this study: (1) cases provided by autopsy or death reports; (2) survival time of 0; (3) missing clinical information. All radiotherapeutic modalities involved in this study were external beam radiation therapy.

2.3 Statistical analysis

Considering the extremely high disease-specific mortality rate in the study population and the potential side effects of treatments such as radiation and chemotherapy, OS was chosen as the study endpoint. Firstly, all patients were randomly divided into training and validation sets in a 7:3 ratio, and the Chi-square/Wilcoxon test confirmed no statistical differences in baseline clinical characteristics between the two sets. Subsequently, univariate Cox regression analysis and multivariate Cox regression analysis were performed in the training set to determine the independent prognostic factors for OS in ATC patients with DM. A nomogram was constructed based on the selected independent risk factors. To evaluate the accuracy and clinical utility of the nomogram, receiver operating characteristic (ROC) curves, decision curve analysis (DCA) curves, and calibration curves were simultaneously plotted in both the training and validation sets. The ROC curve was used to assess the accuracy and recall of the model; the DCA curve was used to evaluate the clinical net benefit; the calibration curve was used to assess the prediction accuracy and consistency of the model. Risk scores for each patient were

calculated based on the model, and patients were stratified into high- and low-risk groups using the median risk score. The Kaplan-Meier (KM) survival curves were employed to demonstrate the model's ability to stratify patient prognosis. Finally, a web-based dynamic nomogram was published for readers' use. All statistical analyses and visualizations in this study were performed using R software (version 4.3.1). A two-sided P value <0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

This study assimilated 322 qualified patients afflicted with ATC, with a median survival duration of three months. The Kaplan-Meier survival plot pertaining to the patient cohort in this investigation, juxtaposed with ATC sufferers devoid of distant metastasis, is demonstrated in Figure 1 (Figure 1). As shown in Table 1, all patients in the study cohort had advanced T stage (T3a and above), with the majority of patients classified as T4b (72.4%). Similarly, the majority of patients had lymph node metastasis, with N1b being the most common stage (56.8%). Most patients received surgical treatment (48.1%), chemotherapy (51.2%), and radiotherapy (63.4%). The mean age for all patients stands at 68.2 (± 12.1). All patients were randomly allocated to the training and validation sets in a 7:3 ratio, and there were no statistically significant differences in clinical variables between the two groups (p>0.05, Table 1).

3.2 Prognostic factors for ATC patients with DM

To explore potential clinical prognostic factors associated with OS in ATC patients with DM, we performed univariate Cox regression analysis on nine potential factors, revealing five variables significantly associated with OS: age, tumor size, surgery, chemotherapy, and radiotherapy. Further multivariate Cox regression analysis (Table 2) demonstrated that age, tumor size, surgery, chemotherapy, and radiotherapy were independent prognostic factors for OS in ATC patients with DM. Specifically, chemotherapy (OR=0.622, 95%CI=0.469-0.826), and radiotherapy (OR=0.739, 95%CI=0.550-0.994) were protective factors for patient OS. However, T stage and N stage were not independent prognostic factors for OS (P>0.05).

3.3 Prognostic nomogram development and validation

Based on the Cox regression analysis results of the five independent prognostic factors, we constructed a nomogram for predicting 3-month, 6-month, and 8-month OS in ATC patients with DM (Figure 2A). Each predictive variable was assigned a specific score based on its position on the corresponding scale, and the cumulative sum of all "points" yielded the "total points," which could be further converted into the probability of death at a specific time point for a particular patient. We also provided a demonstration of survival prediction using randomly selected patient data (Figure 2B). Additionally, we published an online dynamic nomogram (https://jzxwlh.shinyapps.io/DynNomapp/) (Figure 3).

We plotted ROC curves in both the training and validation sets to evaluate the sensitivity and specificity of the model. The results showed that the model achieved AUC values of 0.767, 0.789, and 0.795 for 3-month, 6-month, and 8-month OS, respectively, in the training set (Figure 4A), and AUC values of 0.753, 0.798, and 0.806 for 3-month, 6-month, and 8-month OS, respectively, in the validation set (Figures 4A, B), confirming the excellent accuracy of the model. Calibration curves (Figure 5) and DCA curves (Figure 6) were plotted in both the training and validation sets. The calibration

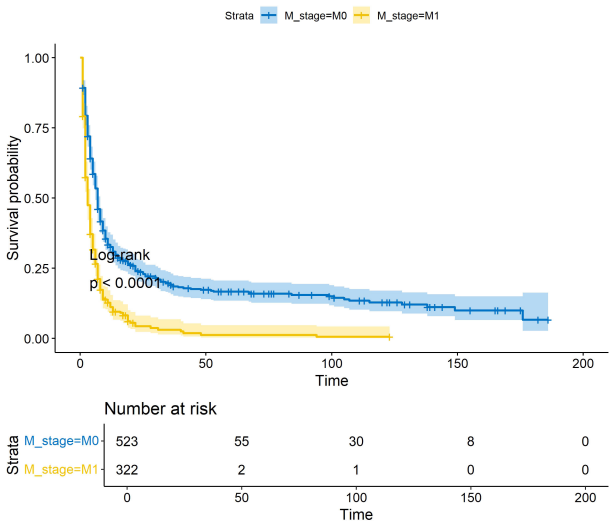

FIGURE 1
KM survival curves for OS in ATC patients with/without distant metastases. * p<0.05; ** p<0.01; *** p<0.001.

TABLE 1 Demographic and clinicopathological characteristics of ATC patients with distant metastases.

	Overall (N=322)	Training cohort (N=225)	Validation cohort (N=97)	p-value
Age				0.727
Mean (SD)	68.3 (12.1)	68.2 (11.9)	68.4 (12.7)	
Median [Min, Max]	69.0 [23.0, 92.0]	69.0 [35.0, 92.0]	69.0 [23.0, 89.0]	
Sex				0.828
Female	168 (52.2%)	116 (51.6%)	52 (53.6%)	
Male	154 (47.8%)	109 (48.4%)	45 (46.4%)	
Race				0.586
White	255 (79.2%)	179 (79.6%)	76 (78.4%)	
Black	23 (7.1%)	14 (6.2%)	9 (9.3%)	
Other	44 (13.7%)	32 (14.2%)	12 (12.4%)	
T stage				0.288
T3a	11 (3.4%)	8 (3.6%)	3 (3.1%)	
T3b	12 (3.7%)	7 (3.1%)	5 (5.2%)	
T4a	66 (20.5%)	52 (23.1%)	14 (14.4%)	
T4b	233 (72.4%)	158 (70.2%)	75 (77.3%)	
N stage				0.744
N0	99 (30.7%)	69 (30.7%)	30 (30.9%)	
N1a	40 (12.4%)	30 (13.3%)	10 (10.3%)	
N1b	183 (56.8%)	126 (56.0%)	57 (58.8%)	
Surgery				0.916
No	167 (51.9%)	115 (51.1%)	52 (53.6%)	
Lobectomy/Isthmectomy	51 (15.8%)	36 (16.0%)	15 (15.5%)	
Subtotal/ total thyroidectomy	104 (32.3%)	74 (32.9%)	30 (30.9%)	
Tumor size				0.960
Mean (SD)	64.1 (27.8)	63.8 (26.6)	64.7 (30.6)	
Median [Min, Max]	64.5 [2.00, 165]	64.0 [2.00, 152]	65.0 [3.00, 165]	
Chemotherapy				0.770
No	157 (48.8%)	108 (48.0%)	49 (50.5%)	
Yes	165 (51.2%)	117 (52.0%)	48 (49.5%)	
Radiotherapy				0.810
No	118 (36.6%)	81 (36.0%)	37 (38.1%)	
Yes	204 (63.4%)	144 (64.0%)	60 (61.9%)	

curves visually demonstrated the accurate performance of the nomogram in predicting OS at different time points, while the DCA curves confirmed the outstanding performance of the nomogram in real clinical practice. KM survival curves (Figure 7) illustrated the model's excellent stratification ability for patient OS in both the training and validation sets.

4 Discussion

Despite the low incidence of ATC, its highly aggressive nature and poor prognosis have attracted increasing attention from scholars (14). Current mainstream treatment modalities for ATC patients include surgery, chemotherapy, radiotherapy, and other

TABLE 2 Univariate and multivariate Cox analyses in ATC patients with distant metastases.

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P
Age	1.019	1.007-1.031	0.001*	1.013	1.001-1.025	0.031*
Sex						
Female	Reference					
Male	1.133	0.858-1.496	0.381			
Race						
White	Reference					
Black	1.028	0.582-1.816	0.924			
Other	1.131	0.766-1.671	0.535			
T stage						
T3a	Reference					
T3b	0.347	0.101-1.185	0.091			
T4a	0.660	0.297-1.466	0.307			
T4b	0.885	0.415-1.891	0.753			
N stage						
N0	Reference					
N1a	0.705	0.439-1.132	0.148			
N1b	1.334	0.983-1.810	0.064			
Surgery						
No	Reference					
Lobectomy/ Isthmectomy excision	0.567	0.382-0.841	0.005*	0.664	0.445-0.993	0.046*
Subtotal/total thyroidectomy	0.517	0.375-0.712	<0.001*	0.624	0.448-0.869	0.005*
Chemotherapy						
No	Reference					
Yes	0.557	0.422-0.735	<0.001*	0.622	0.469-0.826	0.001*
Radiotherapy						
No	Reference					
Yes	0.619	0.465-0.823	<0.001*	0.739	0.550-0.994	0.045*
Tumor size, mm	1.012	1.007-1.018	<0.001*	1.011	1.006-1.017	<0.001*

* p<0.05, statistically significant.

comprehensive treatments. However, the prognosis for ATC patients remains unfavorable (15). Therefore, it is crucial to actively study and explore prognostic factors in ATC patients to assess their risk. In this study, we focused on ATC patients with DM and utilized multicenter data from the SEER database to thoroughly investigate the independent prognostic factors in ATC patients with DM. We also developed a nomogram to assist in determining optimal treatment strategies for these patients. To the best of our knowledge, this study is the first multicenter retrospective study to construct a prognostic model specifically for ATC patients with DM. We further confirmed the excellent performance of the model through a series of evaluation metrics.

Thyroid cancer is the only cancer that considers age as an important prognostic factor for thyroid cancer-specific survival. Similarly, in our study, we observed a similar phenomenon where patients over 75 years of age had significantly worse prognosis compared to other age groups. Our constructed nomogram vividly illustrates this point, where older patients receive higher risk scores. Additionally, we found that larger tumor diameter was directly associated with poorer prognosis. Previous studies have highlighted

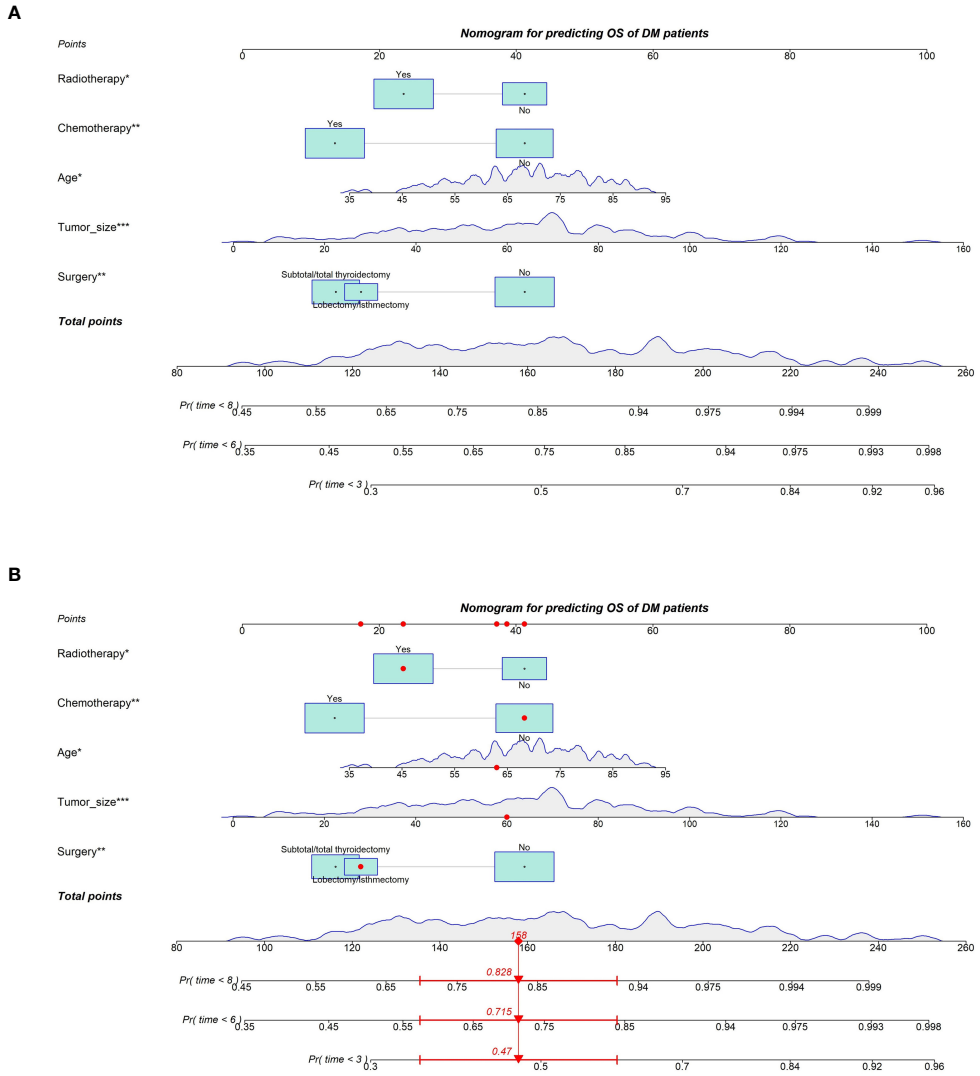

FIGURE 2
Prognostic nomogram predicting OS at 3, 6 and 8 months in SIC ATC patients with distant metastases **(A)**. Schematic of patient application model for prediction **(B)**.

the importance of tumor diameter differences in determining invasiveness (13), but specific research on the relationship between tumor diameter, distant metastasis, and prognosis in ATC is still lacking.

In our study cohort, we were surprised to discover that unlike most tumors, the extent of primary tumor infiltration and regional lymph node metastasis were no longer independent prognostic factors for ATC patients with DM. Instead, surgery, chemotherapy, and radiotherapy were identified as independent prognostic factors. Similar findings have been reported in previous studies (13). We speculate that this is due to the highly invasive nature of ATC, resulting in the majority of ATC patients with DM being diagnosed at an advanced stage where the status of the primary tumor no longer significantly influences patient prognosis.

Furthermore, we noted that various treatment modalities were independent prognostic factors for OS in ATC patients with DM. This emphasizes the importance of actively receiving treatment after diagnosis to prolong patient survival. Previous research has shown that although surgery is indeed a protective factor for patient OS, it is not sufficient to improve long-term prognosis significantly, leading to ongoing debates regarding the extent of the benefits of surgical treatment (16, 17). The guidelines of the American Thyroid Association (18) explicitly state that the surgical goal for patients with ATC at stages IVA/IVB is to perform a resection of all macroscopically visible tumor (R0 or R1) rather than debulking (R2 resection). Additionally, they mention that a subset of patients at stage IVC may consider surgery to control local disease and alleviate or prevent future complications (for instance, impending airway invasion/obstruction, esophageal invasion/obstruction, laryngeal invasion/obstruction), albeit without elaborating in detail on specific surgical recommendations. In this study, we observed superior overall survival (OS) in patients with stage IVC ATC who underwent total/subtotal thyroidectomy compared to those who had only lobectomy/isthmectomy or didn't undergo surgery. Thus, based on our analysis, we posit that debulking surgery targeting the primary tumor can enhance patients' OS to

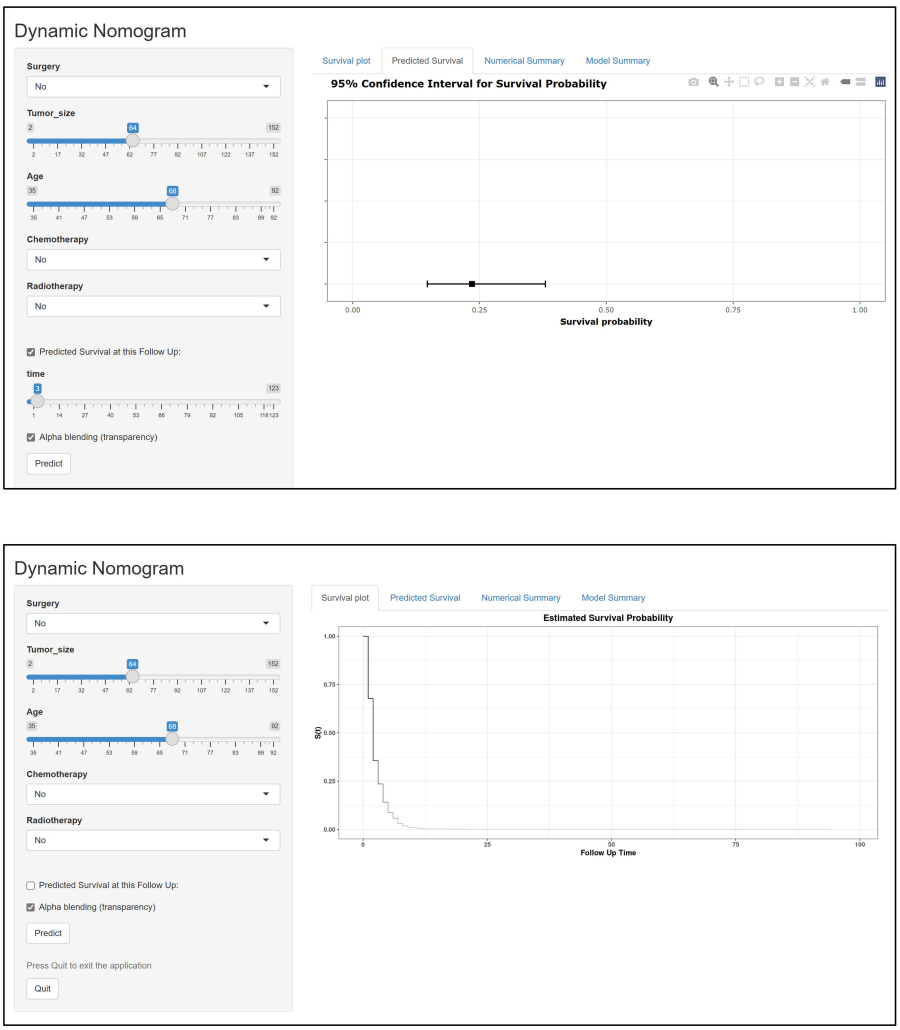

FIGURE 3
Schematic diagram of the interface for using the web version of the dynamic prediction model.

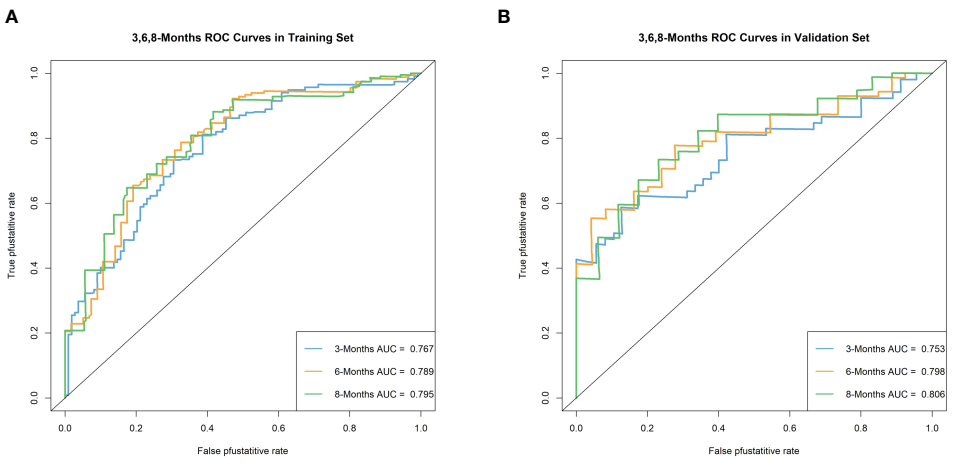

FIGURE 4
Time-dependent ROC curve analysis of the OS nomogram for the 3-, 6-, and 8-month in the training set **(A)** and the validation set **(B)**.

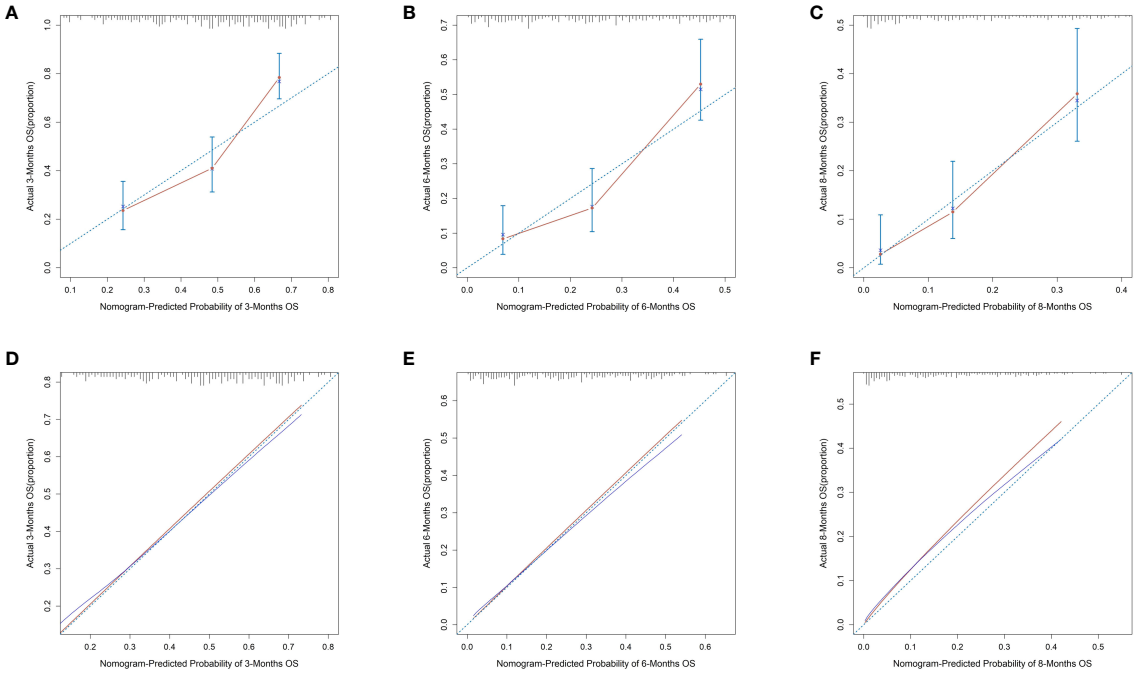

FIGURE 5
Calibration curves for 3-, 6-, and 8-month OS prediction nomogram in the training set **(A–C)** and validation set **(D–F)**.

some extent. Concurrently, guidelines from the American Thyroid Association also indicate that radical surgeries (including laryngectomy, tracheotomy, esophagectomy and/or major vascular or mediastinal resection) are generally not recommended due to the poor prognosis of ATC. Such procedures can be selectively contemplated only after comprehensive discussions within a multidisciplinary team, considering factors including patient mutation targets.

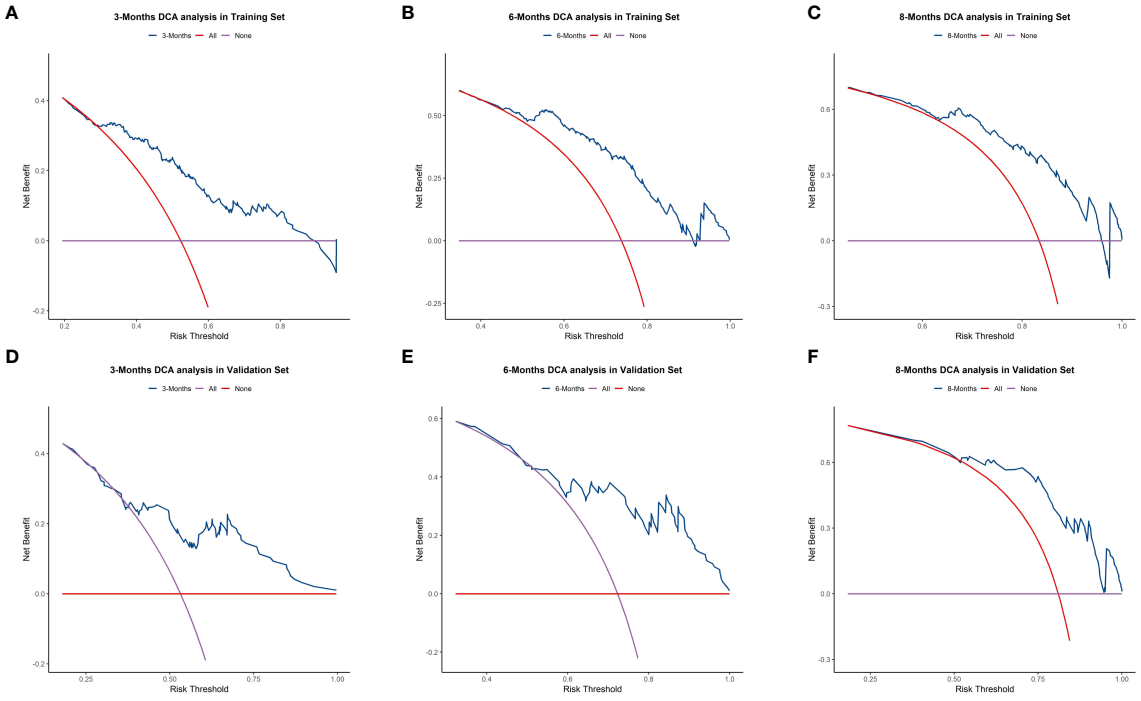

FIGURE 6
Decision Curve Analysis (DCA) curves for 3-, 6-, and 8-month OS prediction nomogram in the training set **(A–C)** and validation set **(D–F)**.

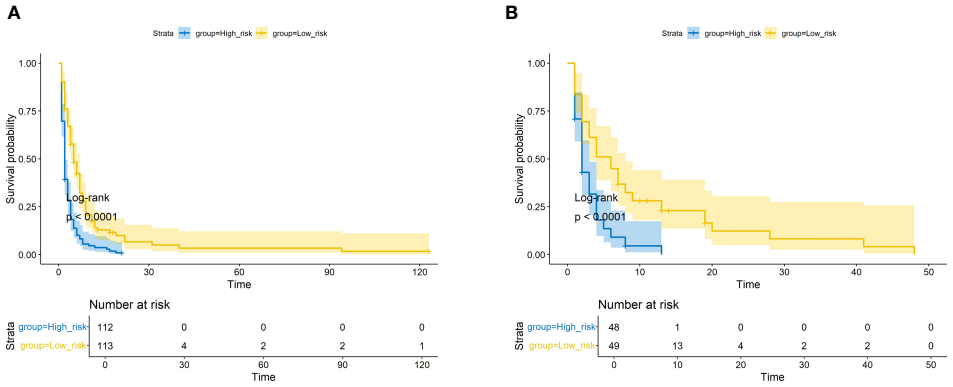

FIGURE 7
The Kaplan–Meier survival curves of the patients in the training set **(A)** and in the validation set **(B)**.

In our study, radiotherapy was found to be the most commonly used treatment modality for ATC patients with DM. According to previous literature, a radiation dose of at least 50 Gy is required to significantly improve patient prognosis (19, 20), and Pezzi et al (21) found that patients receiving radiation doses of 60-75 Gy had better survival rate improvements compared to those receiving lower doses. The NCCN guidelines recommend an adjuvant radiation dose of 60-66 Gy (14). Due to the low incidence and high invasiveness of ATC, patient enrollment in clinical trials evaluating various chemotherapy agents is extremely limited, leading to incomplete evaluation of chemotherapy efficacy in ATC (22). Regarding comprehensive treatments, many previous studies have consistently suggested that surgical treatment combined with adjuvant chemoradiotherapy can effectively improve OS in ATC patients (23, 24), aligning with our study results. However, some studies have found that while concurrent chemoradiotherapy and/or chemotherapy can improve survival rates in stage IVA/B ATC patients, the benefit is limited in stage IVC patients (25). Nevertheless, our study found that stage IVC patients who actively pursued various treatment options had significantly better prognoses than those who did not receive any treatment. Therefore, despite generally poorer prognoses for stage IVC ATC patients, we still advocate for their active treatment. Additionally, there is a pressing need for new treatment strategies to improve the prognosis of late-stage ATC patients.

In recent years, targeted therapy and immunotherapy for ATC have garnered increasing attention. Currently, BRAF mutation is identified as the most common somatic mutation in ATC. The drugs Dabrafenib and Trametinib, targeting BRAF and MEK1/2 respectively, work by inhibiting tumor cell proliferation through disruption of the RAF-MEK-ERK signaling pathway. Clinical studies suggest that the confirmed overall response rate to combined Dabrafenib and Trametinib therapy stands at 69%, with independently reviewed results corroborating this finding. This validates the significant clinical efficacy of combined Dabrafenib and Trametinib therapy in patients with BRAF V600E-mutant ATC (26, 27). Immunotherapy for ATC is still in the experimental stage; however, immune checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated antigen 4 and PD-1/PD-L1 have shown promising clinical efficacy (28, 29). Unfortunately, ATC patient data on targeted/immunotherapies are not recorded in the SEER database, limiting our ability to conduct detailed analyses or incorporate these treatment variables into predictive models.

Of course, we must acknowledge certain limitations of our study. Firstly, as a retrospective analysis, we excluded patients with missing clinical information, which may introduce some selection bias. Secondly, although we included multicenter patient data spanning over a decade, the limited incidence of ATC with DM resulted in an inadequate number of patients in our study. Furthermore, as the SEER database does not include information regarding chemotherapy regimens, radiation dosage, and targeted/immunotherapy treatments, our predictive model did not take these factors into consideration. Lastly, we lack external validation sets to further validate the model. We hope that future researchers can include a larger number of patient data to further enhance our current research findings.

5 Conclusion

In this study, we identified the independent prognostic factors for OS in ATC patients with DM through univariate and multivariate Cox regression analysis. We developed a nomogram based on these factors and also released an online version of the dynamic nomogram. Furthermore, we demonstrated the excellent performance of the model through a series of evaluation metrics.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

Author contributions

LW: Conceptualization, Software, Writing – original draft. YR: Methodology, Visualization, Writing – original draft. PL: Software, Visualization, Writing – original draft. YL: Data curation, Funding acquisition, Investigation, Software, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1375176/full#supplementary-material

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Clinicopathological features affecting the efficacy in ^{131}I ablation therapy of papillary thyroid carcinoma with lymph node metastasis

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Background: Lymph node metastasis is the major cause of increased recurrence and death in patients with papillary thyroid carcinoma (PTC). We evaluate the clinicopathologic factors affecting excellent response (ER) in patients with PTC with lymph node metastasis following operation and ^{131}I ablation therapy.

Methods: A total of 423 patients with PTC with lymph node metastasis who underwent thyroidectomy and postoperative ^{131}I ablation therapy were enrolled. The relationship between clinicopathological factors affecting ER achievement was analyzed.

Results: Multivariate analysis showed that the foci diameter (≤1 cm), unifocal, combination with Hashimoto's thyroiditis (HT), lymph node metastases rate (LR) (≤40%), no postoperative lymph node metastasis, low preablative stimulated thyroglobulin (ps-Tg) level (≤3.87 ng/mL), and the time of ^{131}I ablation therapy (one time) were positively correlated with the ER achievement [odds ratio (OR): 1.744, 3.114, 3.920, 4.018, 2.074, 9.767, and 49.491, respectively; all $p < 0.05$]. The receiver operating characteristic (ROC) curves showed that the cutoff values of ps-Tg and LR were 4.625 ng/mL and 50.50%, respectively. The AUC of ROC of ps-Tg and LR for predicting ER achievement was 0.821 and 0.746, respectively. The Tg and the cumulative risk of non-ER elevated with the increase of LR, especially for the high-level ps-Tg (>4.625 ng/mL) group.

Conclusion: The foci diameter and number, combination with HT, LR, and ps-Tg level are independent factors for ER. Ps-Tg level and LR are valid predictive factors for the efficacy of ^{131}I therapy in patients with PTC. The predictive value of the cumulative risk of non-ER can be improved by the combination of ps-Tg and LR.

KEYWORDS

Papillary thyroid carcinoma (PTC), lymph node metastasis, ^{131}I ablation, excellent response (ER), cumulative risk

1 Introduction

The incidence of papillary thyroid carcinoma (PTC) has increased over the past decades. The disease-related mortality is relatively low (<5%), but the recurrence rate reaches 30% (1). The rate of lymph node metastasis is approximately 20%–90% (1, 2), which is the major cause of recurrence and death in PTC (3). Relapse and prognosis of PTC depend on genetic and environmental interactions, including clinicopathological factors and genetic characteristics, particularly BRAF and TERT promoter mutations (4) and germline polymorphisms in the VEGF pathway (5). The synergistic prognostic effect between BRAF mutations and clinicopathological features has been identified. In addition, Marotta et al. also demonstrated that germline polymorphism of the VEGF pathway is a predictor of recurrence of non-advanced differentiated thyroid cancer (DTC) (4). Therefore, the 2015 American Thyroid Association (ATA) guidelines suggest a personalized non-categorical model including a wider range of variables to fit individual features (4, 6). The assessment of recurrence and prognosis of PTC relies on dynamic evaluation. Predictors with robust positive predictive value (PPV) are needed to elevate the PTC recurrence. Previously, the prediction of recurrence and mortality risk was mostly based on postoperative pathological features. However, because of the limitations of using pathological features alone, the ATA Guidelines for the first time proposed the response-to-therapy assessment system (RTAS) to assess the prognosis by monitoring thyroglobulin (Tg) and imaging examinations after ^{131}I ablation (6). Studies suggest that the recurrence rate of patients with PTC with excellent response (ER) in the system is only 1%–4%, and the risk of tumor-related death is less than 1% (7), indicating that ER patients have a better prognosis.

Recent studies have shown that several clinicopathologic features may affect ER (8–10). However, those results are not consistent, and there is no clear optimal cutoff value as an indicator to predict ER and support treatment decision-making (8–10). Therefore, in this study, we investigated the potential impact of clinicopathologic features on ER after ^{131}I ablation in patients with PTC with lymph node metastasis and evaluated the predictive value for ER and the cumulative risk of non-ER.

2 Participants and methods

2.1 Study design

A total of 423 patients with PTC who underwent total thyroidectomy and postoperative ^{131}I ablation at the Affiliated Hospital of Qingdao University from January 2017 to October 2020 were enrolled. The inclusion criteria were as follows: (1) patients aged 20 to 80 years old who underwent total thyroidectomy, (2) postoperative pathological diagnosis confirmed as PTC, (3) patients received ^{131}I radioiodine therapy at least one time, (4) no distant metastasis was confirmed by imaging and pathology, and (5) patients finished 2 years of follow-up. The participants with the following conditions were excluded: (1) pathologically confirmed as other types of thyroid carcinoma, (2) other underlying diseases including other malignant tumors or autoimmune disorders, and (3) positive thyroglobulin antibody (TgAb). Chest and abdominal computed tomography (CT) scan were performed before ^{131}I ablation. The initial dosage of ^{131}I ablation was set based on the recurrence risk stratification according to the 2015 ATA Guidelines (6). For low- and moderate-risk patients, the initial ^{131}I ablation dose was 50–100 mCi. For high-risk patients with extraglandular invasion (larynx, trachea, esophagus, recurrent laryngeal nerve, striated muscle, etc.), the initial ^{131}I ablation therapeutic dose was 120–180 mCi (6, 11). The patients achieved the goal of TSH > 30 mU/L after L-evothyroxine withdrawal and followed a low-iodine diet for 3–4 weeks. The patients were administrated L-T4 at day 3 after ^{131}I ablation. The whole-body scan (Rx-WBS) and single-photon emission computed tomography/computed tomography (SPECT/CT) were performed within 1 week after ^{131}I ablation (6).

During the 2-year follow-up, the first evaluation was performed at 3 months after initial ^{131}I ablation therapy, and then dynamic evaluation was performed every 6 months during follow-up. Dynamic evaluation involved both serological and imaging measurements, including serum Tg levels, TgAb, thyroid function especially TSH level, and neck ultrasound. ^{131}I diagnostic scanning (Dx-WBS), chest CT scan or ^{18}F-FDG positron emission tomography (PET)-CT scanning, and fine needle aspiration (FNA) biopsy were also used if necessary.

Preablative stimulated thyroglobulin (ps-Tg) was defined as the Tg levels when TSH > 30 IU/mL as patients stopped taking L-T4 before ^{131}I ablation (6). The diagnosis of Hashimoto's thyroiditis (HT) was identified based on postoperative pathological analysis. Pre-operative lymph node metastasis was diagnosed by FNA (cytopathological diagnosis of PTC, or elevated Tg washout measurement) before surgery, or postoperative pathological analysis. Postoperative lymph node metastasis referred to the presence of metastatic lymph nodes detected by ^{131}I-WBS or ultrasound and confirmed by FNA after surgery. Lymph node metastasis rate (LR) referred to the rate of involved lymph nodes, indicating the number of involved lymph nodes/total number of resected lymph nodes, based on postoperative pathological analysis.

2.2 Indication for thyroidectomy and lymph node dissection

In this study, patients with PTC with lymph node metastasis underwent total thyroidectomy according to the 2015 ATA Guidelines (6). Total thyroidectomy was performed for tumor diameter >4 cm. For the tumor diameter <4 cm (including diameter ≤1 cm), total thyroidectomy was performed under the following conditions: (1) bilateral foci; (2) lymph node metastasis in the lateral cervical area or lymph node metastasis number ≥5 or diameter ≥3 cm; (3) extracapsular invasion and metastatic lymph node invasion of surrounding tissues and organs, such as peripheral fat tissue, muscles, trachea, esophagus, laryngeal reentry nerve, and invaded blood vessels; and (4) high-risk factors such as head and

neck radiotherapy history over the course of childhood and adolescence, and thyroid carcinoma family history.

The lymph node dissection was performed as follows: (1) central lymph node dissection: the therapeutic and prophylactic central-compartment lymph node dissection is routinely performed by experienced and skilled surgeons and the surrounding tissues were adequately protected; (2) lateral lymph node dissection: for PTC with lateral lymph node metastases confirmed by preoperative FNA or intraoperative frozen pathological examination, therapeutic lateral lymph node dissection was performed. The prophylactic lateral lymph node dissection is not routinely performed.

2.3 Efficacy evaluation criteria

According to the 2015 ATA Guidelines (6), the response to treatment was categorized into ER, indeterminate response (IDR), biochemical incomplete response (BIR), and structural incomplete response (SIR), based on Tg level and imaging examination. Based on the follow-up at 2 years, the recruited patients were divided into two groups, the ER group and the non-ER group. Patients with IR, BIR, and SIR were assigned as the non-ER group (6). Recurrence risk stratification and TNM staging were determined based on the 2015 ATA Guidelines (6) and the 8th edition TNM staging system of the American Joint Committee on Cancer (AJCC) (12).

2.4 Statistical analysis

Statistical analysis was performed using the SPSS 26.0 software. Categorical variables were presented as frequencies and percentages, and two-group comparison was performed by the χ^2 test. Partial distributed data were presented as the median value and comparisons between two groups were performed using the Mann–Whitney *U* test. Logistic regression analysis was used to analyze the factors affecting the achievement of ER. Prognostic receiver operating characteristic (ROC) curves were applied to obtain the optimal threshold for estimating ER achievement, and the prediction of the cumulative risk of non-ER was performed using the Kaplan–Meier model. The statistical significance was $p < 0.05$ compared between two groups. The comparison among the three groups and four groups was $p < 0.017$ and $p < 0.008$, which were considered statistically significant, respectively.

3 Results

3.1 Clinicopathologic features of patients with PTC

A total of 423 patients with PTC with lymph node metastasis were enrolled, with age ranging from 20 to 78 years (average age, 43.82 ± 11.85 years old). The male-to-female ratio was 1:2.18. The follow-up time was 24–32 months. The maximum diameter of tumor foci was 0.1–5.5 cm, averaging 1.57 ± 1.06 cm. The number of foci was one to eight (average foci number was 1.81 ± 1.09). The number of lymph node metastasis was 1–36, with a median of 4. Lymph node metastasis rate (% of involved metastatic lymph nodes/total number of resected lymph nodes) was 5%–100%, with a median of 40%. There were 226 cases (53.43%) with extracapsular invasion, including 146 cases (34.52%) in the strap muscles, 44 cases (10.43%) with recurrent laryngeal nerve invasion, 18 cases (4.25%) with tracheal invasion, 6 cases (1.41%) with esophageal invasion, 6 cases (1.41%) with blood vessel (internal jugular vein, common carotid artery, and transverse cervical artery) invasion, and 6 cases (1.41%) with surrounding soft tissue invasion. The clinicopathologic features are shown in Table 1.

3.2 Comparison of clinicopathologic features between ER and non-ER groups

Based on the response to ^{131}I ablation after 2 years of follow-up, 314 patients with PTC achieved ER with an ER rate of 74.2%. The patients with PTC were divided into ER and non-ER groups. The results showed that the proportion of female patients, unifocal, primary foci ≤1 cm in diameter, no extracapsular invasion, combination with HT, low ps-Tg level (≤3.87 ng/mL), and low risk of recurrence risk stratification were significantly higher in the ER group than in the non-ER group (all $p < 0.05$). However, age, laterality of tumor foci, and TNM staging did not show significant difference between two groups (all $p > 0.05$) (Table 2).

TABLE 1 Clinicopathologic data of enrolled patients with PTC.

Clinical indicators, *n* (%)	Clinical indicators, *n* (%)
Age (years)	Lymph node metastasis rate #
<55 341 (80.61%)	≤40% 209 (49.41%)
≥55 82 (19.39%)	>40% 214 (50.59%)
Sex	Postoperative lymph node metastasis
Male 133 (31.44%)	No 351 (82.97%)
Female 290 (68.56%)	Yes 72 (17.03%)
Number of primary foci	Metastatic lymph node region
Unifocal 221 (52.25%)	Central only 51 (12.06%)
Multifocal 202 (47.75%)	Lateral only 43 (10.16%)
Unilateral/Bilateral foci of primary tumor	Central+lateral 329 (77.78%)
Unilateral 265 (62.25%)	Initial dose of ^{131}I therapy (mCi)
Bilateral 158 (37.75%)	≤100 (50–100) 270 (63.83%)
Maximum diameter of primary foci (cm)	>100 (120–180) 153 (36.17%)
≤1 176 (41.61%)	Frequency of ^{131}I therapy
>1 247 (58.39%)	1 time 357 (84.40%)
Extracapsular invasion	2 times 51 (12.06%)
Yes 226 (53.43%)	≥3 times (3–4) 15 (3.54%)
No 197 (46.57%)	Total dose of ^{131}I therapy (mCi)
Combination with HT	50–100 250 (59.10%)
Yes 71 (16.78%)	120–150 112 (26.48%)
No 352 (83.22%)	160–200 5 (1.18%)
Laterality of lymph node metastasis	>200 (220–600) 56 (13.24%)
Ipsilateral 305 (72.10%)	Recurrence risk stratification
Bilateral 118 (27.90%)	Low risk 33 (7.8%)
Ps-Tg (ng/mL)	Intermediate risk 184 (43.49%)
≤3.87 213 (50.35%)	High risk 206 (48.71%)
>3.87 210 (49.56%)	TNM staging
Number of lymph node metastases #	Phase I 344 (81.32%)
<5 218 (51.54%)	Phase II 53 (12.53%)
≥5 205 (48.46%)	Phase III 20 (4.73%)
	Phase IV 6 (1.42%)

Presented as median. PTC, papillary thyroid cancer; HT, Hashimoto's thyroiditis.

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TABLE 2 Comparison of clinicopathologic features between ER and non-ER groups at 2 years follow-up (*n*, %).

		ER (*n* = 314, 74.23%)	Non-ER (*n* = 109, 25.77%)	χ^2	p
Sex	Male	93 (29.62)	40 (36.70)	4.529	0.033
	Female	221 (70.38)	69 (63.30)		
Age (years)	<55	248 (78.98)	92 (84.40)	1.600	0.209
	≥55	66 (21.02)	17 (15.60)		
Number of primary tumor foci	Unifocal	176 (56.05)	48 (44.04)	4.688	0.03
	Multifocal	138 (43.95)	61 (55.96)		
Laterality of primary tumor foci	Unilateral	200 (63.69)	64 (58.72)	0.737	0.391
	Bilateral	114 (36.31)	45 (41.28)		
Maximum diameter of primary tumor foci (cm)	≤1	141 (44.90)	35 (32.11)	5.764	0.017
	>1	173 (55.10)	74 (67.89)		
Extracapsular invasion	Yes	158 (50.31)	68 (62.38)	4.735	0.030
	No	156 (49.69)	41 (37.62)		
Combination with HT	Yes	64 (20.38)	7 (6.42)	11.483	0.001
	No	250 (79.62)	102 (93.58)		
ps-Tg (ng/mL) #	≤3.87	198 (63.06)	15 (13.76)	76.945	<0.001
	>3.87	116 (36.94)	94 (86.24)		
Recurrence risk stratification	Low risk	30 (9.55)	3 (2.75)	4.302	0.038
	Medium–high risk	284 (90.45)	106 (97.25)		
TNM staging	Phase I/II	297 (94.6%)	100 (91.7%)	1.134	0.287
	Phase III/IV	17(5.4%)	9 (8.3%)		

ps-Tg value was not normally distributed and was presented as median. ER, excellent response; HT, Hashimoto's thyroiditis.

Comparison of the pathologic characteristics of metastatic lymph nodes between ER and non-ER groups was analyzed. The ER group had a lower number and rate of lymph node metastases, less postoperative lymph node metastases, and a significantly lower proportion of lymph nodes located in the central and cervical lateral region than the non-ER group (all $p < 0.05$) (Table 3).

In this study, the ER group had an increased rate of HT. Therefore, we further analyzed the relationship between HT and clinicopathological features. The results showed that female patients (female patients 84.50% vs. male patients 15.50%) and non-extracapsular invasion (non-extracapsular invasion 61.97% vs. extracapsular invasion 38.03%) in the HT group (71 cases, 16.78%) were significantly higher than those in the non-HT group (352 cases, 83.22%) (all $p < 0.05$), while age, number of primary tumor foci, the maximum diameter of primary foci, unilateral/bilateral foci, number of lymph node metastases, LR, and postoperative lymph node metastasis showed no difference between HT and non-HT groups.

To analyze the relationship between frequency/dosage of ^{131}I ablation and ER, we found that the ER rate in the 1 time ^{131}I ablation therapy group was higher than that in the 2 times and ≥3 times ^{131}I ablation therapy group (all $p < 0.017$). In addition, the ER rate in the low initial ^{131}I ablation dose ≤100 (50–100) mCi group was significantly higher than that in the high-dose >100 (120–180) mCi group ($p < 0.05$). We further divided the patients into four groups based on the total dose of ^{131}I therapy. The results showed that the ER rate of the ^{131}I therapy total dose 50–100 mCi group was significantly higher than that of the 120–150 mCi group, as well as the >200–(220–600) mCi group (all $p < 0.008$) (Table 4).

3.3 The independent risk factors affecting ER achievement after ^{131}I therapy

Multivariate logistic regression analysis was performed to analyze the factors associated with ER after ^{131}I therapy. The results revealed that the maximum diameter of tumor foci (≤1 cm), unifocal, combination with HT, lymph node metastases rate (≤40%), no postoperative lymph node metastasis, lower level of ps-Tg (≤3.87 ng/mL), and the frequency of ^{131}I therapy (one time) were independent risk factors that positively correlated with the ER achievement (OR: 1.744, 3.114, 3.920, 4.018, 2.074, 9.767, and 49.491, respectively; all $p < 0.05$). There was no correlation between ER and the number of metastatic lymph nodes, laterality of lymph node metastasis, extracapsular invasion, or initial dose and total dose of ^{131}I therapy (all $p > 0.05$) (Table 5).

TABLE 3 Comparison of pathologic features of metastatic lymph nodes between ER and non-ER groups (*n*, %).

Groups		ER (*n* = 314, 4.23%)	Non-ER (*n* = 109, 5.77%)	χ^2	p
Number of lymph node metastases #	<5	177 (56.37)	41 (37.61)	11.395	0.01
	≥5	137 (43.63)	68 (62.39)		
Lymph node metastasis rate #	≤40%	169 (53.82)	41 (37.61)	8.502	0.004
	>40%	145 (46.18)	68 (62.39)		
Laterality metastasis of lymph node	Ipsilateral	236 (75.16)	69 (63.30)	5.655	0.017
	Bilateral	78 (24.84)	40 (36.70)		
Metastatic lymph node region	Central	40 (12.73)	10 (9.17)	2.07[a], 1.71[b], 7.46[c]	0.150[a], 0.191[b], 0.006[c]
	Lateral	39 (12.42)	4 (3.67)		
	Central+lateral	235 (74.85)	95 (87.16)		
Postoperative lymph node metastasis	Yes	46 (14.64)	26 (28.85)	4.853	0.028
	No	268 (85.46)	83 (71.15)		

#Grouped by median. a indicates the comparison between the central group and the lateral group. b indicates the comparison between the central group and the central+lateral group. c indicates the comparison between the lateral group and the central+lateral group. Statistically significant differences were considered as $p < 0.017$.

3.4 Predictive value of ps-Tg and LR in ER achievement

The predictive value of ps-Tg level and LR in ER achievement was analyzed, respectively. The results showed that the maximum area under the curve (AUC) of the ROC curve was 0.821 (95% CI 0.777–0.865) and 0.746 (95% CI 0.691–0.800). The best cutoff values were 4.625 ng/mL for ps-Tg and 50.50% for LR, with corresponding sensitivities of 84.4% and 63.3%, specificities of 67.8% and 79.6%, PPVs of 92.6% and 86.2%, and negative predictive values of 48.7% and 51.8%, respectively. Results indicate that ps-Tg ≤ 4.625 ng/mL and LR ≤ 50.50% are effective factors for predicting ER achievement (Figure 1).

The ps-Tg value and LR were analyzed for the joint prediction of the cumulative risk for non-ER. The results revealed that regardless of whether the ps-Tg value was at low level (≤4.625 ng/mL) or high level (>4.625 ng/mL), the cumulative risk of non-ER elevated with the increase of LR, especially for the high-level ps-Tg group, whereas at the same LR, the cumulative risk of non-ER was higher in the high-level ps-Tg group than the low-level ps-Tg group (both $p < 0.05$) (Figure 2).

4 Discussion

Although most patients with PTC have a good prognosis with low mortality and long survival, the recurrence rate can be up to 30% due

TABLE 4 Comparison of times and dosage of ^{131}I ablation therapy between ER and non-ER groups in patients with PTC.

		ER (*n* = 314, 74.23%)	Non-ER (*n* = 109, 25.77%)	χ^2	p
Frequency of ^{131}I therapy	1 time	291 (85.34)	65 (59.63)	46.172[a] 32.869[b] 1.760[c]	<0.001[a] <0.001[b] 0.185
	2 times	20 (6.37)	32 (29.36)		
	≥3 times	3 (8.29)	12 (11.01)		
Initial dose of ^{131}I therapy (mCi)	≤100 (50–100)	221 (70.38)	49 (44.95)	23.511	<0.001
	>100 (120–180)	93 (29.62)	60 (55.05)		
Total dose of ^{131}I therapy (mCi)	50–100	211 (67.19)	39 (35.78)	10.290[d], 0.074[e], 58.723[f], 0.234[g] 18.173[h], 3.864[i]	0.001[d], 0.786[e], <0.001[f], 0.629[g] <0.001[h], 0.049[i]
	120–150	79 (25.15)	33 (30.27)		
	160–200	4 (1.27)	1 (0.92)		
	>200 (220–600)	20 (6.39)	36 (32.13)		

a and b indicate the comparison of the ^{131}I ablation therapy 1 time group with the 2 times group and the ≥3 times group, respectively. c indicates the comparison of the 2 times group with the ≥3 times group. $p < 0.017$ was defined as statistically significant.
d, e, and f indicate the comparison of the total dose of the 50–100 group with the 120–150, 160–200, and >200 (220–600) (mCi) groups, respectively.
g and h indicate the comparison of the total dose of the 120–150 group compared with the 160–200 and >200 (220–600) (mCi) groups, respectively.
i indicates the total dose of the 160–200 group compared with the >200 (220–600) (mCi) group, and the difference was considered statistically significant at $p < 0.008$.

TABLE 5 Multi-factorial analysis of clinicopathological features affecting therapy response to ^{131}I ablation therapy.

Clinicopathological features (1, 0; analyzed variable 1)	OR	95% CI	p
Maximum diameter of tumor foci (≤1 cm, >1 cm)	1.744	1.030–2.951	0.038
Number of primary tumor foci (unifocal/multifocal)	3.114	1.364–7.109	0.007
Combination with HT (yes, no)	3.920	1.646–9.332	0.002
Extracapsular invasion (no, yes)	0.661	0.400–1.091	0.105
Number of metastatic lymph nodes (<5, ≥5)	1.429	0.810–2.522	0.218
Lymph node metastases rate (≤40%, >40%)	4.018	2.351–6.867	0.000
Metastatic lymph node region (central, lateral, central+lateral)	0.902	0.368–2.210	0.822#
Laterality of metastatic lymph nodes (ipsilateral, bilateral)	0.579	0.129–2.612	0.478
Postoperative lymph node metastasis (no, yes)	2.074	1.090–3.3.948	0.026
Ps-Tg values (≤3.87, >3.87)	9.767	5.171–18.448	0.000
Frequency of ^{131}I therapy (1, 2, ≥3 times)	49.491	3.864–633.817	0.003##
Initial dose of ^{131}I ablation therapy [≤ 100 (50–100), >100 (120–180) mCi]	3.274	0.752–14.257	0.114
Total dose of ^{131}I ablation therapy [50–100, 120–150, 160–200, >200 (220–600) mCi]	0.227	0.019–2.752	0.244

# indicates the comparison between metastatic lymph nodes located in the lateral region and those in the central+lateral region; ## indicates the number of 1 time versus ≥3 times ^{131}I therapy.

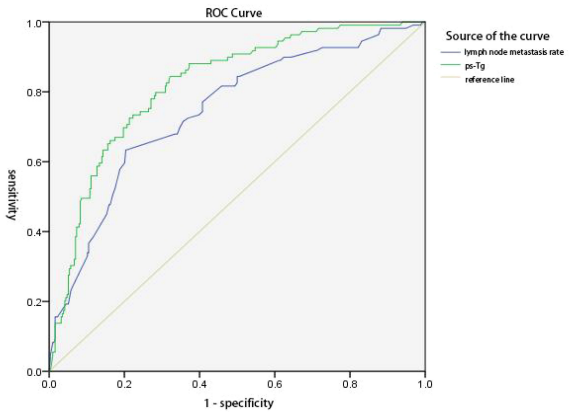

FIGURE 1
ROC curves of ps-Tg values and lymph node metastasis rate (LR) for predicting the excellent response (ER). The area under the curve (AUC) was 0.821 (95% CI 0.777–0.865) and 0.746 (95% CI 0.691–0.800), respectively. The Youden index was 0.522 and 0.429, respectively. The best cutoff values were 4.625 ng/mL for ps-Tg and 50.50% for LR, with a corresponding sensitivity of 84.4% and 63.3%, a specificity of 67.8% and 79.6%, a positive predictive value of 92.6% and 86.2%, and a negative predictive value of 48.7% and 51.8%, respectively.

to the presence of lymph node metastasis (13–15). Therefore, active and rationalized treatment strategies and dynamic follow-up for assessment of PTC with lymph node metastasis are important.

^{131}I ablation therapy as an adjuvant treatment for PTC with lymph node metastasis has been widely applied. Several studies have reported that the effectiveness of ^{131}I ablation therapy in patients with PTC with lymph node metastasis can reach up to 71.4%–88.07% (16, 17). Previously, Gao et al. analyzed the data from low- and intermediate-risk patients with PTC and showed an ER rate of 93.7% and 78.2% after ^{131}I treatment (18), while Zhao et al. showed a 54.5%–73.2% ER achievement, which differed from high–low TSH level stratification (19). In our study, we found that the overall ER rate was 74.2%, which was comparable to the results of previous studies.

In recent years, several studies revealed the factors influencing the clinical outcome after postoperative ^{131}I ablation in patients with PTC. The ps-Tg level has been proven to be the predictor of recurrence risk and prognosis (20, 21). Li et al. (8) reported that low ps-Tg level was more likely to achieve ER in moderate-risk patients with PTC. Wang et al. (9) also concluded that a higher level of ps-Tg was associated with a lower ER rate of the initial ^{131}I ablation. However, there were controversies regarding the relationship between ER and the diameter and number of tumor foci, extracapsular invasion, and the number and rate of lymph node metastasis. Several studies revealed that tumor size, number of lymph nodes, LR, and lymph node size were significantly associated with ER achievement after ^{131}I ablation therapy (8, 9, 22). However, Shangguan et al. (23) reported that the LR did not correlate with ER. In this study, we investigated the relationship between clinicopathological factors and ER. The results showed that tumor diameter (≤1 cm), unifocal, combination with HT, low lymph node

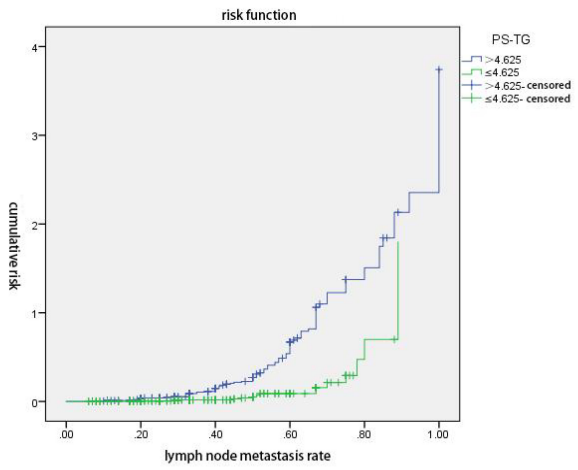

FIGURE 2
ps-Tg combined with lymph node metastasis rate (LR) predicts the cumulative risk of non-excellent response (non-ER). Regardless of whether the ps-Tg value was at low level (≤4.625 ng/mL) or high level (>4.625 ng/mL), the cumulative risk of non-ER elevated with the increase of LR, especially for the high-level ps-Tg group. At the same LR, the cumulative risk of non-ER was higher in the high-level ps-Tg group ($p < 0.05$).

metastases rate (≤40%), the absence of postoperative lymph node metastasis, and the low level of ps-Tg (≤3.87 ng/mL) were independent factors positively correlated with the ER achievement.

The ROC of ps-Tg and LR showed high sensitivity and PPV for ER achievement. Based on the significance of ps-Tg in predicting ER and recurrence or metastasis (20, 24, 25), ps-Tg level was used as an important serological indicator in the evaluation system in guiding the individualized follow-up and treatment of patients with PTC. However, there is variability in the thresholds of ps-Tg level as indicators in different studies, which may be related to the different clinicopathologic characteristics of the selected patients, the area of operation, the dosage and frequency of ^{131}I ablation, and the criteria for evaluating the efficacy, the follow-up frequency.

In clinical practice, patients with PTC usually exhibit two or more malignant pathologic features at the same time, which undoubtedly aggravates the progression and reduces the likelihood of achieving ER. We revealed that serum ps-Tg and lymph node metastasis rate are important indicators to predict ER achievement in this study, and further results showed that the cumulative risk of non-ER elevated with the increase of lymph node metastasis rate, regardless of ps-Tg level (low level ≤4.625 ng/mL or high level >4.625 ng/mL). Moreover, the increase of cumulative risk was more prominent in the high ps-Tg level group. Hence, the prediction of non-ER achievement can be improved by a combination of evaluating ps-Tg and LR, which can avoid the limitation of assessment by a single factor. A combination of ps-Tg and LR could predict the efficacy of ^{131}I ablation in advance, potentially useful for individualized therapeutic assessment.

Regarding the studies on the relationship between HT and PTC, HT is associated with the development of PTC and is widely recognized as a pre-disease state of PTC (26). However, the effect of HT on the pathological features of PTC is inconsistent (27, 28). Studies suggested that HT is a "double-edged sword" in patients with PTC, which increases the risk of PTC but is a protective factor against progression (29), and lymphocyte infiltration and cytokines derived from lymphocytes may attenuate tumor invasiveness and proliferation (27, 28). In contrast, some studies indicated that HT promotes PTC development progression, which is associated with both the endocrine mechanism by promoting TSH increasing and immune mechanism via the reduced expression of major histocompatibility complex (MHC)-I molecules, leading to the upregulation of immunosuppressive components and immune escape (30, 31). Several studies showed that there was no correlation between combined HT and ER (32, 33), while a report from Lim et al. suggested that patients with PTC combined with HT had a low ER rate after ^{131}I ablation (34). A large-scale prospective multicenter study analyzed the relationship between autoimmune thyroiditis and DTC outcomes. The results showed that patients with autoimmune thyroiditis were more frequently categorized as low and intermediate risk. The biochemical persistence was more frequent in autoimmune thyroiditis patients, but no association between AT and structural persistence of disease. Patients with autoimmune thyroiditis had a more frequently indeterminate response. These findings may be explained by the presence of a residual thyroid tissue (35). Of note, our data differed from the above finding, showing that combination with HT is an independent factor of ER achievement, and a higher proportion of patients have an absence of extracapsular extension in the combination with the HT group (61.97% vs. 38.03%) and are positively correlated with ER, suggesting that PTC combined with HT is less invasive, which may contribute to ER achievement. The variability of the findings in different studies may be related to several factors, such as regional differences in the study populations, varying iodine nutritional status, and different genetic backgrounds.

In addition, our study revealed that less time of ^{131}I ablation therapy (only one time) was correlated with ER outcomes, indicating that patients with mild disease have a better outcome. We also found a higher proportion of low risk of recurrence in the ER group, suggesting that the frequency and intensity of follow-up could be reduced.

We acknowledge some limitations of our study. Since the patients were from a single medical center and retrospective study, selection bias could not be ruled out. Second, we cannot exclude the influence of lifestyle (such as iodine content in diet and smoking) or hereditary factors of the enrolled patients. Third, considering the inert nature of PTC, further studies with a long-term follow-up are needed.

In summary, we have found that the diameter of tumor foci ≤1 cm, unifocal, combination with HT, the absence of postoperative lymph node metastasis, lower LR, and a lower level of ps-Tg were independent factors correlated with the ER achievement. The ps-Tg and LR had a predictive value for ER achievement. The predictive value of the cumulative risk of non-ER can be improved by a combination of evaluating ps-Tg and LR.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The ethics committee of the Affiliated Hospital of Qingdao University approved this study. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XX: Formal analysis, Investigation, Writing – original draft. CL: Formal analysis, Investigation, Project administration, Writing – original draft. XY: Investigation, Methodology, Writing – original draft. GW: Methodology, Writing – original draft. YG: Data curation, Formal analysis, Methodology, Writing – original draft. HN: Data curation, Investigation, Writing – original draft. WZ:

Conceptualization, Supervision, Writing – review & editing. YW: Conceptualization, Resources, Supervision, Writing – review & editing. BD: Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prognostic factors in children and adolescents with differentiated thyroid cancer treated with total thyroidectomy and radioiodine therapy: a retrospective two-center study from China

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Purpose: This two-center study aimed to explore the main prognostic factors affecting the final disease status in children and adolescents with differentiated thyroid cancer (caDTC) following total thyroidectomy and radioiodine therapy (RAIT).

Materials and methods: All caDTC patients from two centers in the period from 2004-2022 were retrospectively included. At the last follow-up, the patients' disease status was assessed and classified as an incomplete response (IR) or as an excellent or indeterminate response (EIDR). Then, the difference in preablation stimulated thyroglobulin (ps-Tg) levels between the two groups was compared, and the threshold for predicting IR was determined using receiver operating characteristic (ROC) analysis. Moreover, univariate and multivariate analyses were conducted to identify the factors influencing the patients' ultimate disease outcomes.

Results: A total of 143 patients (98 females, 45 males; median age 16 years) were recruited. After a median follow-up of 42.9 months, 80 patients (55.9%) exhibited an EIDR, whereas 63 patients (44.1%) exhibited an IR. Patients with an IR had significantly greater ps-Tg levels than did those with an EIDR (median ps-Tg 79.2 ng/mL vs. 9.3 ng/mL, $p<0.001$). The ROC curve showed that ps-Tg ≥20 ng/mL was the most accurate for predicting IR at the last follow-up. According to

multivariate analysis, only ps-Tg, T stage and the therapeutic response to initial RAIT were significantly associated with IR.

Conclusion: In caDTC patients, the ps-Tg level, T stage, and response to initial RAIT are critical final outcome indicators.

KEYWORDS

children and adolescents, differentiated thyroid cancer, radioiodine therapy, thyroglobulin, therapeutic response, prognosis

1 Introduction

Although the incidence of differentiated thyroid cancer (DTC) in children and adolescents (caDTC) is low, it has been steadily increasing in recent years (1–3). Compared to adult thyroid cancer, caDTC has distinct differences in terms of its pathophysiological characteristics, clinical features, and long-term prognosis (4–7). Consequently, guidelines and treatment strategies designed for adult thyroid cancer patients are not fully applicable to children and adolescents. The American Thyroid Association (ATA) published its inaugural guidelines for the diagnosis and treatment of pediatric thyroid nodules and DTC in 2015, aiming to standardize the management of caDTC patients (8).

The primary approach to treating caDTC consists of total thyroidectomy, succeeded by adjuvant radioiodine therapy (RAIT) as deemed necessary (9, 10). The substantial benefits of RAIT, including a reduction in the recurrence rate and improvement in overall survival, have been documented among caDTC patients classified as having the highest risk (5, 11). The objective remains to preserve the current low disease-specific mortality rates observed in caDTC patients while minimizing therapy-related complications and the risk of overtreatment (8, 12).

Preablation-stimulated thyroglobulin (ps-Tg) levels have demonstrated a favorable predictive value for therapeutic outcomes and overall survival in the management of adult DTC patients (4, 5, 13, 14). Conversely, the prognostic utility of ps-Tg in caDTC patients has yet to be conclusively determined. Within this clinical context, the objective of our study was to examine the role of certain risk factors, such as ps-Tg, the ATA risk classification, and the therapeutic response to initial RAIT, in predicting the final disease status.

1 Materials and methods

2.1 Patients

The thyroid cancer databases from Shanghai Tenth People's Hospital and the Affiliated Hospital of Qingdao University were retrospectively screened to identify all caDTC patients (aged ≤18 years) who received at least one standardized RAIT between January 2004 and December 2022. This study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Review Committee of the Affiliated Hospital of Qingdao University.

The inclusion criteria were as follows: 1) history of total thyroidectomy; 2) pathological type confirmed as DTC; 3) age ≤18 years at the time of initial RAIT; 4) receipt of standardized RAIT; 5) initial recurrence risk stratified as intermediate or high risk (Supplementary Table 1) (8); and 6) negativity for anti-thyroglobulin antibody (TgAb).The exclusion criteria were 1) incomplete regular follow-up data and 2) other malignant tumors or other antitumor treatments (such as chemotherapy, external radiation therapy, or targeted drug therapy.).

All selected caDTC patients were restaged according to the 8th edition of the American Joint Committee on Cancer (AJCC)/TNM staging system (15). Moreover, the assignment of the initial recurrence risk category adhered to the 2015 ATA pediatric risk stratification system (8).

The main clinical characteristics, which included gender, preoperative thyroid stimulating hormone (TSH) level, age at the initial RAIT, histological type, tumor size, multicentricity, extrathyroidal invasion, T stage, lymph node involvement (Supplementary Table 2), and recurrence risk, were documented. Additionally, the ps-Tg, TgAb, and details regarding RAIT administration (total amount of RAIT received and total number of RAIT sessions) were also recorded.

2.2 RT protocol and follow-up

Patients followed a low-iodine diet and ceased levothyroxine intake for 2-3 weeks to increase their TSH levels above 30 mIU/L (16, 17). Prior to RAIT administration, routine diagnostic procedures, including neck ultrasound and diagnostic whole body scan (Dx-WBS), were conducted (8). For prepubertal patients, the dose administered in each RAIT session was an empirical dosage of 1.0-1.5 mCi/kg (16). After puberty, a single dose of 100-200 mCi was administered based on the patient's disease condition (9).

The therapeutic response to initial RAIT was assessed between 6 and 12 months after the initial RAIT according to the 2015 ATA therapeutic response classification, which categorizes responses into four distinct classes: excellent response (ER), biochemical incomplete response (BIR), structural incomplete response (SIR), and indeterminate response (IDR) (Supplementary Table 3) (4, 8). Subsequently, BIR and SIR were categorized into the incomplete response (IR) group, while ER and IDR were classified into the excellent or indeterminate response (EIDR) group. This reclassification was based on a combination of biochemical (TSH, ps-Tg, suppressed thyroglobulin (sup-Tg), and TgAb) and imaging findings (neck ultrasound, CT, MRI, Dx-WBS and any additional imaging exams) (7).

All patients were intervals of 6-12 months thereafter based on the individual patient's risk and the clinical progression of the disease. Repeated RAIT was administered at least 1 year after the latest treatment session, contingent upon adequate ^{131}I absorption by the lesions and a favorable clinical response (16, 18).

2.3 Definitions of the clinical outcomes

At the last visit, patients were categorized as either having EIDR or exhibiting IR, as determined by integrating laboratory findings and imaging results. IR was defined as sup-Tg ≥1 ng/mL or stimulated thyroglobulin (sTg) ≥10 ng/mL, or an upward trend in TgAb, with or without the presence of structural or functional lesions (16, 19, 20). Conversely, patients who did not meet the above criteria for IR at the last follow-up were classified as having EIDR.

2.4 Statistical analysis

Statistical analyses were performed using IBM SPSS software version 26.0. Categorical variables are represented herein by frequencies and percentages, while continuous variables are described as the mean ± SD or M (P_{25}, P_{75}). A receiver-operating characteristic (ROC) curve was established to predict the efficacy of the RAIT using ps-Tg, identifying the optimal diagnostic threshold. The Mann-Whitney U test, independent sample t test or chi-square test were performed for univariate analyses as necessary, and significant factors were then included in the logistic regression analysis to identify the independent risk factors that affect the efficacy of the RAIT. A p value less than 0.05 was considered to indicate statistical significance.

3 Results

3.1 Description of caDTC patient's characteristics

The clinical characteristics of the 143 eligible caDTC patients are summarized in Table 1. The ratio of males to females was 1: 2.18, and the median age was 16 years at the time of the initial RAIT. PTC accounted for 96.5% of all patients, and the size of the primary tumor was 2.5 (1.5, 3.6) cm. Multicentricity of tumor lesions was present in 86 cases (60.1%), and extrathyroidal invasion was observed in 66 cases (46.2%). Thirty-three patients (23.1%) were reclassified into the T4 stage according to the 8th edition. Most patients (85.3%) were classified as N1b. By the 2015 ATA pediatric risk stratification, 75 patients (52.4%) were categorized into the intermediate-risk group, and 68 (47.6%) were classified into the

TABLE 1 Clinical characteristics of the caDTC patients.

Characteristics	Patients n(%)	Median (IQR)	Range
Age (years)		16 (14, 17)	6-18
Gender			
Male	45 (31.5)		
Female	98 (68.5)		
Histological type			
PTC	138 (96.5)		
FTC	5 (3.5)		
Multicentricity			
Yes	86 (60.1)		
No	57 (39.9)		
Tumor size (cm)		2.5 (1.5, 3.6)	0.5-5.0
Extrathyroidal invasion			
Yes	66 (46.2)		
No	77 (53.8)		
T stage			
T1-3	110 (76.9)		
T4	33 (23.1)		
N stage			
N0-1a	21 (14.7)		
N1b	122 (85.3)		
Recurrence risk			
Intermediate	75 (52.4)		
High	68 (47.6)		
PreoperativeTSH (mIU/L)		2.5 ± 1.0	0.4-6.1
ps-Tg (ng/mL)		19.0 (7.6, 72.0)	2.1-17468.0
Total number of RAIT sessions		1 (1, 2)	1-5
Total ^{131}I activity (mCi)		150 (100, 300)	50-760
Follow-up duration (months)		42.9 (20.7, 62.9)	6.3-113.4

caDTC, children and adolescents patients with differentiated thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; RAIT, radioiodine therapy; T, tumor; N, node; TSH, thyroid stimulating hormone; ps-Tg, preablation stimulated thyroglobulin.

high-risk group. The preoperative TSH level was 2.5 ± 1.0 mIU/L, and the ps-Tg level was 19.0 (7.6, 72.0) ng/mL. All patients underwent RAIT1-5 times, with a median total ^{131}I activity of 150 mCi. The median duration of follow-up was 42.9 months (range 6.3-113.4 months).

3.2 Therapeutic efficacy of RAIT

As shown in Figure 1, 37 (25.9%) caDTC patients had an ER, 31 (21.7%) had an IDR, 35 (24.5%) had a BIR, and 40 (27.9%) had an SIR at the therapeutic response to initial RAIT. Thus, after the initial RAIT, 47.6% (68/143) of patients were classified as having an EIDR, while 52.4% (75/143) were classified as having an IR. After a median follow-up of 42.9 months (range 6.3-113.4 months), EIDR was reported in 80 patients (55.9%), while IR was observed in the remaining 63 patients (44.1%). No deaths were observed among the patients at the last follow-up. Overall, of the 63 patients with an IR at the last follow-up, 23 had a BIR, and the remaining 40 had an SIR.

In this study, 13 caDTC patients with distant metastases (DM) underwent 3-5 RAITs for a total of 420-760 mCi of ^{131}I, and showed SIR at the last follow-up (Figure 1). Among 35 caDTC patients with a BIR after the initial RAIT, only four had structural recurrence (2 patients had lymph node metastasis, and two patients had lung metastasis). Two patients with lung metastases underwent three and five RAIT sessions for a total of 450 and 760 mCi of ^{131}I, respectively, and showed disease progression at the last follow-up. However, among patients with an SIR after the initial RAIT, three RAIT sessions were conducted for 7 patients, four RAIT sessions were conducted for 3 patients, and five RAIT sessions were conducted for 1 patient. Ultimately, 3 patients achieved partial response, 4 patients presented stable disease, and the remaining 4 patients exhibited progressive disease.

3.3 Predictive value of ps-Tg in patients with an IR at the last follow-up

The ps-Tg level in the EIDR group was 9.3 (3.8, 14.9) ng/mL, which was significantly lower than the 79.2 (25.1, 286.0) ng/mL in the IR group (Figure 2A). Furthermore, ROC analysis revealed that ps-Tg ≥20 ng/mL was the best threshold for discriminating IR from EIDR at the last follow-up, with a sensitivity of 88.9%, specificity of 83.8%, and AUC of 0.926 (95% CI: 0.885-0.967) (Figure 2B).

3.4 Univariate and multivariate analyses for the prediction of IR at the last follow-up

Univariate analysis revealed that patients with a larger tumor size (P=0.001), FTC (P=0.015), multicentricity (P=0.035), extrathyroidal invasion (P=0.003), stage T4 (P=0.000), stage N1b (P=0.003), a high recurrence risk (P=0.000), ps-Tg ≥20 ng/mL (P=0.000), IR as the therapeutic response to initial RAIT (P=0.000), a greater total number of RAIT sessions (P=0.000), and greater total ^{131}I activity (P=0.000) had a higher probability of IR (Table 2). However, univariate analysis revealed no significant associations between IR and gender, age, or preoperative TSH level. According to multivariate analysis, only ps-Tg (as continuous variable and dichotomized with 20 ng/mL) (odds ratio (OR): 8.333, 95% confidence interval (CI): 2.143-32.400, P = 0.002), therapeutic response to initial RAIT categories (OR: 7.552, 95% CI: 1.780-32.038, P = 0.006), and T stage (OR: 4.202, 95% CI: 1.132-15.596,

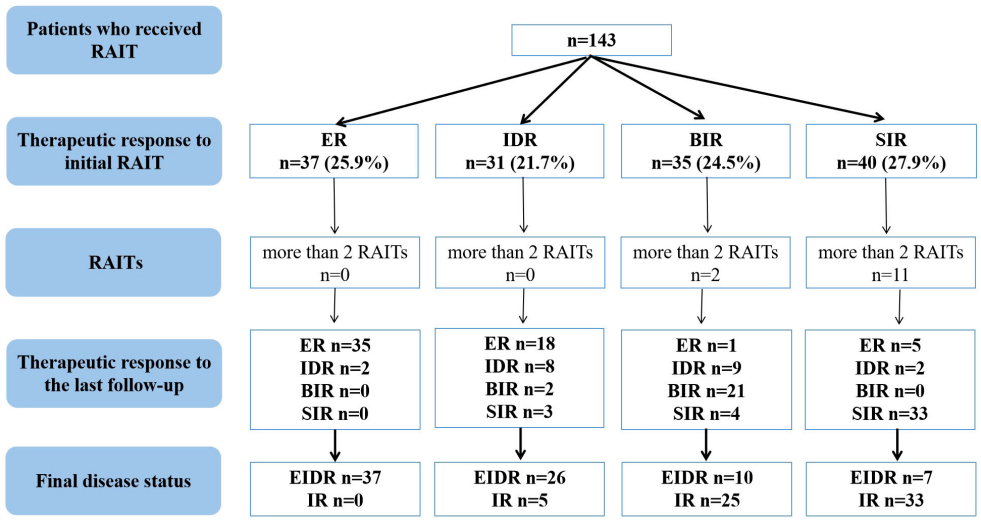

FIGURE 1
Flowchart of the therapeutic efficacy evaluation of RAIT in caDTC patients. caDTC, differentiated thyroid cancer in children and adolescents; RAIT, radioiodine therapy; ER, excellent response; IDR, indeterminate response; BIR, biochemical incomplete response; SIR, structural incomplete response; EIDR, excellent or indeterminate response; IR, incomplete response.

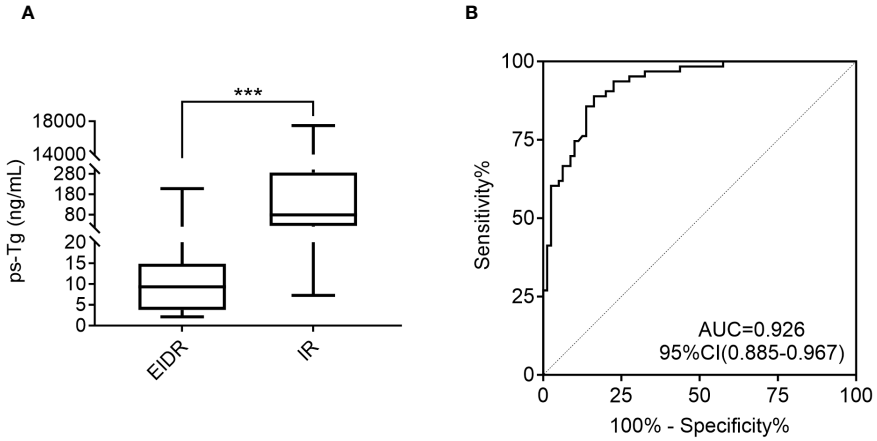

FIGURE 2
(A) Comparison of the ps-Tg levels in the EIDR and IR groups. **(B)** ROC curves of the ps-Tg test for detecting IR at the last follow-up. ps-Tg, preablation stimulated thyroglobulin; EIDR, excellent or indeterminate response; IR, incomplete response; ROC, receiver operating characteristic; AUC, area under the ROC curve; *** P <0.001.

TABLE 2 Univariate analyses for characteristics of IR in caDTC.

Characteristics	n	EIDR group	IR group	χ^2/t/U	P value
Gender				2.293[a]	0.130
Male	45	21(46.7%)	24(53.3%)		
Female	98	59(60.2%)	39(39.8%)		
Histological type				4.437[a]	0.015
PTC	138	80(58.0%)	58(42.0%)		
FTC	5	0(0%)	5(100%)		
Multicentricity				4.421[a]	0.035
Yes	86	42(48.8%)	44(51.2%)		
No	57	38(66.7%)	19(33.3%)		
Extrathyroidal invasion				9.090[a]	0.003
Yes	66	28(42.4%)	38(57.6%)		
No	77	52(67.5%)	25(32.5%)		
T stage				20.997[a]	0.000
T1-3	110	73(66.4%)	37(33.6%)		
T4	33	7(21.2%)	26(78.8%)		
N stage				8.851[a]	0.003
N0-N1a	21	18(85.7%)	3(14.3%)		
N1b	122	62(50.8%)	60(49.2%)		
Recurrence risk				19.351[a]	0.000
Intermediate	75	55(73.3%)	20(26.7%)		
High	68	25(36.8%)	43(63.2%)		
Preoperative TSH (mIU/L)		2.4 ± 0.9	2.7 ± 1.0	-1.322[b]	0.188
Age		16(14, 17)	16(13, 17)	2254.00[c]	0.273

(Continued)

TABLE 2 Continued

Characteristics	n	EIDR group	IR group	χ^2/t/U	P value
Tumor size (cm)		2.0(1.3, 3.2)	3.0(2.2, 4.2)	1716.00[c]	0.001
Total RAIT times		1(1, 1)	2(1, 2)	1224.00[c]	0.000
Total ^{131}I activity (mCi)		100(80, 150)	270(150, 350)	1039.00[c]	0.000
Ps-Tg (ng/mL)				74.477[a]	0.000
<20.0	74	67(90.5%)	7(9.5%)		
≥20.0	69	13(18.8%)	56(81.2%)		
Therapeutic response to initial RAIT				70.864[a]	0.000
IR	75	17(22.7%)	58(77.3%)		
EIDR	68	63(92.6%)	5(7.4%)		

caDTC, differentiated thyroid cancer in children and adolescents; EIDR, excellent or indeterminate response; IR, incomplete response; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; T, tumor; N, node; ps-Tg, preablation-stimulated thyroglobulin; TSH, thyroid stimulating hormone; RAIT, radioiodine therapy; [a]means chi-squared test; [b]means independent sample t test; [c]means Mann-Whitney U test.

P = 0.032) were significantly associated with the risk of IR at the last follow-up (Table 3).

In particular, 81.2% of caDTC patients with baseline psTg≥20 ng/mL showed an IR, while only 9.5% of patients with psTg<20 ng/ml exhibited an IR at the end of follow-up (P<0.001) (Figure 3). Furthermore, among patients with EIDR after the initial RAIT, only 7.4% had an IR, while among patients with an IR after the initial RAIT, 77.3% had an IR at the end of follow-up (P<0.001) (Figure 4A). Moreover, 78.8% of patients with T4 disease showed an IR, while only 33.6% of patients with T1-3 disease showed an IR at the end of follow-up (P<0.001) (Figure 4B).

TABLE 3 Multivariate logistic regression analyses for the prediction of IR in caDTC patients.

Characteristics	P value	OR	95% CI
Histological type (PTC/FTC)	0.894	0.781	0.125-5.160
Tumor size (cm)	0.715	1.094	0.675-1.775
Multicentricity	0.218	0.432	0.114-1.642
Extrathyroidal invasion	0.199	2.673	0.596-11.998
T stage (T1-3/T4)	**0.032**	4.202	1.132-15.596
N stage (N0-N1a/N1b)	0.158	3.725	0.601-23.100
Recurrence risk (intermediate/high)	0.133	0.307	0.066-1.433
Ps-Tg (ng/mL) (<20/≥20)	**0.002**	8.333	2.143-32.400
Therapeutic response to initial RAIT (EIDR/IR)	**0.006**	7.552	1.780-32.038
Total RAIT times	0.942	1.082	0.128-9.144
Total ^{131}I activity (mCi)	0.717	1.002	0.989-1.016

caDTC, differentiated thyroid cancer in children and adolescents; EIDR, excellent or indeterminate response; IR, incomplete response; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; T, tumor; N, node; ps-Tg, preablation stimulated thyroglobulin; RAIT, radioiodine therapy.
Data in bold (p value <0.05) indicate statistical significance.

4 Discussion

RAIT, serving as a pivotal postoperative adjuvant treatment for caDTC patients, can significantly improve the overall survival rate of patients, and reduce their risk of recurrence, metastasis, and death (7–9, 21). In this retrospective study, we compiled data from two centers in China. Despite covering an extended period from 2004 to 2022 and including diverse geographical locations, we adhered to uniform international guidelines for the management of caDTC patients, allowing for the sharing and analysis of these data.

At the last follow-up, approximately 44.1% (63/143) of patients were assessed for real-time dynamics as having progressed to an IR. As a primary finding, we demonstrated that the ps-Tg could predict the ultimate efficacy of RAIT with an optimal cutoff threshold established at 20 ng/ml. In this context, ps-Tg appears to be the

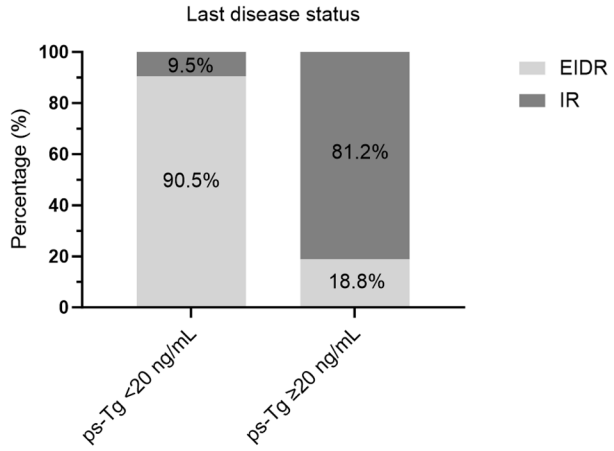

FIGURE 3
Evaluation of the last disease status in caDTC patients with high or low ps-Tg levels. ps-Tg, preablation stimulated thyroglobulin; EIDR, excellent or indeterminate response; IR, incomplete response.

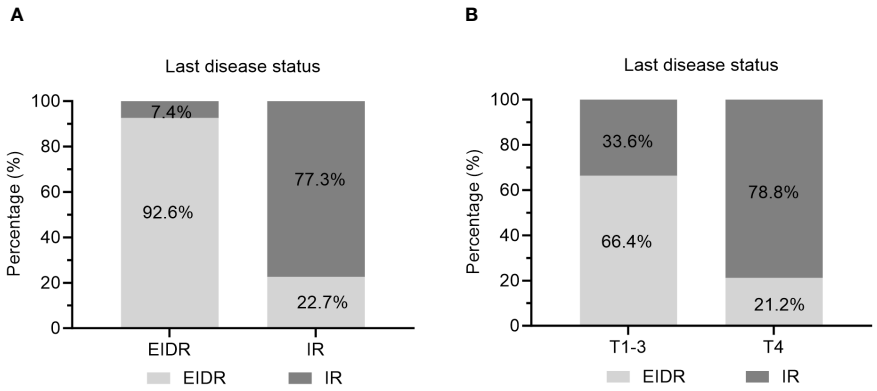

FIGURE 4
Evaluation of the last disease status in caDTC patients with **(A)** EIDR or IR after initial RAIT and **(B)** T1-3 or T4 disease. EIDR, excellent or indeterminate response; IR, incomplete response; T, tumor.

principal predictive marker of disease response, having a significantly greater impact on risk assessment than does the risk classification of the 2015 pediatric ATA guidelines (8). Moreover, we found that high ps-Tg levels, T4 stage, and IR to the initial RAIT were significantly associated with adverse outcomes.

Patients who exhibit an ER to initial RAIT generally have favorable prognoses, with lower rates of recurrence and higher survival probabilities (22). Conversely, those with an IR, particularly an SIR, face a greater risk of adverse outcomes (7, 8). Sung et al. (19) demonstrated that individuals in the indeterminate and incomplete response groups face a greater risk of recurrent or persistent disease than those in the an excellent response group. In the present study, approximately 47.6% (68/143) of caDTC patients were evaluated as having an EIDR to their initial RAIT. Moreover, the therapeutic response to the initial RAIT emerged as a critical determinant of long-term outcomes. Patients demonstrating an EIDR to initial RAIT exhibited markedly lower rates of IR (Figure 4A), emphasizing the importance of early and effective disease control. Our findings align with those reported by Cistaro et al. (5), which showed in a cohort of 276 caDTC patients who consecutively underwent total thyroidectomy and RAIT that the 1-year treatment response category was independently associated with the final disease status.

Tg serves as a highly specific and sensitive biomarker for detecting the presence of follicular thyroid cells (7, 12). The measurement of serum Tg is pivotal in the clinical management of DTC patients, and is widely regarded as the most sensitive technique for identifying the persistence or recurrence of the disease (4, 23–25). A meta-analysis conducted by Webb et al. (13), which included nearly 4,000 adult patients with DTC, demonstrated that with a threshold of 10 ug/mL, the negative predictive value of ps-Tg for predicting long-term disease remission reached an impressive 94%. This finding suggested that patients with low ps-Tg levels have a favorable prognosis and a reduced rate of tumor recurrence. Our investigation reaffirms that elevated ps-Tg levels are significantly associated with IR, which is consistent with previous reports in adult populations but tailored to the pediatric context (26, 27). A ps-Tg level of ≥20 ng/mL enhances the risk of recurrence, facilitating tailored therapeutic approaches and vigilant follow-up protocols.

Our investigation highlights T4 staging as a critical independent risk factor for RAIT efficacy in caDTC patients. Specifically, patients classified as having T4 disease exhibited substantially worse outcomes following RAIT than those classified as having T1-3 disease (Figure 4B). This finding aligns with the literature, which suggests that advanced T staging typically correlates with diminished treatment responses, particularly in RAIT, due to the aggressive nature and extensive local invasion characteristic of the T4 stage (7, 8, 28). Moreover, Wang et al. (29) quantitatively assessed the correlation between T4 stage and survival metrics such as overall survival (OS) and disease-specific survival (DSS). These studies confirm that T4 staging adversely affects survival outcomes, underscoring the urgency of adopting tailored therapeutic strategies for patients with higher T stages. Similarly, a study by Li et al. (30) revealed that the T stage significantly influences the prognosis of stage IV B DTC patients. In caDTC patients, the T4 stage is often associated with a greater tumor burden and increased local invasiveness, which may impede the absorption and effectiveness of iodine-131. Additionally, patients at this stage are likely to have higher recurrence rates and poorer long-term survival outcomes, necessitating more aggressive and personalized treatment approaches in clinical practice.

TSH is a growth factor that influences the initiation and progression of DTC. However, the relationship between preoperative TSH levels and DTC remains controversial. Previous studies have demonstrated that elevated preoperative TSH concentrations are associated with an increased risk of thyroid malignancy (31, 32). A multicenter retrospective study by Aihong Mao et al. (33), which included 1,997 patients with papillary thyroid microcarcinoma (PTMC), suggested that the preoperative TSH concentration should be considered a risk predictor for tumor progression in PTMC patients. In contrast, in this study, we found no significant difference in preoperative TSH levels between patients in the EIDR group and those in the IR group

(2.4 ± 0.9 vs. 2.7 ± 1.0 mIU/L, P=0.188), confirming that the preoperative TSH level is not a predictive factor for RAIT efficacy in caDTC patients.

Therefore, we suggest that higher ps-Tg levels, T4 stage, and IR to initial RAIT might predict higher IR rates in caDTC patients receiving RAIT. For patients with these high-risk factors, a single RAIT session may be insufficient to achieve optimal efficacy. A comprehensive assessment of the patient's condition is necessary, and a more aggressive or multimodal treatment strategy should be considered. This strategy may include more frequent monitoring, higher RAIT doses, combined treatments (such as surgery, external radiotherapy or targeted therapy), and close follow-up. By identifying these high-risk factors, clinicians can develop more flexible treatment plans, avoid a one-size-fits-all approach, and truly achieve personalized treatment. For low-risk patients (such as ps-Tg<20 ng/mL, T1-3 staging, and the response to initial RAIT as EIDR), taking TSH suppression therapy and reducing the intensity and frequency of RAIT can minimize treatment-related side effects and improve quality of life.

Our study is subject to several limitations, First, although we strictly followed the inclusion and exclusion criteria to select the samples, selection bias might still have existed because of the small number of patients eventually included. Second, given the typically prolonged survival of pediatric patients, a longer follow-up period is necessary to fully understand the long-term outcomes and to provide a more comprehensive analysis. Third, there was heterogeneity of the management and follow-up approaches, considering the long period of nearly 20 years in the two research centers. Therefore, further multicenter or larger cohort-based and extended observation period studies are required to corroborate our results.

5 Conclusion

In conclusion, our study provides compelling evidence that multiple factors influence RAIT efficacy in caDTC patients, with ps-Tg levels, T stage, and the therapeutic response to initial RAIT serving as key prognostic indicators. These insights underscore the importance of a tailored, risk-adapted approach for managing caDTC, paving the way for enhanced therapeutic strategies and improved patient outcomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethical Committee of the Affiliated Hospital of Qingdao University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

CW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Writing – original draft. YL: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. GW: Data curation, Investigation, Writing – original draft. XL: Writing – review & editing. YZ: Data curation, Investigation, Writing – original draft. CL: Data curation, Investigation, Writing – original draft. JL: Data curation, Investigation, Writing – original draft. NH: Data curation, Writing – original draft. ZW: Data curation, Investigation, Writing – original draft. ZS: Data curation, Investigation, Writing – original draft. FL: Writing – review & editing. GL: Data curation, Writing – original draft. RW: Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. XW: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1419141/full#supplementary-material

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Analysis of risk factors for papillary thyroid carcinoma and the association with thyroid function indicators

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Objective: This study aims to analyze the relationship between papillary thyroid carcinoma (PTC) and various factors.

Methods: The study involved two groups—PTC patients and non-PTC controls. We utilized binary logistic regression and Least Absolute Shrinkage and Selection Operator (Lasso) regression for variable selection and risk factor analysis. Correlation analysis was performed using Spearman's rank correlation. The diagnostic value of thyroid stimulating hormone (TSH) levels for PTC was assessed using Receiver Operating Characteristic (ROC) curves.

Results: PTC patients exhibited higher body mass index (BMI) (23.71 vs. 22.66, $p<0.05$) and TSH levels (3.38 vs. 1.59, $p<0.05$). Urinary iodine concentration (UIC) was an independent predictor of PTC (OR=1.005, $p<0.05$). The optimal TSH threshold for PTC diagnosis was 2.4 mIU/L [The Area Under the Curve (AUC)=67.3%, specificity=71.4%, sensitivity=70.1%]. TSH levels positively correlated with BMI ($r=0.593$, $p<0.05$) and UIC ($r=0.737$, $p<0.05$).

Conclusions: UIC may be an independent predictor of PTC, and TSH levels have some diagnostic value for identifying PTC.

KEYWORDS

PTC, TSH, iodine, BMI, ROC curve

Introduction

Thyroid cancer (TC) represents one of the most common malignancies within the endocrine system (1–4), arising from thyroid follicular epithelial cells or parafollicular epithelial cells (5–7). The primary types comprise papillary thyroid carcinoma (PTC), follicular thyroid carcinoma, medullary thyroid carcinoma, and anaplastic thyroid

carcinoma (8, 9). Since the 1970s, the incidence of TC has steadily increased (10–13), with PTC representing up to 90% of all cases (14–20). This rise is partly attributed to the widespread use of thyroid ultrasound and fine-needle aspiration biopsy (21–23), which has led to the overdiagnosis of TC (24, 25). Compared to other types of malignant cancers, TC exhibits one of the best prognostic outcomes, with a five-year survival rate that exceeds 95% (26, 27). The primary treatment for patients with TC consists of surgical interventions, complemented by radioactive iodine therapy (28, 29). Although the treatment approaches for TC are well-established, the underlying mechanisms of its pathogenesis remain elusive (30, 31). Iodine constitutes an essential micronutrient necessary for human growth and development (3, 32), playing a crucial role in the synthesis of thyroid hormones. The relationship between thyroid diseases and iodine intake exhibits a U-shaped curve (33), indicating that both iodine deficiency and excess are closely linked to the occurrence of thyroid disorders. However, research investigating the association between iodine intake and the risk of TC continues to yield conflicting results. Following the nationwide implementation of the iodized salt program in China, the issue of inadequate iodine intake among the population was significantly mitigated. Simultaneously, high iodine intake has increasingly become a focal point of research concerning thyroid diseases (34). Urinary iodine and blood iodine constitute two crucial biomarkers that reflect the iodine intake in populations. Owing to the advantages of urinary iodine as a biomarker—its convenience, cost-effectiveness, and non-invasive nature—it is considered the preferred biomarker for assessing population iodine intake in many studies. The World Health Organization (WHO) recommends utilizing the median urinary iodine (MUI) to assess iodine intake levels (34). With the notable improvement in the national economic level, living conditions have significantly improved (35), leading to a rising incidence of overweight and obesity (36–40). In numerous studies, being overweight or obese is considered a major risk factor for several types of cancer, being associated with an increased risk of various cancers (41, 42). Although the underlying mechanisms linking overweight or obesity with the risk of TC are yet to be fully elucidated (23), some studies suggest that changes in the levels of adipocytokines may be associated with the development of TC (24). The Body Mass Index (BMI) is considered an effective composite indicator for assessing changes in weight and height (43, 44). Thyroid-stimulating hormone (TSH), secreted by the anterior pituitary gland, is crucial for maintaining the normal functioning of the thyroid gland by influencing the production of thyroid hormones. Numerous studies have demonstrated an association between serum TSH levels and the occurrence of TC, suggesting a threshold effect on the risk levels of TC (8, 10). However, some research indicates that the connection lacks significance, particularly among populations with childhood TC (45). Epidemiological studies have established that radiation-induced thyroid cancer (46, 47), particularly among individuals exposed to radiation in occupational settings and those with a history of childhood ionizing radiation (48, 49), is well-documented. In addition to this well-known high-risk factor for TC, various other factors including age, sex, vitamin D deficiency (4), family history of genetic predispositions (50), smoking, alcohol consumption (51), insulin resistance, fluoride exposure, pregnancy (52), inflammatory responses (53), and environmental pollutants (such as nitrates and heavy metals) are also considered significant contributors to the risk of TC (54). In recent years, machine learning applications have proliferated in the biomedical field. Compared to traditional statistical methods, machine learning can uncover more complex interactions among variables within datasets, thereby providing deeper insights (16). Key algorithms employed include logistic regression, Lasso regression, random forests, support vector machines, and decision trees (55). In the domain of research concerning risk factors for thyroid diseases, machine learning exhibits considerable advantages and great potential. This study aims to investigate risk factors associated with PTC using several widely-used machine learning methods.

Materials and methods

Study subjects

From October 2022 to February 2024, this study was conducted at Beidahuang Industry Group General Hospital in Harbin, Heilongjiang Province, China, that involved two groups of individuals. One group comprised individuals undergoing medical examinations and was found to have no thyroid nodules on thyroid ultrasound. The other group included hospitalized patients initially diagnosed with suspicious malignant thyroid nodules using thyroid ultrasound and thyroid fine needle aspiration biopsy. Their diagnoses were subsequently confirmed as PTC after a postoperative pathological examination. For both groups, we administered questionnaires, collected urine samples, measured body metrics, and gathered data on thyroid function panel, and biochemical markers. The survey questionnaire solicited information, including age, sex, height, weight, educational background, and marital status. The inclusion criteria comprised: 1) Individuals aged 18 and above; 2) Individuals with comprehensive clinical records; 3) Individuals undergoing tests for five thyroid function indicators and biochemical levels in the hospital. The exclusion criteria included: 1) Pregnant or lactating individuals; 2) Individuals suffering from severe liver or kidney failure; 3) Individuals with Type 1 diabetes; and 4) Individuals with autoimmune diseases, including autoimmune thyroid disorders. All participants provided written informed consent, and the study received approval from the Ethical Committee of Harbin Medical University.

Physical examination, thyroid ultrasound, and thyroid fine-needle aspiration biopsy

Height and weight measurements were conducted by professional medical staff, with participants being barefoot and dressed in light clothing. The formula for calculating the BMI is the weight (in kilograms) divided by the square of the height (in

meters squared, kg/m^2). Prior to the thyroid ultrasound examination, patients are required to lie in a supine position. The examinations were conducted by experienced thyroid sonography specialists utilizing a 6-15 MHz transducer (LOGIQ E9), to assess the presence of thyroid nodules and to determine their sizes and quantities. Thyroid nodules are radiologically defined as discrete lesions within the thyroid gland, distinct from the surrounding thyroid tissue. The criteria for identifying the presence of thyroid nodules include lesions with a diameter of 3 mm or greater (56). For the evaluation of suspicious malignant thyroid nodules, an initial diagnosis is conducted via thyroid fine-needle aspiration (FNA) biopsy under ultrasound guidance, whereby tissue samples are extracted for pathological examination and analysis. Under ultrasound guidance, FNA should employ 22-23 gauge needles. The aspiration process should be conducted rapidly within the thyroid lesion under ultrasound guidance, and should be completed within a few seconds. The sampling procedure involves the following steps: (1) Sterilize the skin surface; (2) Locate the lesion using ultrasound guidance; (3) Insert the needle into the lesion; (4) Rapidly and repeatedly aspirate within the lesion for a few seconds to obtain cells via the needle's cutting action; (5) Withdraw the needle and apply pressure to the puncture site to achieve hemostasis. For most ultrasound-guided fine needle aspirations, obtaining an adequate sample typically necessitates 2-3 punctures. Ultimately, the presence of PTC is determined based on the results of the postoperative pathological examination.

Laboratory examination

Urine samples were collected from participants between 8:00 AM and 11:00 AM, without requiring fasting. Each participant's urine sample was collected in a clean plastic tube, with a minimum volume of 5 mL, and subsequently stored at -20°C. The measurement of urinary iodine concentration (UIC) was performed using the As^{3+}-Ce^{4+} catalytic spectrophotometry method, in accordance with the Chinese health standard WS/T107.1-2016. Internal quality control samples for urinary iodine level assessment were provided by the National Reference Laboratory for Iodine Deficiency Disorders (56, 57). Serum levels of TSH, free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TGAb) were determined using a chemiluminescence immunoassay (specifically, the magnetic particle chemiluminescence method) provided by New Industries Biomedical Engineering Co., Ltd., Shenzhen, China. The reference ranges for these measurements were as follows: TSH, 0.3–4.5 mIU/L; FT3, 2.0–4.2 pg/mL; FT4, 0.8–1.72 ng/dL; TGAb, 0–100 IU/mL; TPOAb, 0.38–16 IU/mL. Serum levels of potassium (K), sodium (Na), chloride (Cl), calcium (Ca), and uric acid (UA) were assessed using a fully automated Beckman AU 5800 biochemical analyzer, manufactured by Beckman Coulter, China.

Statistical analysis

Data collection was conducted using Microsoft Office Excel 2019, while statistical analyses were carried out using IBM SPSS Statistics Version 26. The Kolmogorov-Smirnov test was utilized to evaluate the normality of the data. Continuous variables with a normal distribution were characterized as mean ± standard deviation (mean ± SD) and analyzed using independent samples t-tests. For continuous variables not normally-distributed, the 25th and 75th percentiles were utilized for characterization, and analyses were conducted using the Mann-Whitney U test. Categorical variables were depicted as counts or percentages and evaluated using the chi-square test or Fisher's exact test. Spearman's rank correlation analysis was utilized to investigate the relationship between TSH levels and other factors. Binary logistic regression analysis was conducted to assess risk factors for PTC, with odds ratios (OR) and 95% confidence intervals (95% CI) being calculated to elucidate their associations with PTC. The Least Absolute Shrinkage and Selection Operator (Lasso) regression analysis represents a method of shrinkage and variable selection for linear regression models. Lasso regression analysis imposes constraints on model parameters, resulting in some regression coefficients shrinking to zero. Variables whose coefficients shrink to zero during this process are excluded from the model, whereas those with non-zero coefficients are identified as strongly correlated with the response variable. This method enhances model performance, not by excluding more independent variables beyond a certain threshold, but by precisely identifying the most significant predictors. The Lambda.1se is selected to derive models that exhibit excellent performance and incorporate a minimal number of independent variables. The Lasso method is utilized to analyze the data and identify the optimal predictors of current risk factors. Lasso regression analyses were conducted using the "glmnet" package in R version 4.2.2 to screen for risk factors associated with PTC; furthermore, plots of Lasso coefficient paths and Lasso regularization paths were generated. The "pROC" package was employed to generate Receiver Operating Characteristic (ROC) curve plots. Bubble charts were generated employing the "ggplot2" package. A p-value of less than 0.05 was deemed statistically significant.

Results

Study population and general information

This study enrolled a total of 258 participants (aged 18 and above; possessing complete clinical records; who had provided urine samples; and who had undergone thyroid function and biochemical marker level testing in the hospital): the first group of individuals (who underwent thyroid ultrasound and in whom no thyroid nodules were detected) was classified as the non-papillary thyroid carcinoma group (n=139), and the second group of inpatients (diagnosed with PTC through thyroid ultrasound, thyroid fine needle aspiration biopsy, and postoperative pathological examination) was classified as the papillary thyroid carcinoma group (n=119). In the non-papillary thyroid carcinoma group, in accordance with the exclusion criteria, two individuals who were pregnant or lactating, eleven with severe hepatic or renal dysfunction, five with Type 1 diabetes, and nine with autoimmune

diseases were excluded. Ultimately, a total of 112 participants were retained in the non-papillary thyroid carcinoma group. In the papillary thyroid carcinoma group, in accordance with the exclusion criteria, one pregnant or lactating inpatient, three inpatients with severe hepatic or renal dysfunction, three inpatients with Type 1 diabetes, and five inpatients with autoimmune diseases were excluded. Ultimately, a total of 107 participants were retained in the papillary thyroid carcinoma group, as depicted in Figure 1. Age, sex, BMI, educational background, and marital status for both groups are detailed in Table 1. No statistically significant differences were observed between the groups in terms of age (54.99 vs. 57.08, t=1.52, p=0.13), sex (χ^2=0.12, p=0.76), and education levels (χ^2=2.28, p=0.52), with the majority having completed middle or high school education and a minority possessing either elementary education or higher academic degrees. However, significant statistical differences were noted in BMI (23.71 vs. 22.66, t=-3.36, p<0.05) and marital status (χ^2=11.12, p<0.05). The majority of participants in both groups were married, with unmarried, widowed, and divorced individuals constituting a smaller proportion.

Comparison of thyroid function indicators

As indicated in Table 2, a statistically significant difference exists between the two groups in terms of TSH levels (3.38 vs. 1.59, Z=-4.43, p<0.05). No statistical differences were noted in FT3 (3.04 vs. 3.05, Z=-0.54, p=0.59), FT4 (1.26 vs. 1.28, Z=-0.72, p=0.48), TGAb (14.7 vs. 11.95, Z=-0.26, p=0.80), or TPOAb (2.32 vs. 2.39, Z=-0.26, p=0.79). In this study, with PTC status designated as the dependent variable and

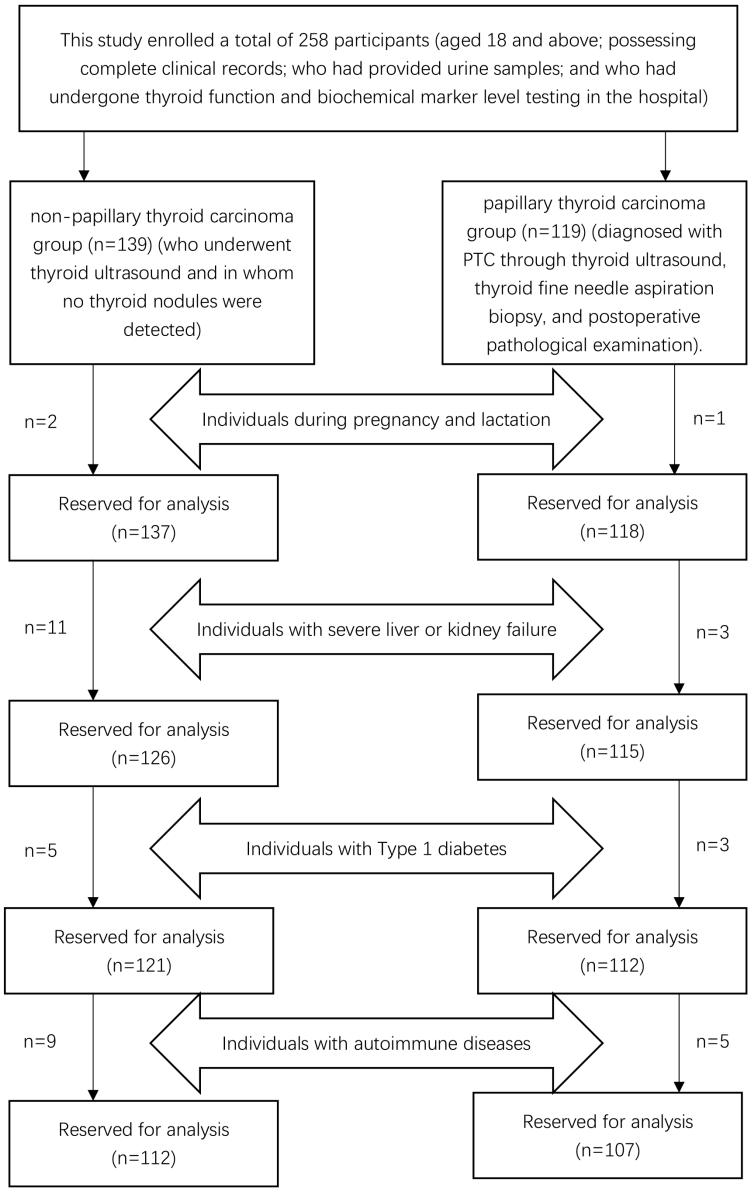

FIGURE 1
Flowchart of the participants' screening process.

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TABLE 1 Basic information for papillary thyroid carcinoma group and non-papillary thyroid carcinoma group.

Variables	Thyroid Cancer (-)	Thyroid Cancer (+)	t (χ^2)	P
Age (year)	57.08 ± 9.55	54.99 ± 10.79	1.52	0.13
BMI (kg/m^2)	22.66 ± 2.21	23.71 ± 2.38	-3.36	<0.05
Sex			0.12	0.76
Male	27 (24%)	28 (26%)		
Female	85 (76%)	79 (74%)		
Marital Status			11.12	<0.05
Unmarried	0 (0%)	3 (3%)		
Married	98 (88%)	87 (81%)		
Widowed	14 (12%)	10 (9%)		
Divorced	0 (0%)	7 (7%)		
Education Level			2.28	0.52
Primary school and below	18 (16%)	22 (21%)		
Junior high school	56 (50%)	43 (40%)		
Senior high school	30 (27%)	32 (30%)		
College and above	8 (7%)	10 (9%)		

Thyroid Cancer (-), non-papillary thyroid carcinoma group; Thyroid Cancer (+), papillary thyroid carcinoma group; BMI, body mass index.

TSH as the independent variable, the ROC curve analysis was utilized to identify the optimal TSH threshold for distinguishing between the two groups. The identified optimal TSH threshold was established at 2.4 mIU/L, exhibiting a specificity of 71.4% and a sensitivity of 70.1%. The area under the curve (AUC) was calculated to be 67.3% (95% CI: 59.9%-74.7%), as illustrated in Figure 2.

Comparison of serum ions, uric acid, and urinary iodine concentrations

As demonstrated in Table 3, a statistically significant difference was observed between the two groups in terms of UIC (226.45 vs. 121.23, Z=-4.99, p<0.05). However, no significant differences were detected in K (3.95 vs. 4.00, t=0.99, p=0.32), Na (141.72 vs. 141.74, t=0.07, p=0.95), Cl (106.01 vs. 105.76, t=-0.51, p=0.62), Ca (2.30 vs. 2.28, Z=-0.87, p=0.39), or UA (300 vs. 292, Z=-0.77, p=0.44).

Independent predictive factors for PTC

In our study, PTC was designated as the dependent variable, and the initial binary logistic regression model was constructed with K, Na, Cl, Ca, UA, and UIC serving as independent variables. The analysis revealed a significant positive association between UIC (OR=1.005, 95% CI: 1.002-1.007, p<0.05) and the prevalence of PTC, while no significant associations emerged for K, Na, Cl, Ca, and UA in relation to PTC. Upon further incorporating age, sex, and BMI as covariates, a second binary logistic regression model was developed. In this model, although BMI exhibited significance in univariate analysis (OR=1.047, 95% CI: 0.907-1.21, p=0.53), it did not retain its statistical significance. However, UIC (OR=1.004, 95% CI: 1.001-1.007, p<0.05) continued to be significantly associated with an increased risk of PTC. Finally, upon integrating five thyroid function indicators into the third binary logistic regression model, TSH, despite its significance in univariate analysis (OR=0.991, 95% CI: 0.894-1.1, p=0.869), did not exhibit statistical significance in this iteration. Yet, the association between UIC (OR=1.005, 95% CI: 1.001-1.008, p<0.05) and the risk of PTC continued to demonstrate positive significance, as illustrated in Table 4. To further validate the results of the third binary logistic regression model, PTC was employed as the dependent variable and all independent variables from the third model were incorporated into a Lasso regression model for variable selection. As illustrated in Figure 3A, the increase in the lambda value is observed to coincide with a gradual decrease in the coefficient values until they reach zero. Correspondingly, the horizontal axis demonstrates that there is a reduction in the number of variables retained as the lambda value increases. As depicted in Figure 3B, the left dashed line (lambda.min=0.047) identifies the model minimizing the Mean-Squared Error (MSE), whereas the right dashed line (lambda.1se=0.082) signifies the model that lies within one standard error of the minimum MSE, albeit with reduced complexity. Pursuing the model at the lambda.min value, BMI and UIC remained as independent variables. However, this study selected the model at the lambda.1se value as the optimal model, with UIC emerging as the sole variable, as shown in Table 5.

The correlation analysis of TSH

Based on the outcomes of our previous analysis, Spearman's rank correlation was employed to further scrutinize the correlation

TABLE 2 Comparison of thyroid function indicators between papillary thyroid carcinoma group and non-papillary thyroid carcinoma group group.

Variables	Thyroid Cancer (-)	Thyroid Cancer (+)	Z	P
TSH (mIU/L)	1.59 (0.92,3.46)	3.38 (2.1,4.45)	-4.43	<0.05
FT3 (pg/mL)	3.05 (2.78,3.34)	3.04 (2.82,3.35)	-0.54	0.59
FT4 (ng/dL)	1.28 (1.14,1.41)	1.26 (1.13,1.4)	-0.72	0.48
TGAb (IU/mL)	11.95 (5.28,24.15)	14.7 (5,25.6)	-0.26	0.8
TPOAb (IU/mL)	2.39 (1.26,4.67)	2.32 (1.26,4.48)	-0.26	0.79

Thyroid Cancer (-), non-papillary thyroid carcinoma group; Thyroid Cancer (+), papillary thyroid carcinoma group; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TGAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies.

between TSH and other independent variables. The findings indicated a positive correlation between TSH and both BMI (r=0.593, p<0.05) and UIC (r=0.737, p<0.05). With an increase in UIC, a corresponding rise in TSH levels is observed; conversely, an increment in TSH levels is associated with a tendency for the circle color to become lighter, as demonstrated in Table 6 and Figure 4.

Discussion

TC represents the most common malignant tumor within the endocrine system (1, 53), with surgery as the primary treatment modality for affected patients. The underlying mechanisms of TC development remain elusive (13, 54), rendering research into the risk factors of TC critically important for its prevention. Numerous studies have demonstrated that estrogen promotes mitosis in thyroid cancer cells (36, 43), with estrogen receptors highly expressed in these cancers (35). Upon binding with these receptors, there is an increased probability of proliferation in thyroid cancer cells (25, 41). However, the biological mechanisms through which sex hormones might facilitate the progression of TC remain undetermined and warrant further evaluation. In our study, we observed no significant differences in sex or age between the papillary thyroid carcinoma group and the non-papillary thyroid carcinoma group.

Large-scale epidemiological studies utilizing the Global Burden of Disease (GBD) public database have identified a high BMI as a significant risk factor for TC (13). Extensive research exploring the biological mechanisms that link overweight or obesity to an increased risk of TC is currently being undertaken by numerous medical research institutions. These studies primarily focus on a range of biological explanations. Firstly, insulin resistance may play a prominent role in the onset and progression of TC (22, 30). Insulin and insulin-like growth factors (IGFs) share receptor

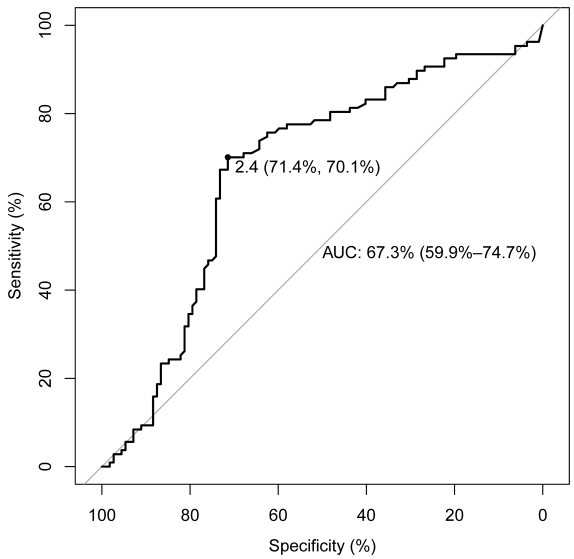

FIGURE 2
ROC curve for determining the TSH threshold in papillary thyroid carcinoma patients. The threshold for TSH concentration is set at 2.4 mIU/L, with a sensitivity of 70.1% and a specificity of 71.4%. The AUC is 67.3% (95% CI: 59.9%-74.7%).

TABLE 3 Comparison of serum ions, uric acid, and urinary iodine concentrations between the papillary thyroid carcinoma group and the non-papillary thyroid carcinoma group.

Variables	Thyroid Cancer (-)	Thyroid Cancer (+)	t (Z)	P
K (mmol/L)	4.00 ± 0.42	3.95 ± 0.37	0.99	0.32
Na (mmol/L)	141.74 ± 2.33	141.72 ± 2.23	0.07	0.95
Cl (mmol/L)	105.76 ± 2.97	106.01 ± 4.31	-0.51	0.62
Ca (mmol/L)	2.28 ± 0.11	2.30 ± 0.13	-0.87	0.39
UA (umol/L)	292 (240,343)	300 (252,343)	-0.77	0.44
UIC (mg/L)	121.23 (98.76,233.72)	226.45 (155.58,293.68)	-4.99	<0.05

Thyroid Cancer (-), non-papillary thyroid carcinoma group; Thyroid Cancer (+), papillary thyroid carcinoma group; K, serum potassium; Na, serum sodium; Cl, serum chloride; Ca, serum calcium; UA, serum uric acid; UIC, urinary iodine concentration.

TABLE 4 Establishment of a binary logistic regression model for papillary thyroid carcinoma.

Model 1					Model 2					Model 3				
		OR (95% CI)					OR (95% CI)					OR (95% CI)		
Variables	OR	Lower limit	Upper limit	P	Variables	OR	Lower limit	Upper limit	P	Variables	OR	Lower limit	Upper limit	P
K (mmol/L)	0.55	0.256	1.18	0.125	Age	0.982	0.955	1.011	0.224	Age	0.981	0.952	1.01	0.197
Na (mmol/L)	0.967	0.837	1.117	0.651	BMI (kg/m²)	1.047	0.907	1.21	0.53	BMI (kg/m²)	1.059	0.913	1.228	0.448
Cl (mmol/L)	1.045	0.95	1.15	0.369	Sex (Female v.s. Male)	1.035	0.534	2.008	0.919	Sex(Female v.s. Male)	1.063	0.544	2.077	0.859
Ca (mmol/L)	3.89	0.3	50.466	0.299	K (mmol/L)	0.569	0.262	1.234	0.153	K (mmol/L)	0.561	0.254	1.238	0.152
UA (umol/L)	1.001	0.997	1.005	0.54	Na (mmol/L)	0.957	0.827	1.108	0.56	Na (mmol/L)	0.975	0.838	1.133	0.738
UIC (mg/L)	1.005	1.002	1.007	<0.05	Cl (mmol/L)	1.051	0.954	1.159	0.314	Cl (mmol/L)	1.048	0.948	1.158	0.364
					Ca (mmol/L)	3.41	0.26	44.791	0.351	Ca (mmol/L)	2.879	0.211	39.311	0.428
					UA (umol/L)	1.001	0.997	1.005	0.538	UA (umol/L)	1.001	0.997	1.005	0.526
					UIC (mg/L)	1.004	1.001	1.007	<0.05	UIC (mg/L)	1.005	1.001	1.008	<0.05
										TSH (mIU/L)	0.991	0.894	1.1	0.869
										FT3 (pg/mL)	1.207	0.827	1.763	0.33
										FT4 (ng/dL)	0.844	0.174	4.093	0.833
										TGAb (IU/mL)	1.005	0.988	1.022	0.598
										TPOAb (IU/mL)	0.966	0.886	1.054	0.438

BMI, body mass index; K, serum potassium; Na, serum sodium; Cl, serum chloride; Ca, serum calcium; UA, serum uric acid; UIC, urinary iodine concentration; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TGAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies.

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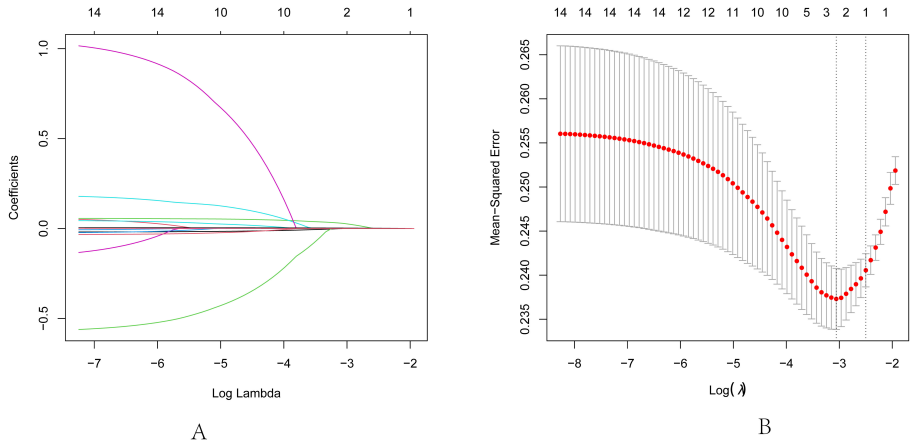

FIGURE 3
Lasso regression analysis for feature selection. **(A)** Lasso coefficient path diagram: The x-axis represents log-lambda, reflecting the degree of regularization. It shows that as the lambda value increases, the coefficient values reduce gradually to zero, and the number of retained variables decreases. **(B)** Lasso regularization path diagram: The x-axis is log (lambda); the upper axis denotes the number of non-zero coefficients, while the left y-axis represents the Mean-Squared Error (MSE). This graph demonstrates the variation in MSE with different lambda values and the confidence interval of MSE ± one standard deviation. The two vertical lines in the diagram represent the two results selected by the algorithm. The left dashed line is lambda.min, where the lambda value minimizes the MSE, and the right dashed line is lambda.1se, where the lambda value maintains the MSE within one standard error of the minimum MSE, thereby reducing the complexity of the model.

homology, thereby enabling insulin to influence the synthesis and biological activity of insulin-like growth factor-1 (IGF-1) (30, 37, 48). While insulin exerts an inducing effect on tumor growth, numerous physiological activities, including the regulation of human aging processes, are mediated through IGF-1 (35).

TABLE 5 Coefficient table for predictor selection via lasso regression.

Variables	Coef (lambda.min=0.047)	Coef (lambda.1se=0.082)
Age	.	.
BMI	0.0087	.
Sex(Female v.s. Male)		.
K (mmol/L)	.	.
Na (mmol/L)	.	.
Cl (mmol/L)	.	.
Ca (mmol/L)	.	.
UA (umol/L)	.	.
UIC (mg/L)	0.0005	0.0003
TSH (mIU/L)	.	.
FT3 (pg/mL)	.	.
FT4 (ng/dL)	.	.
TGAb (IU/mL)	.	.
TPOAb (IU/mL)	.	.

BMI, body mass index; K, serum potassium; Na, serum sodium; Cl, serum chloride; Ca, serum calcium; UA, serum uric acid; UIC, urinary iodine concentration; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TGAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies.

Numerous tissues are capable of secreting IGFs, which primarily act in an autocrine or paracrine manner to stimulate tissue proliferation and differentiation (39, 42). Specifically, IGF-1 is closely associated with TSH-mediated thyroid cell proliferation and is considered a critical pathway in regulating thyroid gene expression (35, 42), as well as the proliferation and differentiation of thyroid cells, through the insulin/IGF-1 signaling pathway (39, 43, 48). Additionally, a majority of cancer tissues express insulin-like growth factor receptors. A study found that the expression of insulin-like growth factor-1 receptor (IGF-1R) protein and mRNA in thyroid tissues of patients with PTC was markedly higher compared to that in a healthy control group (30). Furthermore, individuals with elevated circulating levels of IGF-1 exhibit an increased risk for certain types of cancer (24). This phenomenon could be attributed to the oncogenic effects of elevated IGF-1 levels (43), which are known to promote cell mitosis and inhibit apoptosis, processes that are crucial in both cell proliferation and the inhibition of cell apoptosis. Being overweight or obese is a significant risk factor for metabolic syndrome, a condition characterized by chronically elevated levels of circulating insulin (30). The prevalence of insulin resistance is particularly high among individuals who are overweight or obese. This association may partly explain the increased risk of TC among individuals who are overweight or obese (24). Furthermore, adipose tissue secretes adipokines such as leptin, adiponectin, and prostaglandins (36, 40), which under normal physiological conditions act primarily locally in adipose tissue or affect distant target organs via the bloodstream, regulating their growth, metabolism, and tissue restructuring. However, under pathological conditions, the synthesis and secretion of adipokines become dysregulated, thereby stimulating the hypothalamic-pituitary-thyroid axis and leading to increased TSH secretion (8, 28), which promotes cell proliferation (35, 44). A perspective suggests that the binding of

TABLE 6 Spearman rank correlation analysis for TSH.

Variables	TSH (mIU/L)	
	r	p
Age	0.004	0.949
BMI	0.593	<0.05
Sex(Female v.s. Male)	-0.096	0.156
K (mmol/L)	-0.018	0.796
Na (mmol/L)	-0.089	0.191
Cl (mmol/L)	-0.031	0.645
Ca (mmol/L)	0.041	0.549
UA (umol/L)	-0.062	0.361
UIC (mg/L)	0.737	<0.05

BMI, body mass index; K, serum potassium; Na, serum sodium; Cl, serum chloride; Ca, serum calcium; UA, serum uric acid; UIC, urinary iodine concentration; TSH, thyroid stimulating hormone; r, correlation coefficient.

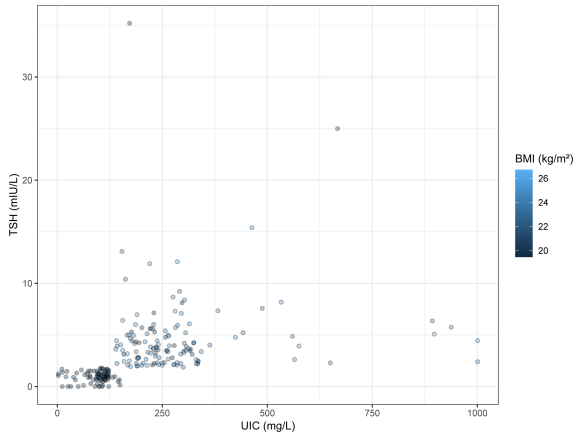

FIGURE 4
Bubble Chart. The x-axis represents UIC, and the y-axis indicates TSH concentration. The colors of the circles denote BMI values.

TSH to its receptors on adipocytes stimulates the production of interleukin-16 (IL-16) (8, 39), which mediates leptin secretion (28). Leptin may disrupt the negative feedback regulation of thyroid hormones. Additionally, leptin can directly act on thyrotropin-releasing hormone (TRH) neurons through its receptors on thyroid cells, thereby influencing TRH expression (39). As body fat increases, so too does the level of leptin secretion. In this study, univariate analysis revealed that the BMI of the papillary thyroid carcinoma group was significantly higher than that of the non-papillary thyroid carcinoma group. Furthermore, a positive correlation was observed between TSH levels and BMI, with TSH levels increasing concomitantly as BMI increased. Another study on the development of TC in relation to Bisphenol A (BPA) exposure found an interaction between BPA exposure and excessive adipose tissue, promoting the occurrence of TC. BPA in the environment tends to be stored in adipose tissue, and continuous low-level BPA exposure exacerbates chronic inflammation in these tissues. After adjusting for the study model, it was determined that metabolic syndrome is a necessary condition for BPA to promote TC. BPA may further aggravate insulin resistance, thereby influencing the incidence of TC (58). However, many studies have confirmed the increased risk of TC associated with metabolic syndrome, which is a controllable risk factor. Overweight and obesity are significant components of metabolic syndrome. Guiding the public to focus on weight management and maintaining a reasonable weight is crucial for reducing the risk of TC (59).

Iodine is an essential trace element (15, 34), crucial for the healthy development of children and pregnant women. Iodine deficiency can severely impair children's brain development and cognitive functions. Furthermore, iodine is a vital component for the synthesis of thyroid hormones (8, 33), which are essential for promoting the metabolism of sugars and lipids, facilitating growth and development, and maintaining metabolic homeostasis within the body. In the past, severe iodine deficiency was widespread across most regions of China, where dietary iodine was predominantly obtained from fish and seafood (33). In recent years, the implementation of iodized salt programs has significantly improved the iodine nutrition status in regions previously deficient in iodine. This has subsequently led to an excess of iodine in many areas. Epidemiological studies have found that an increase in iodine intake is positively correlated with the risk of PTC (35), and that the ratio of PTC to follicular thyroid cancer is correlated with iodine intake levels. In certain iodine-rich areas of China, research has revealed that the mutation rate of the BRAF gene exhibits a positive correlation with the iodine concentration in drinking water (15). This data suggests that high iodine intake could potentially trigger BRAF mutations (34), which may indirectly lead to the development of PTC (40). Another epidemiological study indicates that after iodine is ingested from external sources, it is subsequently transported into thyroid cells by the sodium-iodide symporter (NIS) (8). Iodine, hydrogen peroxide, and thyroglobulin (Tg) are then oxidized by thyroid peroxidase (TPO) to form iodinated thyroglobulin. Prolonged high iodine intake could accelerate this process, potentially leading to a shortage of hydrogen peroxide. This imbalance could trigger thyroid inflammation or the development of tumors. In a laboratory study, it was observed that iodine upregulates MAPK1 and inhibits miR-422a (34), thereby potentially stimulating the progression of TC. In this study, urine samples were collected from participants to measure urinary iodine concentrations (15). Typically, more than 80% of daily iodine intake is excreted in urine, rendering urinary iodine an effective biomarker of population iodine intake (34). In this research, urinary iodine levels emerged as an independent predictive factor for PTC. Higher urinary iodine concentrations might exhibit a positive correlation with the risk of developing PTC. Furthermore, analyses were conducted on K, Na, Cl, and Ca levels, yet no significant correlation was observed between these elements and the incidence of PTC.

TSH is recognized as a critical hormone secreted by the anterior pituitary gland, playing an integral role in the regulation of thyroid function. This encompasses the modulation of thyroid cell proliferation, in addition to the secretion and synthesis of thyroid hormones and the regulation of the thyroid's blood supply (39).

Pituitary disorders may directly impair the synthesis and release of TSH, while hypothalamic diseases can affect the secretion of thyrotropin-releasing hormone (TRH), thereby indirectly modulating TSH secretion (8). TSH modulates the secretion of thyroid hormones and regulates basal energy expenditure, thus potentially contributing to the etiology of TC. TSH plays a role in the mitotic activities of the thyroid gland (22), and a positive correlation has been observed between TSH levels and the risk of TC (36). Prolonged exposure to elevated levels of TSH may stimulate thyroid cell proliferation and elevate the risk of malignant mutations in these cells (14, 31, 45), potentially precipitating the onset of TC (6, 43). An additional biological mechanism proposed involves TSH potentially influencing the downregulation of p53 protein expression, which may affect the progression of TC. The specific biological mechanisms warrant further investigation (8). The relationship between TSH and TC is multifaceted. Determining whether TSH acts as a trigger for the onset of TC or as a promoter of its progression underscores the importance of further research into the connection between TSH and TC (10). In this investigation, the levels of TSH were observed to be significantly higher in the papillary thyroid carcinoma group than in the non-papillary thyroid carcinoma group. The ROC curve was utilized to evaluate the diagnostic value of TSH in PTC. A threshold concentration of TSH was identified at 2.4 mIU/L, with an area under the curve (AUC) of 67.3%, and both sensitivity and specificity exceeded 70%. Moreover, Spearman's rank correlation analysis was employed to assess the relationship between TSH and other indicators. It was found that BMI and UIC were positively correlated with TSH, suggesting that TSH levels could be influenced by these factors. Uric acid (UA), the end product of purine metabolism, acts as an antioxidant (60). High levels of UA have been associated with various diseases. Epidemiological studies have suggested that elevated UA levels may constitute a risk factor for the development of thyroid nodules (61). However, there have been no prior studies addressing the relationship between UA and PTC. In this investigation, the connection between UA and PTC was analyzed. A clear link between UA levels and the presence of PTC was not found. Finally, the significance of our study lies in its ability to provide direction for exploring the etiology of PTC through statistical analysis of potential risk factors. Furthermore, regarding disease prevention, the public should consider their own conditions. High-risk individuals, in particular, should monitor changes in their indicators and undergo timely health check-ups.

This study has several limitations. Firstly, our study population, primarily derived from a hospital setting, posed challenges in avoiding selection bias in participant selection, diagnosis of target groups, and study implementation. Future research should aim to be conducted across multiple hospitals to consider diverse risk factors, foster collective intelligence, and enhance experimental design quality. Secondly, Future research should expand the sample size and include different geographic regions to validate the generalizability of the current results. Lastly, although 24-hour urinary iodine excretion is an effective indicator of overall iodine levels, its reliance on urine samples makes it susceptible to external influences such as diet. Despite these limitations, this research continues to provide valuable directions and insights for studies on PTC.

Conclusions

UIC serves as an independent predictive factor for the occurrence or progression of PTC. TSH possesses significant diagnostic value for PTC, with a defined diagnostic threshold. A close relationship has been observed between TSH, BMI, and UIC. TSH levels are influenced by these indicators, potentially showing an upward trend with increases in UIC and BMI.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of Harbin Medical University. All participants consent to participate in this study. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JL: Writing – original draft. ZF: Writing – review & editing. RG: Writing – review & editing. PL: Writing – review & editing. FM: Writing – review & editing. LF: Writing – review & editing. LL: Writing – review & editing. YD: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Dynamic estimates of survival of patients with poorly differentiated thyroid carcinoma: a population-based study

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Background: The real-time prognostic data of patients with poorly differentiated thyroid carcinoma (PDTC) after surviving for several years was unclear. This study aimed to employ a novel method to dynamically estimate survival for PDTC patients.

Methods: A total of 913 patients diagnosed with PDTC between 2014 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database, was recruited in our study. Kaplan–Meier method was used to estimate the overall survival (OS). The conditional survival (CS) outcomes of PDTC were analyzed and CS rates were calculated using the formula CS(y/x) = OS(y+x)/OS(x), whereby CS(y/x) denotes the probability of a patient enduring an additional y years subsequent to surviving x years following the diagnosis of PDTC. The least absolute shrinkage and selection operator (LASSO) regression was employed to identify prognostic predicters and multivariate Cox regression was utilized to develop a CS-nomogram. Finally, the performance of this model was evaluated and validated.

Results: Kaplan–Meier survival analysis unveiled patient outcomes demonstrating an OS rate of 83%, 75%, and 60% respectively at the end of 3, 5, and 10 years. The novel CS analysis highlighted a progressive enhancement in survival over time, with the 10-year cumulative survival rate progressively augmenting from its initiation of 60% to 66%, 69%, 73%, 77%, 81%, 83%, 88%, 93%, and finally 97% (after surviving for 1-9 years, respectively) each year. And then 11 (11/15) predictors including age at diagnosis, sex, histology type, SEER stage, T stage, N stage, M stage, tumor size, coexistence with other malignancy, radiotherapy and marital status, were selected by LASSO analysis under the condition of lambda.min. Multivariate Cox regression analysis further highlighted the significant impact of all these predictors on the OS of PDTC and we successfully established and validated a novel CS-nomogram for real-time and dynamic survival prediction.

Conclusions: This was the first study to analyze the CS pattern and demonstrate a gradual improvement in CS over time in long-term PDTC survivors. We then successfully developed and validated a novel CS-nomogram for individualized, dynamic, and real-time survival forecasting, empowering clinicians to adapt and

refine the patient-tailored treatment strategy promptly with consideration of evolving risks.

KEYWORDS

poorly differentiated thyroid carcinoma, SEER, prognosis, conditional survival, nomogram

Introduction

Poorly differentiated thyroid carcinoma (PDTC), a predominantly rare clinical entity, comprises approximately 2-15% of the total diagnosed thyroid cancers (1–4). The term of PDTC emerged initially during the 1980s, yet its definitive acknowledgement as a unique pathological classification did not occur until the issuance of the most recent version of the Endocrine Tumor Classification system by the World Health Organization (WHO) in 2004 (5). As defined by the WHO classification, PDTC possesses a unique natural course and histopathological traits which establish it as an intermediary entity between well-differentiated and undifferentiated (anaplastic) thyroid malignancies (6). And in these tumors, advanced stage metastases are prevalent, with lung and bone representing the most frequent sites of disseminated metastases (7). Owing to its aggressive characteristics, PDTC stands as the predominant contributor to cancer-specific mortality within non-anaplastic follicular cell-derived thyroid carcinomas, signifying an urgent demand for further research on this disease.

With advancements in screening methodology and treatment strategy, the survival of these PDTC patients has improved significantly, demonstrating 5- and 10-year overall survival (OS) rates of 70% and 50%, respectively (8, 9). Nevertheless, these survival data offer solely a restricted predictive value for new individuals who receive their diagnoses. And long-term survivors may exhibit heightened concern regarding precise information on survival evaluation. However, traditional survival evaluations, estimated from the time of diagnosis, failed to provide accurate survival predictions for individuals who maintained survival for multiple years. Thus, utilization of an innovative prognostication computation methodology is imperative to supply precise and real-time survival data for these patients.

Conditional survival (CS), which was defined as the probability that a patient would survive for a further β years after surviving for α years after diagnosis, could calculate real-time survival data and provide continuously updated predictive insights for cancer patients (10–12). And CS analysis, compared to traditional survival methods like Kaplan-Meier estimates, offers the unique ability to provide dynamic survival probabilities that evolve over time, reflecting the changing risk for patients who have already survived a certain period post-diagnosis. And this novel computational methodology has been extensively employed across several cancer types (13–16); however, the CS outcomes for PDTC remains unexplored.

Therefore, the aim of the present study was to analyze the CS of PDTC patients and propose a novel CS-integrated nomogram model for dynamic prognosis prediction based on the latest version of the Surveillance, Epidemiology and End Results (SEER) database.

Methods

SEER data source, patients and clinical variables

The SEER database, which covers approximately 34.6% of the population of the United States, possessing prospective data collection, obviated the necessity for institutional review board approval for this research. PDTC cases diagnosed between 2004 and 2015 were extracted from the SEER database using SEER*Stat (version 8.3.8) software. A total of 913 poorly differentiated grade III samples recognized with a pathologically verified PDTC as defined by the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) site classification, encompassing papillary thyroid carcinoma (PTC, 8050/3, 8260/3, and 8340/3), follicular thyroid carcinoma (FTC, 8330/3), and insular thyroid carcinoma (ITC, 8337/3).

Variables of interest included age at diagnosis (aged ≤40, 41-60 and >60 years), sex, race (white and nonwhite), histology type (PTC, FTC and ITC), SEER stage (localized, regional and distant), tumor size (<20mm, 20-39mm, and ≥40mm), coexistence with other malignancy, T stage (T1, T2, T3 and T4), N stage (N0 and N1), M stage (M0 and M1), as well as surgical procedures performed (non-total thyroidectomy and total thyroidectomy), receipt of radiotherapy treatment (no and yes), marital status categories (single, married and unknown), rural-urban (nonmetropolitan and metropolitan) and household income (<$65000 and ≥$65000). In the context of the SEER database, the definition for radiotherapy relates exclusively to treatment employing beam radiation, radioiodine, or a blend of the aforementioned.

Statistical analysis

The primary endpoint of this study was OS, with designated duration being the period extending from the time of initial diagnosis until either mortality or the final documented follow-up

appointment. Categorical data was presented in the form of counts and associated percentages.

Conditional survival analysis

The Kaplan-Meier method was used to estimate OS and absolute hazard ratio. The CS rate was calculated using the formula CS(y/x) = OS(y+x)/OS(x), whereby CS(y/x) denotes the probability of a patient enduring an additional y years subsequent to surviving x years following the diagnosis of PDTC; and OS(y/x) and OS(x), respectively refer to the (y/x)-and x-year OS rates estimated via the Kaplan-Meier approach.

Annual hazard rate

The annual hazard was computed by subdividing temporal duration into distinct sections over years, then determining the mortality statistic independently for each section, i.e., annual hazard rate=the count of casualties within a year/cumulative follow-up patients in the year (17).

CS-nomogram development

To establish the CS-nomogram, the identified patients were haphazardly stratified into the training and testing cohorts in a proportionate ratio of 7 to 3. For the predictor selection, we employed the Least Absolute Shrinkage and Selection Operator (LASSO) regression technique in conjunction with a stringent 10-fold cross-validation protocol, thereby mitigating the potential drawbacks of model overfitting. The filtered predictive indicators were elucidated regarding their influence on PDTC survival via multivariate Cox regression, subsequently utilized in the development of a CS-nomogram model. Our novel research endeavor incorporated the CS formula into the bespoke nomogram to allow for personalized predictors and dynamic survival estimation for individuals afflicted by PDTC.

Risk classification system construction

The CS-nomogram quantified these predictive factors as points, where incorporating the patient's unique variables could culminate into a total point score. Then we developed a risk classification system based on the optimal threshold of point scores among all patients to execute risk stratification for these patients. The Kaplan–Meier method with a log-rank test was conducted to evaluate the discrepancies in OS across different risk groups.

Prediction model evaluation and validation

Calibration plots were employed for comparative evaluation of the projected survival outcomes from our nomogram against the observed outcome data. The discriminatory power of the CS-nomogram was critically evaluated via varies methodologies, encompassing the concordance index (C-index), and receiver operating characteristic (ROC) curves paired with the area under this curve (AUC). The C-index is a metric used to assess the predictive accuracy of survival models. The C-index value ranges from 0.5 to 1, with values closer to 1 indicating stronger predictive capability of the model. And the time-dependent ROC curve allows for the assessment of a model's predictive performance at various time points. By examining these curves, one can evaluate how well the model performs throughout the follow-up period and discern whether it excels in early or late predictions. Moreover, the efficacy of the clinical application of this prediction model was verified through Decision Curve Analysis (DCA), which quantified the potential net advantage garnered by utilizing the nomogram.

This study's statistical analysis was conducted utilizing the R (version 4.1.0), with a significance level set at P values inferior to 0.05 for binary analyses.

Results

Demographic and clinicopathological features

We incorporated clinical data of 913 individuals diagnosed with PDTC from the SEER database within our analysis, randomizing them into two distinct cohorts, including a training group and testing group at a ratio of 7:3. Among all individuals diagnosed with PDTC, those over the age of 60 represented 44.0%, females comprised 61.2%, and a substantial 77.9% were white. Concerning the clinical pathological attributes, the vast majority of PDTCs were of the PTC subtype (69.3%), exceeding 40mm in size (47.6%) and exhibiting a localized/regional stage (81.2%). Regarding treatment, the vast majority underwent total thyroidectomy (88.8%) and radiotherapy in 69.8% of patients. Detailed information on these PDTC patients is depicted in Table 1.

Conditional survival and annual hazards over time in PDTC patients

Traditional survival analysis unveiled patient outcomes demonstrating an OS rate of 83%, 75%, and 60% respectively at the end of 3, 5, and 10 years. The novel CS analysis highlighted a progressive enhancement in survival over time, with the 10-year cumulative survival rate progressively augmenting from its initiation of 60% to 66%, 69%, 73%, 77%, 81%, 83%, 88%, 93%, and finally 97% (after surviving for 1-9 years, respectively) each year (Figure 1A). The CS(1|x) curve, demonstrating the probability of patients enduring multiple years preceding an additional year of survival, showed graphically a potentially substantial enhancement in survival within the initial year post-diagnosis (Figure 1B). Moreover, the annual hazard curve elucidated the non-linear enhancement in PDTC survival over time by evaluating the instantaneous mortality of survivors and the Figure 1C showed the annual mortality rate of PDTC progressively declined from the initial diagnosis.

Prediction model variable screening and nomogram construction

We then carried out the LASSO regression with 10-fold cross-validation in training cohort to screen prognostic factors for CS-

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TABLE 1 Patient clinicopathologic characteristics in PDTC.

Variables	All (N=913)	Training (N=639)	Validation (N=274)
Age at diagnosis			
≤40	167 (18.3%)	113 (17.7%)	54 (19.7%)
41-60	344 (37.7%)	244 (38.2%)	100 (36.5%)
>60	402 (44.0%)	282 (44.1%)	120 (43.8%)
Sex			
Male	354 (38.8%)	240 (37.6%)	114 (41.6%)
Female	559 (61.2%)	399 (62.4%)	160 (58.4%)
Race			
White	711 (77.9%)	492 (77.0%)	219 (79.9%)
Nonwhite	202 (22.1%)	147 (23.0%)	55 (20.1%)
Histology type			
PTC	633 (69.3%)	440 (68.9%)	193 (70.4%)
FTC	132 (14.5%)	95 (14.9%)	37 (13.5%)
ITC	148 (16.2%)	104 (16.3%)	44 (16.1%)
SEER stage			
Localized	389 (42.6%)	272 (42.6%)	117 (42.7%)
Regional	352 (38.6%)	242 (37.9%)	110 (40.1%)
Distant	172 (18.8%)	125 (19.6%)	47 (17.2%)
Tumor size			
<20	189 (20.7%)	145 (22.7%)	44 (16.1%)
20-39	289 (31.7%)	197 (30.8%)	92 (33.6%)
≥40	435 (47.6%)	297 (46.5%)	138 (50.4%)
Coexistence with other malignancy			
No	656 (71.9%)	451 (70.6%)	205 (74.8%)
Yes	257 (28.1%)	188 (29.4%)	69 (25.2%)
T			
T1	149 (16.3%)	110 (17.2%)	39 (14.2%)
T2	167 (18.3%)	119 (18.6%)	48 (17.5%)
T3	417 (45.7%)	279 (43.7%)	138 (50.4%)
T4	180 (19.7%)	131 (20.5%)	49 (17.9%)
N			
N0	614 (67.3%)	437 (68.4%)	177 (64.6%)
N1	299 (32.7%)	202 (31.6%)	97 (35.4%)
M			
M0	808 (88.5%)	561 (87.8%)	247 (90.1%)
M1	105 (11.5%)	78 (12.2%)	27 (9.9%)
Surgery			
Non-total thyroidectomy	102 (11.2%)	74 (11.6%)	28 (10.2%)
Total thyroidectomy	811 (88.8%)	565 (88.4%)	246 (89.8%)
Radiotherapy			
No	276 (30.2%)	186 (29.1%)	90 (32.8%)
Yes	637 (69.8%)	453 (70.9%)	184 (67.2%)
Marital status			
Single	354 (38.8%)	245 (38.3%)	109 (39.8%)
Married	521 (57.1%)	369 (57.7%)	152 (55.5%)
Unknown	38 (4.2%)	25 (3.9%)	13 (4.7%)
Rural-Urban			
Nonmetropolitan	85 (9.3%)	62 (9.7%)	23 (8.4%)
Metropolitan	828 (90.7%)	577 (90.3%)	251 (91.6%)
Household income			
<$65000	409 (44.8%)	290 (45.4%)	119 (43.4%)
≥$65000	504 (55.2%)	349 (54.6%)	155 (56.6%)

PDTC, poorly differentiated thyroid carcinoma. PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; ITC, insular thyroid carcinoma.

nomogram construction. Ultimately, 11 (11/15) predictors including age at diagnosis, sex, histology type, SEER stage, T stage, N stage M stage, tumor size, coexistence with other malignancy, radiotherapy and marital status, were selected by LASSO analysis under the condition of lambda.min (Figures 2A, B). In LASSO regression, lambda.min is determined as the value of lambda that minimizes the cross-validated prediction error. And multivariate Cox regression analysis further highlighted the significant impact of all these predictors on the OS of PDTC (Figure 2C, P<0.05) and was used to develop a CS-nomogram model. Compared to traditional survival prediction models, the CS-nomogram utilized in this study yielded CS predictions, enabling patients to ascertain not only 3-, 5- and 10-year OS after inputting personalized clinicopathological factors but also 10-year CS contingent upon the number of years they had survived post-diagnosis (Figure 3).

CS-nomogram evaluation and validation

The present investigation evaluated the performance of the model in regards to accuracy, discrimination and utility. The C-index was applied to quantify the prediction ability of the nomogram model, yielding respective values of 0.798 and 0.703 in internal training and validation cohorts. Subsequently, nomogram calibration curves were depicted for 3-year, 5-year and 10-year intervals within each cohort, indicating a substantial consistency between anticipated and actual survival probabilities in both cohorts (Figures 4A, B). Besides, the time-dependent ROC at 3-,

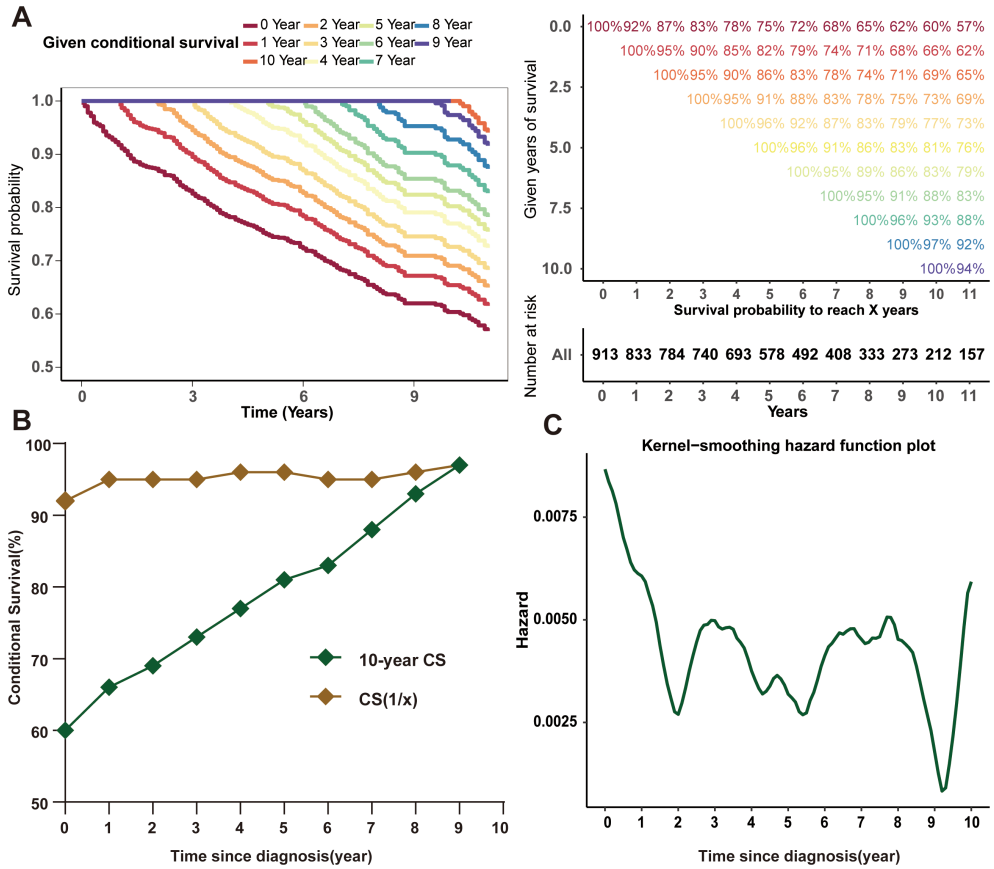

FIGURE 1
Conditional survival of PDTC patients. Kaplan-Meier method for estimating conditional survival after surviving for 0-9 years **(A)**; 10-year conditional survival curves for PDTC patients and the survival rate curve for the next year after surviving a certain time **(B)**; Annual hazard rate curve **(C)**.

5-, and 10-year AUC values in predicting CS were 0.83, 0.82, and 0.86 for the training set as well as 0.81, 0.81 and 0.81 for the validation set, respectively (Figures 4C, D). These results demonstrated the model had strong and consistent predictive performance across different time points, with stable AUC values in both the training and validation sets, indicating its robustness and reliable long-term predictive capability. Ultimately, DCA analysis was employed to evaluate the demonstrable clinical utility and advantages of the CS-nomogram in terms of predicting CS for PDTC patients. And these analyses at 3, 5 and 10 years demonstrated elevated net benefits across a range of mortality risks in both training and validation cohort for our novel CS-nomogram (Figures 5A, B), confirming the practical value of this clinical tool.

Risk stratification system development

Finally, a risk stratification system based on the CS-nomogram-derived scores was successfully developed. The CS-nomogram model was capable of quantifying all integrated variables as points and we calculated risk score for each individual. Then, based on the identified optimal threshold of 190, included patients were divided into low and high-risk groups (Figures 6A, B). Further analysis in the training and validation cohorts revealed that, for PDTC patients, individuals within the low-risk group exhibited significantly superior survival outcomes compared to those in the high-risk group (Figures 6C, D).

Discussion

PDTC, an intermediate level of aggression of thyroid malignancies, remains under the investigation of limited research literature. This study was the first to analyze the CS outcomes of these patents, and to develop a novel CS-integrated nomogram model. And the strong predictive performance of this prediction model was verified via a series of evaluation methods. Finally, a risk stratification system was successfully established for a more accurate risk stratification for PDTCs.

In clinical practice, uncertainty about the prognosis of individuals who have survived multiple years postdiagnosis could impede clinical decision-making and potentially impact upon their psychological well-being and overall quality of life (18). In most prior investigations, the prognosis of PDTC was usually analyzed using traditional survival analysis (4, 19–22), but failing to provide more prognosis data for survivors who have survived for several years. The present investigation underscored the pivotal function of

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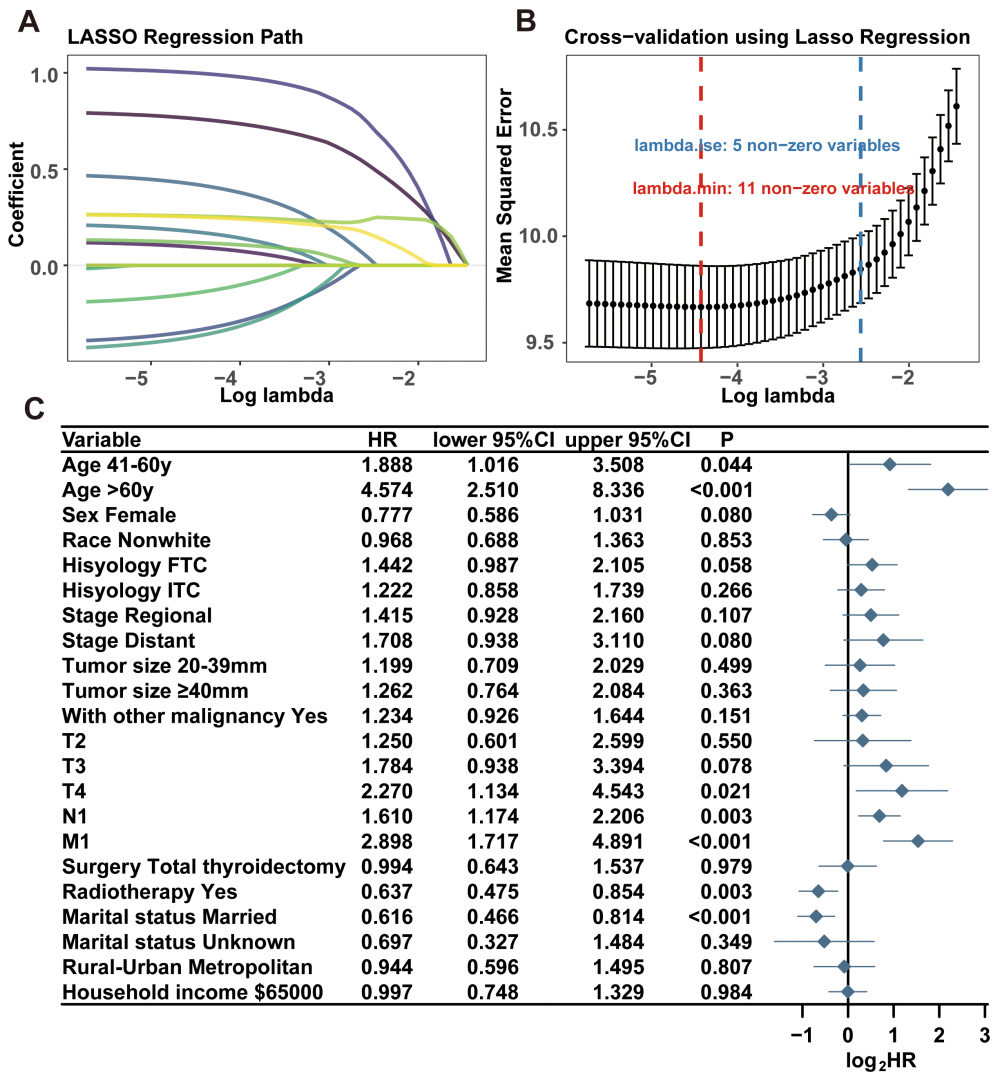

FIGURE 2
Prognostic factors identification. The least absolute shrinkage and selection operator (LASSO) regression for screening prognostic factors **(A, B)**. Multivariate Cox regression forest plot showing the effect of predictors on overall survival of PDTC **(C)**. HR, hazard ratio; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; ITC, insular thyroid carcinoma.

the CS in overcoming this limitation of traditional survival analysis. And our novel CS analysis demonstrated a progressive enhancement in the updated real-time survival over time. And it was notable to observe that within the initial stages post-diagnosis, the progressive enhancement in survivor rates overtime was considerable and was concurrent with the steepest trajectory on the survival rate curve. These findings underlined the necessity for increasing the intensity of therapeutic strategies and surveillance during the initial phases following diagnosis for this disease.

Surveillance subsequent to the diagnosis of this disease is an ongoing activity, necessitating the establishment of a dynamic survival estimation tool capable of generating precise predictive information in real-time, enabling tailored surveillance strategies (16). And there are some prognosis prediction models and survival staging systems having been proposed for PDTC patients (5, 20, 23, 24). Jin et al. constructed and validated a nomogram for forecasting the 5- and 10-year cancer-specific survival based on a large cohort with real-world samples (23). Sun et al. also developed a survival staging system providing a more accurate risk stratification for patients with PDTC than the 8th AJCC staging system (5). Nevertheless, despite all these currently published PDTC models, none have offered in real-time, updated prognostication data for survival patients. Consequently, our team developed an innovative CS-nomogram and a risk stratification system to contribute towards filling this existing research gap for PDTCs.

Our nomogram model integrated CS analysis with dynamic survival prediction capability. Moreover, it seamlessly incorporated individualized variables including age at diagnosis, sex, histology type, SEER stage, T stage, N stage M stage, tumor size, coexistence with other malignancy, radiotherapy and marital status, to enhance precise outcome evaluation. On one hand, these variables were identified using the LASSO algorithm; on the other hand, they have demonstrated a correlation with prognosis in clinical practice. Therefore, the predictive model built on these variables is both

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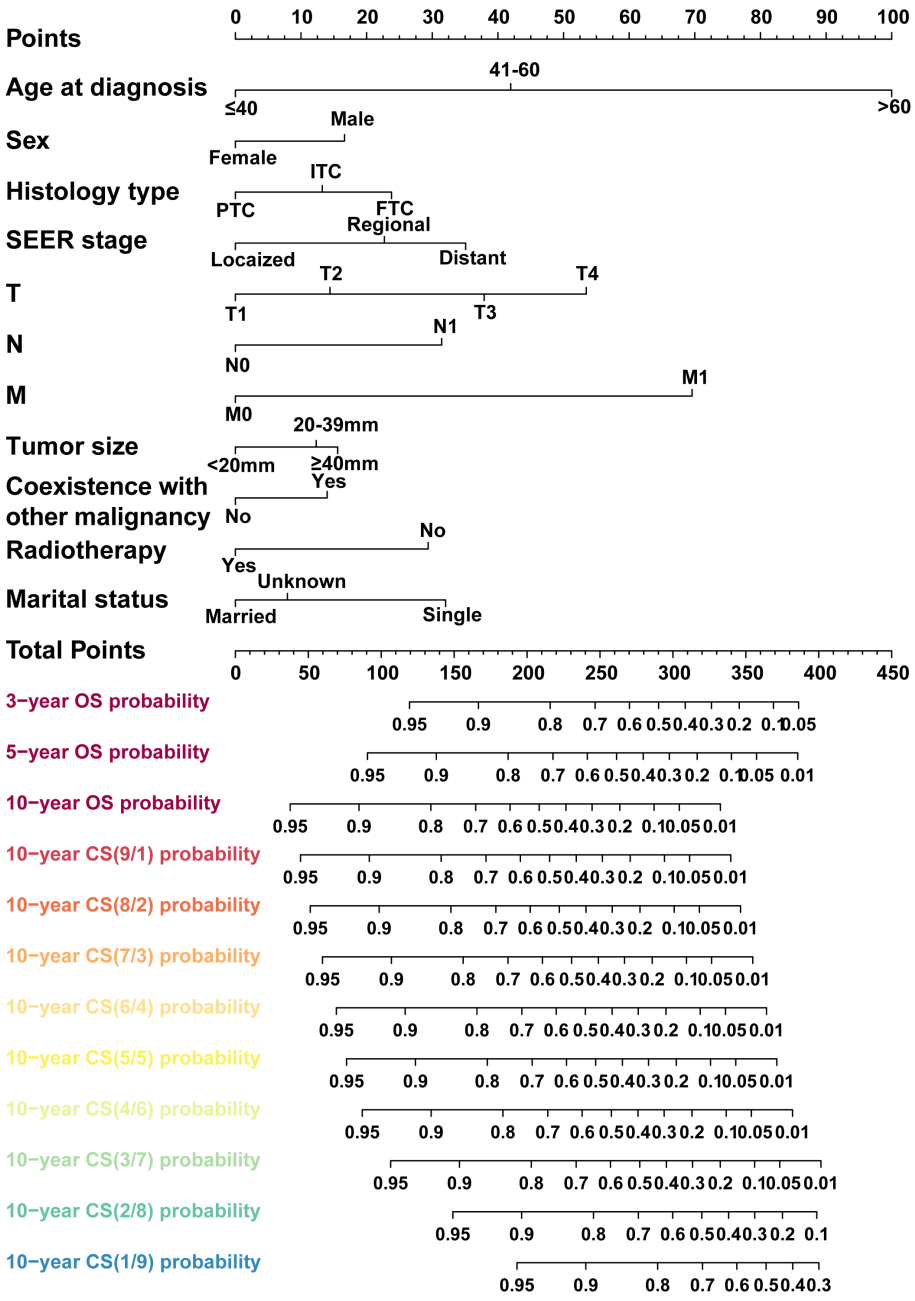

FIGURE 3
A conditional survival-based nomogram model was successfully developed for predicting 10-year CS for PDTC patients. PDTC, poorly differentiated thyroid carcinoma. PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; ITC, insular thyroid carcinoma.

reasonable and robust. The application of the nomogram model across different clinical scenarios can significantly enhance its practical value. By inputting patients' clinical characteristics, real-time survival probabilities can be obtained, which can be used to optimize clinical management and decision-making, and facilitate effective communication between doctors and patients. Moreover, this CS-nomogram has potential for providing continually updated prognostic data, empowering clinicians to adapt and refine the patient-tailored surveillance strategy promptly with consideration of evolving risks.

Indeed, the complexity of CS analysis necessitates a relatively large sample size and extended duration for follow-up study, thus, we employed SEER database to carry out this study at a population level. Concerning the performance of the CS-nomogram, it was verified that prediction model established in this study had favorable discriminative ability and accuracy for predicting 10-year CS of PDTC patients. Further DCA analysis demonstrated good clinical utility of the CS-nomogram in clinical practice. These results confirmed that our proposed model could substantially aid clinicians in predicting CS, thereby facilitating them in devising suitable therapeutic interventions for individuals with PDTC.

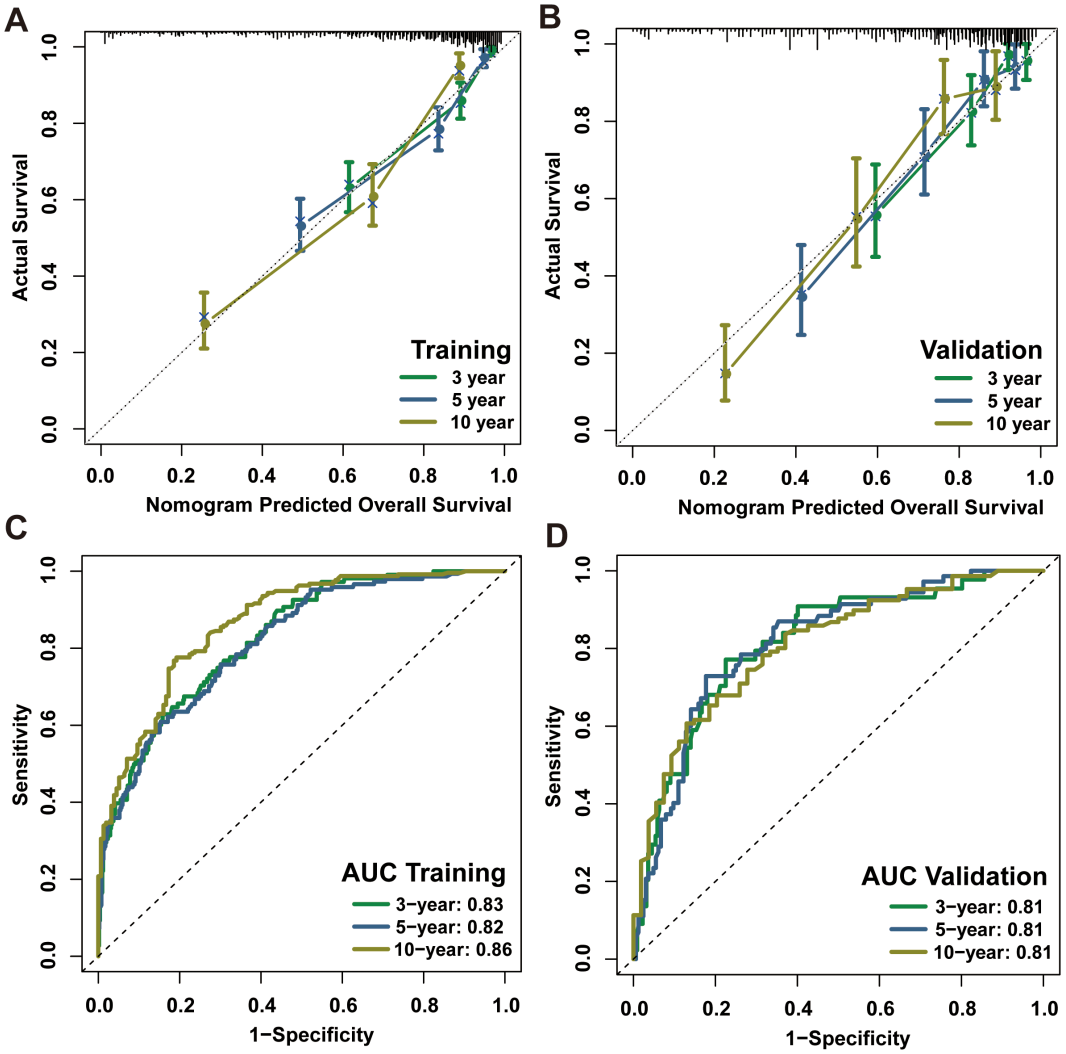

FIGURE 4
Calibration plots and ROC curves with AUC values for the CS-nomogram at 3, 5 and 10 years. Calibration plots of the CS-nomogram in training **(A)** and validation **(B)** cohorts; ROC curves of the CS-nomogram in training **(C)** and validation **(D)** cohorts. AUC, areas under the ROC curve; ROC, receiver operating characteristic curve; CS, conditional survival.

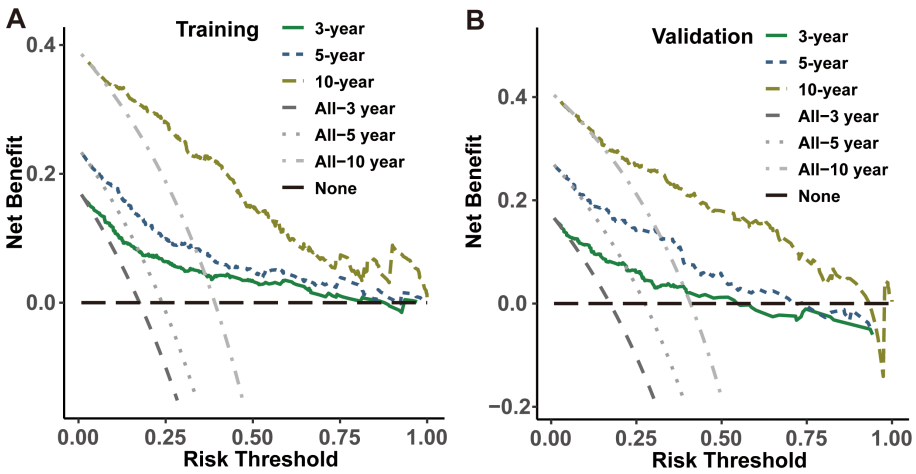

FIGURE 5
Decision curve analysis for the CS-nomogram in both the training **(A)** and validation **(B)** cohorts.

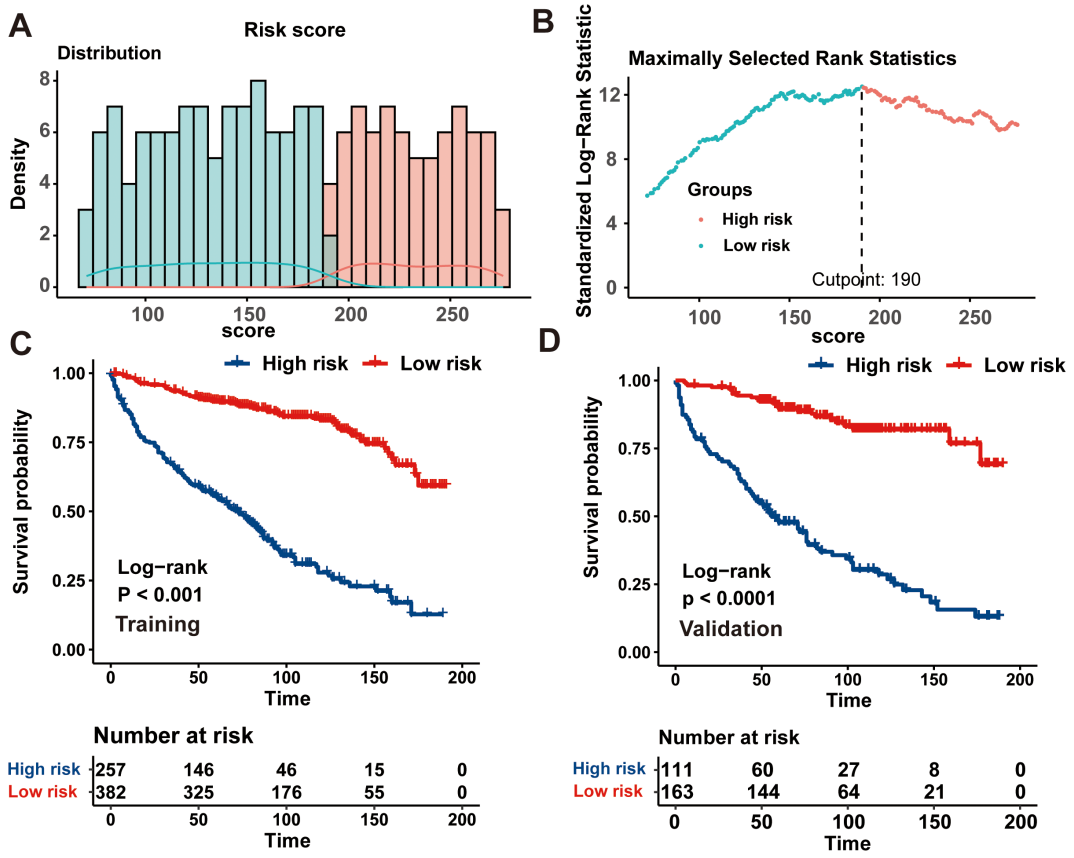

FIGURE 6
Establishment of a risk stratification system based on the condition survival- nomogram. **(A)** Distribution of risk points; **(B)** The standardized log-rank statistics; **(C, D)** Kaplan-Meier analysis utilizing the log-rank test for disparate risk groups across both training and validation cohorts.

There are some limitations should be acknowledged in our study. Firstly, this was a retrospective study and potential bias are inevitable. If the SEER database fails to encompass the entire spectrum of patient demographics or treatment contexts, the findings may not apply to populations that differ from those in the database. For example, if specific demographic groups are underrepresented or certain treatment methods are not well-represented, the observed outcomes might not accurately reflect the results for these groups or scenarios. And during sample selection phase, participants with incompletely documented variables were excluded, potentially introducing bias into the results. Secondly, due to the inherent limitation of SEER database, we were unable to procure specific data on patient treatment, including specific radiotherapeutic protocols and surgical type. Thirdly, although our nomogram had been designed and verified within the SEER database, it remains imperative to perform prospective external validations for this predictive model. Finally, it's imperative to dissect imaging and genetic factors associated with the prognosis of PDTC patients, and further optimize our prognostic nomogram.

Conclusion

This was the first study to analyze the CS pattern and demonstrated a gradual improvement in CS over time in long-term PDTC survivors. We then successfully developed and validated a novel CS-nomogram for individualized, dynamic, and real-time survival forecasting. And a risk classification system was also constructed for PDTC patient for risk stratification. We further confirmed excellent discriminative ability and potential clinical application of these models.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://seer.cancer.gov/data-software.

Author contributions

ZL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. QX: Data curation, Formal Analysis, Investigation, Project administration, Supervision, Validation, Writing – review & editing. HX: Data curation, Formal Analysis, Investigation, Project administration, Supervision, Validation, Writing – review & editing.

MW: Data curation, Formal Analysis, Investigation, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A comprehensive prediction model for central lymph node metastasis in papillary thyroid carcinoma with Hashimoto's thyroiditis: BRAF may not be a valuable predictor

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Purpose: Papillary thyroid carcinoma (PTC) frequently coexists with Hashimoto's thyroiditis (HT), which poses challenges in detecting central lymph node metastasis (CLNM) and determining optimal surgical management. Our study aimed to identify the independent predictors for CLNM in PTC patients with HT and develop a comprehensive prediction model for individualized clinical decision-making.

Patients and methods: In this retrospective study, a total of 242 consecutive PTC patients who underwent thyroid surgery and central lymph node dissection between February 2019 and December 2021 were included. 129 patients with HT were enrolled as the case group and 113 patients without HT as control. The results of patients' general information, laboratory examination, ultrasound features, pathological evaluation, and BRAF mutation were collected. Multivariate logistic regression analysis was used to identify independent predictors, and the prediction model and nomogram were developed for PTC patients with HT. The performance of the model was assessed using the receiver operating characteristic curve, calibration curve, decision curve analysis, and clinical impact curve. In addition, the impact of the factor BRAF mutation was further evaluated.

Results: Multivariate analysis revealed that gender (OR = 8.341, P = 0.013, 95% CI: 1.572, 44.266), maximum diameter (OR = 0.316, P = 0.029, 95% CI: 0.113, 0.888), multifocality (OR = 3.238, P = 0.010, 95% CI: 1.319, 7.948), margin (OR = 2.750, P = 0.046, 95% CI: 1.020, 7.416), and thyrotropin receptor antibody (TR-Ab) (OR = 0.054, P = 0.003, 95% CI: 0.008, 0.374) were identified as independent predictors for CLNM in PTC patients with HT. The area under the curve of the model was 0.82, with accuracy, sensitivity, and specificity of 77.5%, 80.3% and 75.0%, respectively. Meanwhile, the model showed satisfactory performance in the internal validation. Moreover, the results revealed that BRAF mutation cannot further improve the efficacy of the prediction model.

Conclusion: Male, maximum diameter > 10mm, multifocal tumors, irregular margin, and lower TR-Ab level have significant predictive value for CLNM in PTC patients with HT. Meanwhile, BRAF mutation may not have a valuable predictive role for CLNM in these cases. The nomogram constructed offers a convenient and valuable tool for clinicians to determine surgical decision and prognostication for patients.

KEYWORDS

papillary thyroid carcinoma, Hashimoto's thyroiditis, central lymph node metastasis, prediction model, BRAF mutation, nomogram

1 Introduction

Thyroid carcinoma (TC) is the predominant malignancy in the endocrine system, originating from thyroid follicular epithelial cells or parafollicular cells, accounting for approximately 3.4% of all newly diagnosed malignancies annually (1). Among these, papillary thyroid carcinoma (PTC), which originates from follicular cells, encompassing over 90% of reported cases (2). The majority of patients exhibit a favorable prognosis due to timely surgical intervention and radioactive iodine therapy, resulting in a 20-year survival rate exceeding 90%. Although the incidence rate of TC has increased yearly, the overall mortality rate of TC patients has remained stable at around 0.2% in the past five decades, hence TC is often characterized as a relatively indolent cancer (3). Nevertheless, approximately 40-90% of the cases experience cervical lymph node metastasis (LNM), mainly including central lymph node metastasis (CLNM) and lateral lymph node metastasis (LLNM), which is identified as a principal risk factor for postoperative recurrence and distant metastasis (4–7). For the PTC patients confirmed by cytopathology, prophylactic central lymph node dissection (pCLND) has been suggested during the surgery. However, as early as 2015, the American Thyroid Association (ATA) has stated that lobectomy alone is sufficient for clinical node-negative (cN0) patients, and a large number of pCLND will inevitably lead to overtreatment (8). Furthermore, the presence of Hashimoto's thyroiditis (HT) is associated with less advanced PTC and may serve as a protective factor against cancer progression (9). Therefore, accurate preoperative prediction of CLNM in PTC patients with HT is crucial for guiding surgical decisions and improving prognostic accuracy.

Over recent years, the widespread application of high-resolution ultrasonography, facilitated by advancements in ultrasonic technology and equipment, has paralleled an uptrend in PTC incidence (10). Ultrasound assumes a pivotal role in preoperative assessment for PTC patients. However, although ultrasound exhibits high diagnostic value for cervical lymph node metastasis in PTC, its sensitivity in detecting lymph node metastasis in the central neck region is less than 50%, particularly evident in patients with HT (11). Previous studies have observed frequent reactive hyperplasia of cervical lymph nodes in HT patients, with enlarged lymph nodes posing challenges in distinguishing them from LNM on ultrasound imaging (12).

Prior studies have identified certain ultrasound characteristics of PTC as risk factors for CLNM (13). Nevertheless, uneven glandular echoes in patients with HT may affect the ultrasound detection of potential malignant nodules, as these nodules are prone to show irregular or blurry margin (14). The influence of subtle variations in TC ultrasound features on CLNM prediction remains unclear. BRAF mutations are detectable in up to 45% of PTC cases (15). BRAF detection under fine-needle aspiration (FNA) significantly improves the accuracy of papillary thyroid cancer diagnosis, and BRAF mutations correlate closely with larger tumor size, extrathyroidal invasion, multifocality, lymph node metastasis, and advanced staging (16, 17). According to a recent meta-analysis, PTC patients with HT are 55% less likely to have BRAF mutations than PTC patients without HT, but the incidence of multifocal lesions is higher (18). In addition, another study reported that HT is only a protective factor for PTC patients without BRAF but not for patients with BRAF (19). Overall, the role of BRAF mutation in PTC patients with HT remains contentious.

In our study, we retrospectively reviewed consecutive PTC patients with and without HT to identify independent predictors of CLNM. The aim of our study was to develop an accurate and reliable prediction model and to construct a nomogram for evaluating the risk of CLNM for PTC patients with HT, aiming to guide the optimal selection of surgical modality and improve prognostic accuracy for the patients. Additionally, our study further evaluated the impact of BRAF mutation on CLNM in PTC patients with HT.

2 Materials and methods

2.1 Study design and population

This retrospective study was conducted with the approval of the Ethics Committee of the Affiliated Hospital of Jiangsu University. Patients were admitted to the hospital due to thyroid nodules from February 2019 to December 2021 and informed consents were

obtained from all the participants enrolled in the study. All patients underwent high-resolution ultrasound, FNA, and thyroid surgery including subtotal or total thyroidectomy with pCLND. Postoperative pathological analysis confirmed all cases as PTC. Inclusion criteria comprised: (1) ultrasound evidence of malignant features; (2) at least one FNA procedure; (3) absence of prior neck disease. Exclusion criteria included: (1) history of radiation exposure during adolescence or family history of TC; (2) previous neck surgery; (3) without cytopathological results; (4) histopathological findings suggestive of non-PTC; (5) without ultrasound or laboratory examination data. Finally, a total of 242 patients were enrolled in our study (Figure 1).

2.2 Data collection

Patient data collected included general information, laboratory examination, ultrasound features, pathological evaluation and BRAF mutation. General information contained age and gender of patients. Laboratory examination involved measurement of free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), thyroglobulin antibody (TG-Ab), thyroid peroxidase antibody (TPO-Ab), thyroglobulin (TG), thyroid-stimulating hormone receptor antibody (TR-Ab), and calcitonin (CT). Ultrasound features included the location, maximum diameter, markedly hypoechoic, vascularity, aspect ratio, microcalcification, margin and boundary of the nodules. Pathological evaluation included cytopathological and histopathological results. Cytopathological evaluation was interpreted and reported according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which was further classified into grades 1-6 (20). In our study, grades 1-4 were recorded as negative and 5-6 as positive. The detection of BRAF mutation specifically targeted the BRAFV600E mutation, which is a well-recognized marker for PTC. Postoperative histopathological evaluation was performed by two expert pathologists blinded to

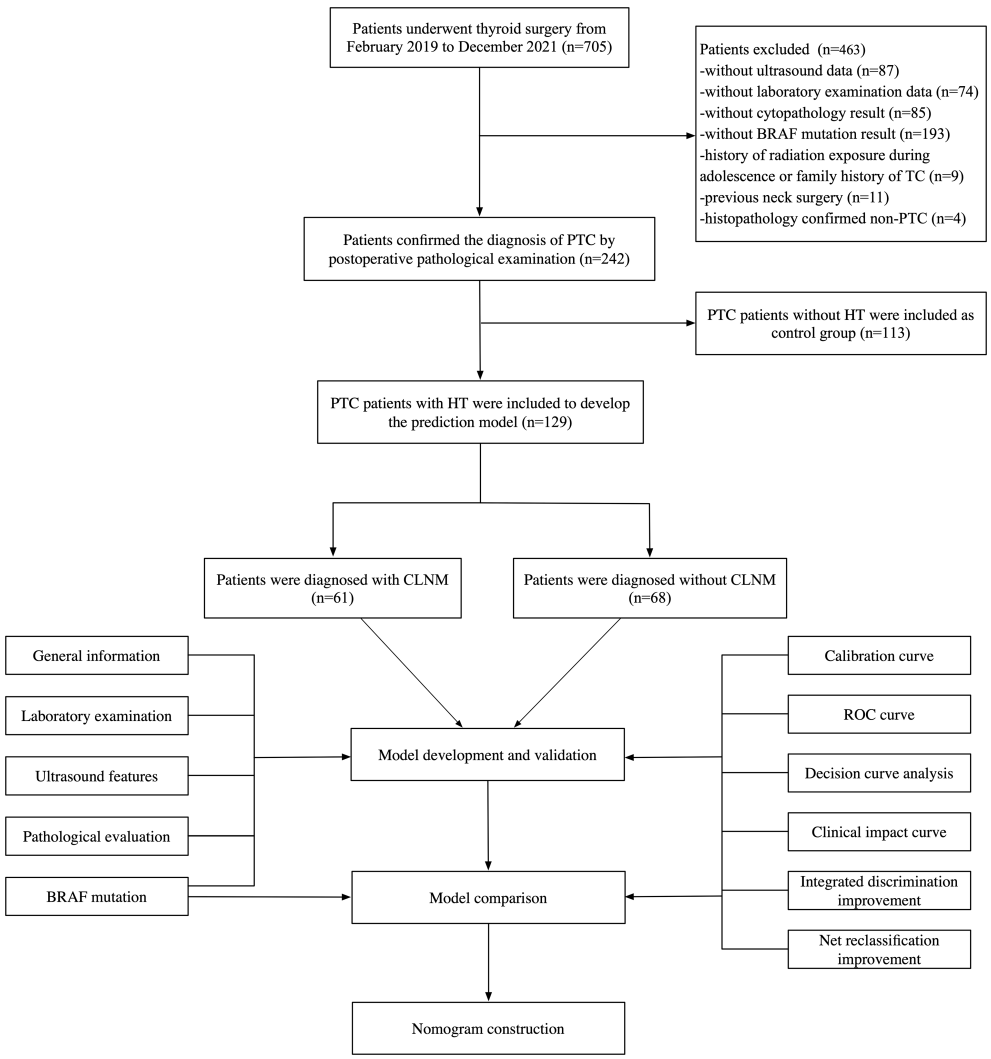

FIGURE 1
The flowchart of the study, including patient inclusion and exclusion, and statistical analysis. PTC, papillary thyroid carcinoma; HT, Hashimoto's thyroiditis.

other clinical data throughout the study. Multifocality was defined as the presence of two or more PTC lesions within the thyroid gland. Extrathyroidal extension (ETE) was defined as the invasion of surrounding structures, including the strap muscles, trachea, larynx, vasculature, esophagus, and recurrent laryngeal nerve, as observed by intraoperative frozen section evaluation.

2.3 Statistical analysis

Statistical analyses were performed using SPSS 26.0 (IBM, New York, USA) and R 4.0.2 (the R Foundation for Statistical Computing, Vienna, Austria). Initially, variables with significant differences ($P < 0.05$) between the metastatic group (CLNM) and the non-metastatic group (NCLNM) were identified as potential predictors through univariate analysis. Normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation and analyzed using independent-samples t-test, while non-normally distributed variables were expressed as median (interquartile range) and analyzed using the Mann-Whitney U test. Categorical variables were presented as frequencies (percentages) and analyzed using the Chi-squared test. Subsequently, a prediction model was established using multivariate logistic regression analysis with a two-way elimination method. When the model has the minimum Akaike information criterion (AIC) value and the model has the best goodness of fit, variables with $P < 0.05$ are considered as risk factors and included in the model. The performance of the model was evaluated using receiver operating characteristic (ROC) curves and the area under the curve (AUC). Variance inflation factor (VIF) was employed to detect multicollinearity among factors. Internal validation was conducted using the enhanced bootstrap method with 100 resampling iterations. The calibration of the prediction model was assessed using the Hosmer-Lemeshow goodness-of-fit test and calibration plots.

To compare prediction models with and without the factor BRAF mutation, AUC and area under the decision curve (AUDC) were compared using the DeLong test. Decision curve analysis (DCA) and clinical impact curve (CIC) analysis were performed. Additionally, the diagnostic ability of the two models was compared using net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Finally, static and dynamic nomograms were developed to visualize the final prediction model.

3 Results

3.1 Clinicopathological characteristics of the patients

A total of 242 patients were ultimately included in this retrospective study, including 129 patients with HT and 113 patients without HT. The clinical baseline information of patients is summarized in Table 1. Among the patients with HT, 61 patients (47.3%) developed CLNM (CLNM group), while 68 patients (52.7%) did not (NCLNM group). The cohort comprised 16 male patients (12.4%) and 113 female patients (87.6%). In the NCLNM group, there were 3 male patients (4.4%) and 65 female patients (95.6%), while in the CLNM group, there were 13 male patients (21.3%) and 48 female patients (78.7%). Gender distribution between the two groups showed a significant difference ($P = 0.004$). The median age of patients in the NCLNM group was 45 years (interquartile range, IQR: 18.75), and in the CLNM group, it was 44 years (IQR: 22.50), with no statistical difference observed between the groups ($P = 0.755$).

Regarding laboratory indicators, a significant difference was found between the two groups in TR-Ab, with values of 0.85 U/L (IQR: 0.57) in the NCLNM group and 0.63 U/L (IQR: 0.59) in the CLNM group ($P = 0.009$). However, no significant differences were observed in levels of FT3 ($P = 0.567$), FT4 ($P = 0.245$), TSH ($P = 0.914$), TG-Ab ($P = 0.932$), TG ($P = 0.256$), TPO-Ab ($P = 0.204$), and CT ($P = 0.504$) between the two groups.

Among ultrasound features of thyroid nodules, statistically significant differences were observed in maximum diameter ($P < 0.001$), aspect ratio ($P = 0.013$), and margin ($P = 0.027$) between the two groups. However, no significant differences were found in calcification ($P = 0.426$), boundary ($P = 0.765$), markedly hypoechoic ($P = 0.166$), vascularity ($P = 0.114$), and location ($P = 0.129$).

Regarding pathological evaluation and BRAF mutation, TBSRTC ($P = 0.032$), multifocality ($P = 0.001$), and extrathyroidal extension (ETE) ($P = 0.039$) showed significant differences between the two groups, while BRAF mutation did not ($P = 0.148$).

Additionally, 113 patients without HT were included in the study as control. Among them, 67 patients (59.3%) developed CLNM (CLNM group), while 46 patients (40.7%) did not (NCLNM group). The results showed that age ($P = 0.010$), maximum diameter ($P = 0.013$), microcalcification ($P = 0.012$), ETE ($P = 0.007$) and multifocality ($P = 0.002$) were significant different between the CLNM and NCLNM groups.

3.2 Development of the prediction model

The aforementioned results identified eight candidate variables significantly associated with CLNM among patients with HT: gender, TR-Ab, maximum diameter, aspect ratio, multifocality, margin, cytopathology, and ETE. These variables were included in multivariate logistic regression analysis to develop the prediction model. The continuous variable TR-Ab, which did not follow a normal distribution, was logarithmically transformed (log10) to achieve normality before analysis. Multivariate analysis revealed that gender, maximum diameter, multifocality, margin, and TR-Ab were significant independent predictors for CLNM in the final model (Table 2).

3.3 Evaluation and validation of the prediction model

The ROC curve of the prediction model was plotted (Figure 2A). The AUC value of the prediction model was 0.82 (95% CI: 0.75, 0.89), with an accuracy rate of 77.5%. The sensitivity and specificity of the model were 80.3% and 75.0%, respectively. Moreover, the positive predictive value and negative predictive value were 74.2% and 81.0%, respectively.

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TABLE 1 Comparison of the clinicopathological characteristics between CLNM and NCLNM group of the PTC patients with and without HT.

Variable	Group	HT				Non-HT			
		Cases (n=129)	CLNM (n=61)	NCLNM (n=68)	P	Cases (n=113)	CLNM (n=67)	NCLNM (n=46)	P
General information									
Age (years)			44.00 (22.50)	45.00 (18.75)	0.755		40.94 (11.89)	47.15 (13.19)	**0.010**
	<55	95	45 (73.8)	50 (73.5)	0.975	88	49 (73.1)	39 (84.8)	0.143
	≥55	34	16 (26.2)	18 (26.5)		25	18 (26.9)	7 (15.2)	
Gender					**0.004**				0.726
	Male	16	13 (21.3)	3 (4.4)		34	21 (31.3)	13 (28.3)	
	Female	113	48 (78.7)	65 (95.6)		79	46 (68.7)	33 (71.7)	
Laboratory examination									
FT3 (pmol/L)			4.71 (0.77)	4.71 (0.97)	0.567		4.96 ± 0.75¶	4.90 ± 0.64¶	0.626
FT4 (pmol/L)			15.30 ± 4.59¶	14.44 ± 3.77¶	0.245		16.90 ± 2.44¶	16.02 ± 2.32¶	0.055
TSH (μIU/mL)			2.09 (1.74)	2.09 (2.09)	0.914		1.74 (1.01)	1.74 (0.97)	0.919
TG-Ab (IU/mL)			225.80 (329.49)	244.10 (422.20)	0.932		20.36 (19.17)	18.69 (11.74)	0.640
TPO-Ab (IU/mL)			95.11 (301.61)	216.20 (409.74)	0.204		4.96 (7.73)	2.46 (8.85)	0.083
TG (ng/mL)			4.30 (11.70)	7.90 (18.28)	0.256		36.20 (67.14)	32.64 (52.59)	0.312
TR-Ab (U/L)			0.63 (0.59)	0.85 (0.57)	**0.009**		0.63 (0.67)	0.58 (0.35)	0.660
CT (pg/ml)			5.35 (1.69)	5.35 (1.57)	0.504		6.36 (3.86)	6.94 (5.15)	0.813
Ultrasound features									
TI-RADS					0.186				0.216
	3	5	4 (6.6)	1 (1.5)		1	1 (1.5)	0 (0)	
	4a	64	26 (42.6)	38 (55.9)		55	28 (41.8)	27 (58.7)	
	4b	41	19 (31.1)	22 (32.4)		45	28 (41.8)	17 (37.0)	
	4c	8	4 (6.6)	4 (5.9)		9	8 (11.9)	1 (2.2)	
	5	11	8 (13.1)	3 (4.4)		3	2 (3.0)	1 (2.2)	
Maximum diameter (mm)					**< 0.001**				**0.013**
	≤10	68	22 (36.1)	46 (67.6)		76	39 (58.2)	37 (80.4)	
	>10	61	39 (63.9)	22 (32.4)		37	28 (41.8)	9 (19.6)	
Aspect ratio					**0.013**				0.405
	<1	80	31 (50.8)	49 (72.1)		52	33 (49.3)	19 (41.3)	
	≥1	49	30 (49.2)	19 (27.9)		61	34 (50.7)	27 (58.7)	
Microcalcification					0.426				**0.012**
	No	36	15 (24.6)	21 (30.9)		60	29 (43.3)	31 (67.4)	
	Yes	93	46 (75.4)	47 (69.1)		53	38 (56.7)	15 (32.6)	
Boundary					0.765				0.815
	Clear	68	33 (54.1)	35 (51.5)		58	35 (52.2)	23 (50.0)	
	Unclear	61	28 (45.9)	33 (48.5)		55	32 (47.8)	23 (50.0)	
Margin					**0.027**				0.720
	Smooth	42	14 (23.0)	28 (41.2)		69	40 (59.7)	29 (63.0)	

(Continued)

TABLE 1 Continued

Variable	Group	HT				Non-HT			
		Cases (n=129)	CLNM (n=61)	NCLNM (n=68)	P	Cases (n=113)	CLNM (n=67)	NCLNM (n=46)	P
Ultrasound features									
	Irregular	87	47 (77.0)	40 (58.8)		44	27 (40.3)	17 (37.0)	
Markedly hypoechoic					0.166				0.167
	No	101	51 (83.6)	50 (73.5)		58	38 (56.7)	20 (43.5)	
	Yes	28	10 (16.4)	18 (26.5)		55	29 (43.3)	26 (56.5)	
Vascularity					0.114				0.146
	Sparse	97	42 (68.9)	55 (80.9)		46	31 (46.3)	15 (32.6)	
	Abundant	32	19 (31.1)	13 (19.1)		67	36 (53.7)	31 (67.4)	
Location					0.129				0.587
	Upper	38	23 (37.7)	15 (22.1)		34	17 (25.4)	17 (37.0)	
	Middle	41	14 (23.0)	27 (39.7)		56	36 (53.7)	20 (43.5)	
	Lower	45	22 (36.1)	23 (33.8)		17	10 (14.9)	7 (15.2)	
	Isthmus	5	2 (3.3)	3 (4.4)		6	4 (6.0)	2 (4.3)	
Pathology and BRAF									
TBSRTC					**0.032**				0.345
	Negative	37	12 (19.7)	25 (36.8)		9	4 (6.0)	5 (10.9)	
	Positive	92	49 (80.3)	43 (63.2)		104	63 (94.0)	41 (89.1)	
BRAF mutation					0.148				0.118
	Negative	26	9 (14.8)	17 (20.6)		39	27 (40.3)	12 (26.1)	
	Positive	103	52 (85.2)	51 (79.4)		74	40 (59.7)	34 (73.9)	
Extrathyroidal extension					**0.039**				**0.007**
	No	103	44 (72.1)	59 (86.8)		64	31 (46.3)	33 (71.7)	
	Yes	26	17 (27.9)	9 (13.2)		49	36 (53.7)	13 (28.3)	
Multifocality					**0.001**				**0.002**
	No	77	27 (44.3)	50 (73.5)		56	25 (37.3)	31 (67.4)	
	Yes	52	34 (55.7)	18 (26.5)		57	42 (62.7)	15 (32.6)	

CLNM, central lymph node metastasis; NCLNM, no central lymph node metastasis; PTC, papillary thyroid carcinoma; HT, Hashimoto's thyroiditis; TSH, thyrotropin; FT3, free triiodothyronine; FT4, free thyroxine; TG-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody; TG, thyroglobulin; TR-Ab, thyroid-stimulating hormone receptor antibody; CT, calcitonin; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology.
Except where indicated, data are presented as frequency (percentage) or median (interquartile spacing).
¶The data are presented as means ± SD (standard deviation).
Bold P values indicate statistical significance ($P < 0.05$).

Then, 65 patients (50% of the development cohort) were randomly selected as the internal validation cohort. The AUC value of the validation cohort was 0.84 (95% CI: 0.73, 0.894) (Figure 2B). The repeatability of the model development process was tested through the internal validation of the model, and the enhanced bootstrap method was used to draw the calibration curve of the model with 100 resampling iterations. According to Hosmer-Lemeshow goodness-of-fit test, the chi-square statistic was 12.40 (P=0.19), suggesting that the calibration of the model was perfect (Figure 2C).

3.4 Exploring the impact of including BRAF mutation into the prediction model

Although there was no statistical significance in BRAF mutation between the CLNM and NCLNM groups (P=0.148) in the previous results, BRAF mutation remains a pivotal factor in the progression of PTC, as evidenced by previous studies and clinical practice. Therefore, our study attempted to investigate whether the inclusion of BRAF mutations as a predictor can improve the predictive efficacy of the model has been constructed.

TABLE 2 Multivariate analysis of factors associated with CLNM in PTC patients with HT.

Variable	Group	Cases	OR	95% CI		P
				Lower	Upper	
Gender						
	Male	16	8.341	1.572	44.266	**0.013**
	Female	113	1.000			
Maximum diameter						
	≤10	68	0.316	0.113	0.888	**0.029**
	>10	61	1.000			
Aspect ratio						
	<1	80	1.000			
	≥1	49	2.020	0.728	5.610	0.177
Multifocality						
	No	77	1.000			
	Yes	52	3.238	1.319	7.948	**0.010**
Margin						
	Smooth	42	1.000			
	Irregular	87	2.750	1.020	7.416	**0.046**
TBSRTC						
	Negative	37	1.000			
	Positive	92	2.607	0.883	7.703	0.083
Extrathyroidal extension						
	No	103	1.000			
	Yes	26	2.416	0.783	7.455	0.125
TR-Ab						
		129	0.054	0.008	0.374	**0.003**

CLNM, central lymph node metastasis; PTC, papillary thyroid carcinoma; HT, Hashimoto's thyroiditis; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology; TR-Ab, thyroid-stimulating hormone receptor antibody.
The data of TR-Ab were logarithm transformed to meet the normal distribution. Bold P values indicate statistical significance ($P < 0.05$).

Statistical results shown that the AUC of the model with BRAF mutation (referred to as the new model) was 0.83 (95% CI: 0.76, 0.90), slightly higher than that of the model without BRAF mutation (referred to as the old model), which was 0.82 (95% CI: 0.75, 0.89). However, the Delong test yielded Z=-0.85761 and P=0.39, indicating no statistically significant difference between the AUCs of the two models (Figure 3A). Additionally, decision curves for both models were plotted, revealing an area under the decision curve of 0.23 for the old model and 0.24 for the new model. Analysis of the decision curves did not demonstrate that the new model yielded greater net clinical benefits compared to the old model (Figure 3B). Similarly, the clinical impact curves of the two models did not illustrate greater clinical effective rates in the new model (Figures 3C, D).

To further evaluate the reclassification performance of the new model compared with the old model, the reclassification indicators that can quantify this degree, i.e. net reclassification improvement (NRI) and integrated discrimination improvement (IDI), were calculated. The categorical NRI, continuous NRI, and IDI were 0.0017 (95% CI: -0.086, 0.089, P=0.97), 0.2637 (95% CI: -0.014, 0.542, P=0.06), and 0.0259 (95% CI: -0.001, 0.053, P=0.06), respectively, which further indicated that the performance was not significantly improved after the integration of the BRAF into the model.

3.5 Construction of the nomogram for central lymph node metastasis

Multivariable analysis demonstrated that gender, maximum diameter, multifocality, margin and TR-Ab were independent predictors of CLNM in PTC patients with HT. A nomogram based on these predictors was developed to visually represent the prediction model (Figure 4A). Moreover, leveraging the static nomogram, we established a dynamic nomogram online (https://cywujs.shinyapps.io/htptc/) for convenient generation of predicted values of CLNM for PTC patients with HT (Figure 4B).

4 Discussion

Thyroid carcinoma ranks as the most common malignant tumor of the endocrine system, with papillary thyroid carcinoma (PTC) comprising the majority (21, 22). While PTC generally exhibits a favorable prognosis as a well-differentiated papillary carcinoma, lymph node metastasis remains prevalent among patients, serving as the primary risk factor for recurrence (23). Notably, Hashimoto's thyroiditis (HT), characterized by lymphocytic infiltration of the thyroid gland causing central cervical lymph node enlargement, poses a challenge in distinguishing it from central lymph nodes metastasis (CLNM) preoperatively (24). Several studies have indicated a negative correlation between HT and lymph node metastasis in PTC. Patients with HT demonstrate more favorable pathological characteristics and prognoses, including higher rate of clinical remission and longer recurrence-free survival (25–30).

However, the ultrasound features of CLNM present a diagnostic challenge due to the complex anatomy close to the thoracic. According to previous research, the general rate of occult CLNM in PTC has been reported up to 82% (31–33). However, the results of previous studies have shown that the impact of lymph node metastasis (LNM) on the long-term prognosis of PTC patients remains controversial. Based on the analysis of the Surveillance, Epidemiology, and End Results (SEER) database by Liu et al., in some young and middle-aged PTC patients, LNM may disappear spontaneously, and the tumor may become smaller (34). In contrast, other studies shown that progressive lymph node burden independently increases the risk of distant metastasis of PTC (35, 36). Moreover, CLNM may associated with compromised survival in young patients (37). Consequently, several institutions opt for prophylactic central cervical lymph node dissection (pCLND) in PTC patients, even in the absence of imaging

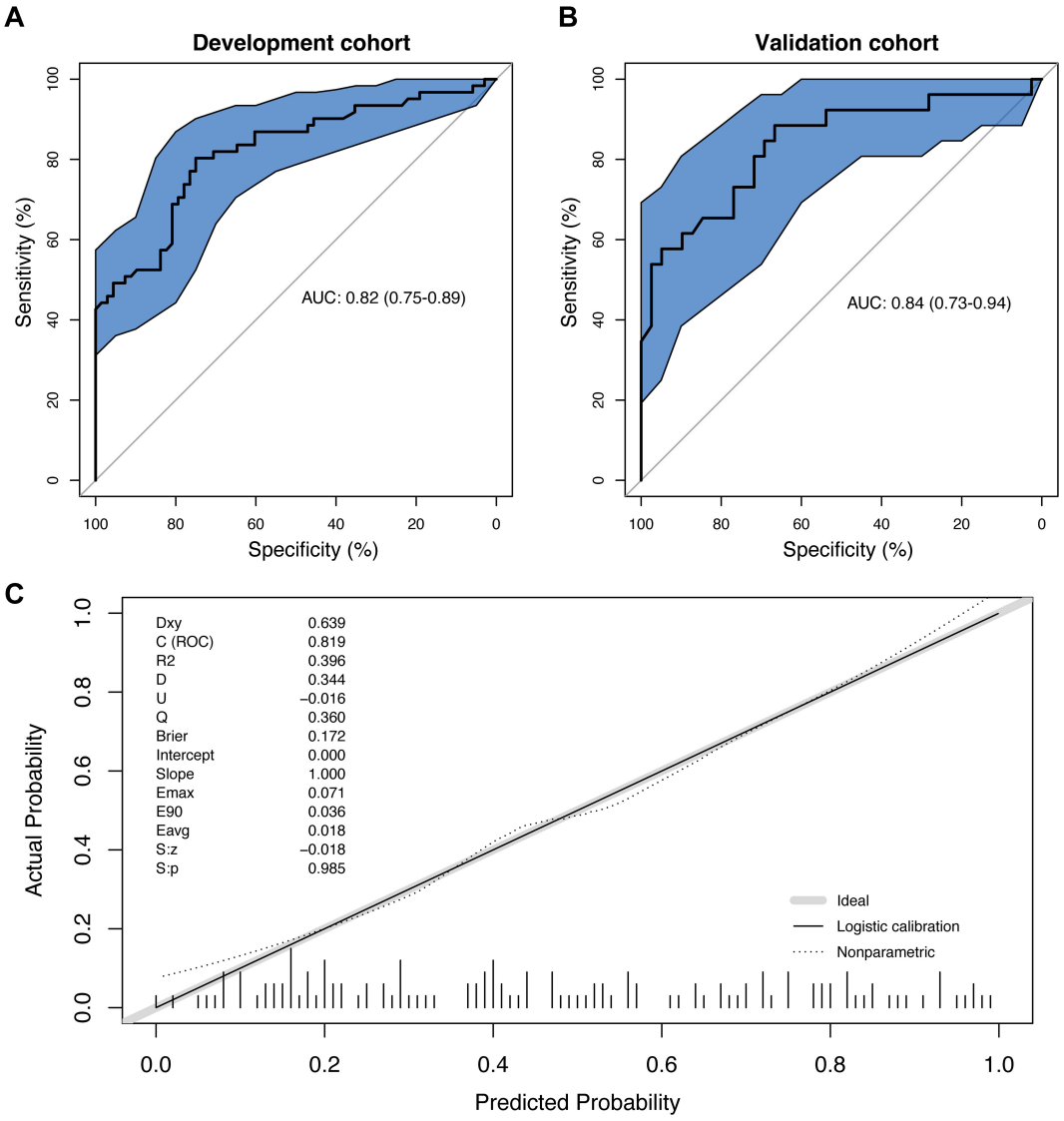

FIGURE 2
The evaluation of the prediction model. **(A)** The receiver operating characteristics (ROC) curve and area under the curve (AUC) in the development cohort; **(B)** The ROC curve and AUC in the validation cohort; **(C)** The calibration curve derived from the 100 resampling bootstrap analysis.

evidence. However, this approach carries the risk of complications such as recurrent laryngeal nerve injury, hypoparathyroidism, and chyle leakage (38–41). Therefore, accurate preoperative prediction model for CLNM at the time of initial surgery is imperative to guide clinicians in selecting the optimal therapeutic strategy and ultimately improve the outcomes of patients.

In this retrospective study, we enrolled 129 PTC patients with HT and conducted a comprehensive statistical analysis to establish a prediction model for CLNM. Univariate analysis revealed that gender, TR-Ab, maximum diameter, aspect ratio, margin, cytopathology, multifocality, ETE and multifocality were significantly correlated with CLNM among PTC patients with HT, which was different from the finding of the control group that consisted of 113 PTC patients without HT. On multivariate analysis, gender, maximum diameter, multifocality, margin and TR-Ab were independent predictors for CLNM. Subsequently, a prediction model for CLNM was constructed based on these predictors, achieving an AUC of 0.82 in the ROC curve analysis. Moreover, we developed a nomogram to visually represent the model, facilitating clinicians in predicting the risk of CLNM for PTC patients with HT.

Among the general information of patients, gender emerged as an independent predictor (P=0.01), consistent with findings from a previous meta-analysis by Mao et al. (42). Despite the higher incidence of PTC in females compared to males, our results suggest that male PTC patients may present with more aggressive features (43). Notably, age did not show significant differences between the CLNM and NCLNM groups in our study. Previous research by Du et al. identified age over 45 years as a significant independent predictor of CLNM, whereas Awny et al. reported a

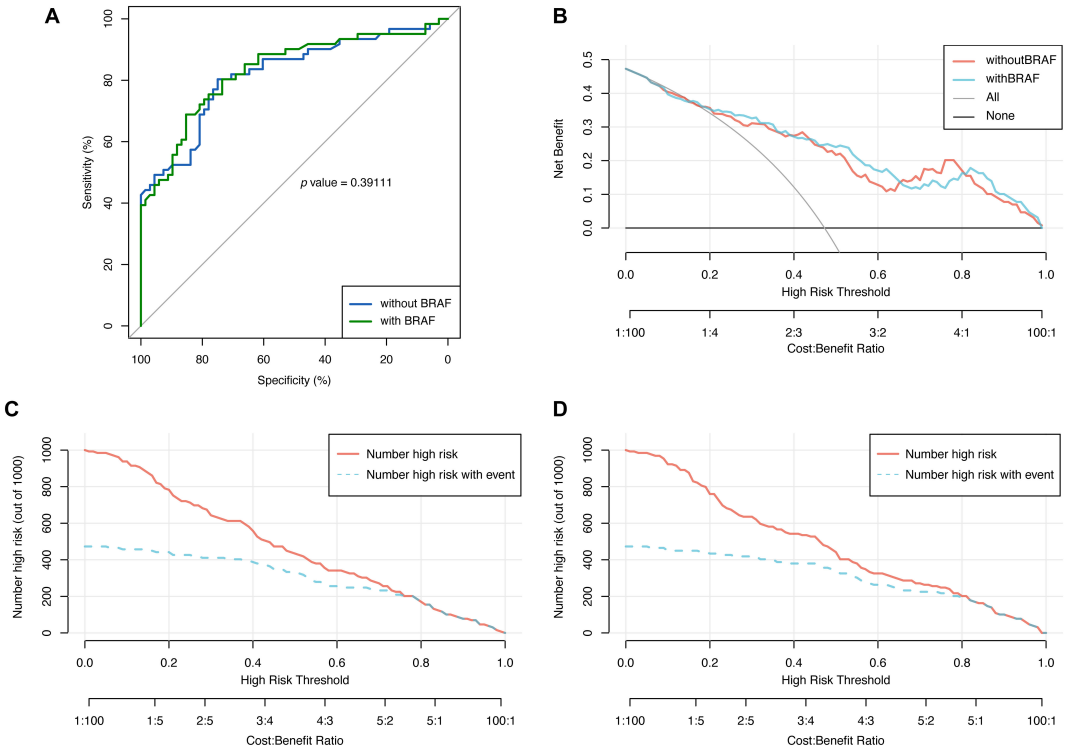

FIGURE 3
The comparison of the models with and without BRAF mutation via receiver operating characteristics (ROC) curve, decision curve and clinical impact curve. **(A)** ROC curve was used to evaluate the performance of the models with and without BRAF mutation. **(B)** Decision curve was used to evaluate the net benefit of the models with and without BRAF mutation. Clinical impact curve was used for assessing the clinical effective rates of the model without **(C)** and with BRAF mutation **(D)**.

higher likelihood of CLNM in patients younger than twenty years (44, 45). Thus, the impact of age on CLNM remains controversial and warrants further investigation.

While ultrasound is a commonly utilized method for detecting CLNM, its effectiveness is limited due to the presence of certain lymph nodes in deep anatomical locations near the trachea and surrounding structures (6, 46). In fact, PTC patients with HT have a larger number of cervical lymph node enlargements, which can be seen in about 23% of patients and bring certain challenges to the preoperative ultrasound scanning for CLNM (47). Therefore, more and more studies have tried to investigate the ultrasound characteristics of PTC to predict CLNM. In a previous study by Chen et al., which included 133 PTC patients with HT, significant statistical differences were found in nodule size (P<0.001), aspect ratio (P=0.019), and calcification (P=0.046) between patients with and without CLNM. Further multivariate analysis revealed that nodules larger than 10 mm were considered a risk factor for CLNM (P<0.001) (48). Our study corroborates these findings, with maximum diameter (P<0.01) and margin (P=0.03) emerging as independent predictors for CLNM. Interestingly, certain factors deemed important in previous studies were not included in our prediction model. For instance, some studies have suggested that tumors located in the upper pole of the thyroid are more prone to CLNM due to the rich blood supply and lymphatic drainage in this region, or due to continuous physical pressure from adjacent thyroid cartilage (49, 50). However, our study found no significant difference in tumor location between the CLNM and NCLNM groups (P=0.129), consistent with the results reported by Yu et al. (P=0.357) (51).

Thyroid peroxidase antibody (TPO-Ab) and thyroglobulin antibody (TG-Ab) are autoantibodies targeting thyroid antigens and are considered important clinical markers for Hashimoto's thyroiditis (HT), with positivity rates of approximately 75% and 90% in HT patients, respectively (52). Noel et al. evaluated the significance of TPO-Ab and TG-Ab levels associated with lymph node metastases (LNM) in patients with differentiated thyroid carcinoma (DTC), finding that preoperative TG-Ab was an independent predictor of LNM (53). However, a meta-analysis by Zhang et al. suggested that the presence of TPO-Ab is associated with an increased prevalence of DTC, while its effectiveness as a prognostic marker for DTC patients requires further investigation (54). In our study, TPO-Ab (P=0.204) and TG-Ab (P=0.932) did not show statistically significant differences in CLNM between the CLNM and NCLNM groups. Notably, thyroid stimulating hormone (TSH) has been confirmed to be a growth factor that affects the occurrence or progression of PTC (55, 56). In contrast to previous study by Liu et.al, our results revealed that TSH was not an independent predictor for PTC patients with HT (57). In view of this, we tried to include TSH into the prediction model as a predictor variable to improve its performance. However, the new model did not show better predictive ability than the old model (Supplementary Material 1). Unexpectedly, thyroid-stimulating

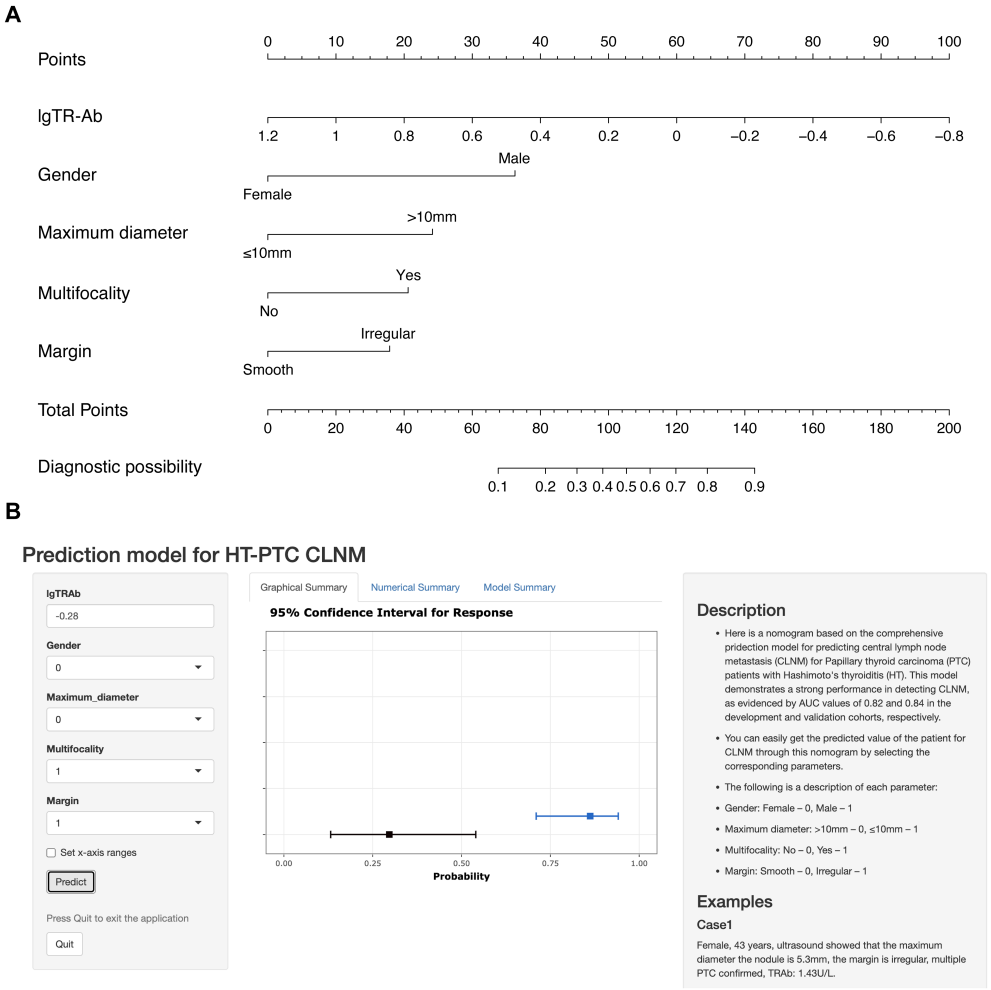

FIGURE 4
The nomogram constructed for predicting CLNM in PTC patients with HT. **(A)** the static nomogram; **(B)** the dynamic nomogram online (https://cywujs.shinyapps.io/htptc/).

hormone receptor antibody (TR-Ab), a hallmark for thyrotoxicosis and assisting in the diagnosis of Graves' disease, emerged as an independent predictor according to our results (58). TR-Ab can be further divided into two types, including stimulating (TS-Ab) and blocking (TB-Ab) which can be transformed into each other, the increased level of TR-Ab can be also detected in HT patients (59, 60). Previous studies have reported that the thyroid-stimulating hormone receptor (TSHR) is expressed not only in thyrocytes but also in TC cells, exerting significant effects on TC occurrence, development, and immune evasion (61, 62). Our results indicated that TR-Ab (P=0.009) was negatively correlated with CLNM. Of note, while significant differences were observed, most patients' TR-Ab levels remained within the normal range (0-1.5U/L), and only 5 cases in the NCLNM group (5/68, 7.35%) and 1 case in the CLNM group (1/61, 1.64%) exhibited the elevation of TR-Ab levels. We speculate that the inhibitory subtype of TR-Ab may block the binding of TSHR to TSH on PTC cells, thereby reducing the activation effect of TSH on them. The specific underlying mechanism remains to be further explored.

The BRAF mutation is widely recognized as a pivotal factor in the development and progression of PTC. Previous studies have suggested that patients harboring the BRAF mutation are closely associated with aggressive pathological features, including LNM, extrathyroidal extension, and advanced disease stages (63–65). Additionally, it correlates with the overexpression of tumor-promoting factors such as VEGF and MET, and with more aggressive tumor variants like the tall cell variant of PTC. However, its utility as a prognostic marker is debated due to its low specificity in predicting disease recurrence (66). Meanwhile, it was also revealed that for newly diagnosed well-differentiated thyroid carcinoma, BRAF does not independently predict the risk of cancer-related mortality (67). In our study, the results did not reveal a significant difference in BRAF mutation status between the groups (P=0.148). Despite the essential role of BRAF, when artificially included as a predictor in our prediction model, the new model did not demonstrate significant differences from the original model in terms of various evaluation metrics, including AUC, AUDC, CIC, NRI and IDI. These findings further suggest that BRAF mutation

status may not be related to CLNM in PTC patients with HT in our study. A recent study by Zhao et al. on the correlation between BRAF mutation and lymph node metastasis and recurrence of papillary thyroid microcarcinoma also reported similar results (68). This finding necessitates a reconsideration of current clinical practices that rely on BRAF status for risk assessment and treatment decisions. Comprehensive evaluation should be carried out by focusing on a broader range of predictors to develop personalized treatment plans, rather than relying excessively on BRAF. In addition, studies with larger sample sizes are needed to verify the limited role of BRAF in predicting CLNM in PTC patients with HT, promoting more evidence-based management strategies. This transformation will improve the accuracy of risk stratification, improve patient prognosis, and optimize resource utilization.

Among the pathological predictors, multifocality (P=0.001) and extrathyroidal extension (ETE) (P=0.039) exhibited significant differences between the two groups. Tumor multifocality is common in PTC patients, with a prevalence ranging from 18% to 87% (69). Our results indicated that multifocality (P<0.01) was an independent predictor for CLNM in PTC patients with HT, in agreement with earlier studies (70, 71). ETE has long been regarded as an unfavorable factor for DTC and previous research conducted by Bortz et al. showed that all levels of ETE were significantly associated with lymph node and distant metastasis (72). Although univariate analysis identified ETE as being associated with CLNM, there was no statistical significance in multivariate analysis in our study.

Despite the promising findings of our study, several limitations should be acknowledged. Firstly, due to the problems of image quality and the replacement of laboratory index standards, the cases in early years cannot be well included in the statistics, limiting the total volume of samples. Secondly, while the prediction model was internally validated in our study, external validation using data from other centers was lacking, which limits the assessment of its universality and applicability in different populations. Future research should focus on validating the model using independent datasets from different institutions to confirm its generalizability and robustness. Lastly, the ultrasound technology utilized in this study, including two-dimensional ultrasound and color Doppler flow imaging, did not incorporate newer ultrasound techniques such as contrast-enhanced ultrasound and elastography, which may have different characteristics relevant to CLNM.

In summary, our findings indicate that male, maximum diameter > 10mm, multifocal tumors, irregular margin and lower TR-Ab level are significantly associated with CLNM in PTC patients with HT. The developed nomogram provides a valuable tool for accurately predicting the risk of CLNM in these patients, aiding clinicians in decision-making regarding pCLND and providing important clinical reference for the prognosis of patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Affiliated Hospital of Jiangsu University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YC: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Conceptualization, Writing – review & editing. SZ: Writing – review & editing, Investigation, Resources. ZZ: Data curation, Validation, Writing – review & editing. ZC: Formal analysis, Resources, Writing – review & editing. BJ: Investigation, Writing – review & editing. MA: Data curation, Writing – review & editing. MS: Investigation, Validation, Writing – review & editing. XW: Funding acquisition, Methodology, Writing – review & editing. XZ: Funding acquisition, Visualization, Writing – review & editing. BC: Funding acquisition, Methodology, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1429382/full#supplementary-material

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Rethinking the prognosis model of differentiated thyroid carcinoma

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Background: The prediction efficiency of long-term cancer-specific survival (CSS) in guiding the treatment of differentiated thyroid carcinoma (DTC) patients is still unsatisfactory. We need to refine the system so that it more accurately correlates with survival.

Methods: This is a retrospective study using the Surveillance, Epidemiology, and End Results (SEER) database, and included patients who underwent surgical treatment and were diagnosed with DTC from 2004 to 2020. Patients were divided into a training cohort (2004–2015) and validation cohort (2016–2020). Decision tree methodology was used to build the model in the training cohort. The newly identified groups were verified in the validation cohort.

Results: DTC patient totals of 52,917 and 48,896 were included in the training and validation cohorts, respectively. Decision tree classification of DTC patients consisted of five categorical variables, which in order of importance were as follows: M categories, age, extrathyroidal extension, tumor size, and N categories. Then, we identified five TNM groups with similar within-group CSS. More patients were classified as stage I, and the number of stage IV patients decreased significantly. The new system had a higher proportion of variance explained (PVE) (5.04%) and lower Akaike information criterion (AIC) (18,331.906) than the 8th TNM staging system (a PVE of 4.11% and AIC of 18,692.282). In the validation cohort, the new system also showed better discrimination for survival.

Conclusion: The new system for DTC appeared to be more accurate in distinguishing stages according to the risk of mortality and provided more accurate risk stratifications and potential treatment selections.

KEYWORDS

differentiated thyroid carcinoma, cancer-specific survival, decision tree methodology, proportions of variance explained, TNM staging system

Introduction

As the most common type of thyroid cancer, the incidence of differentiated thyroid carcinoma (DTC) has shown a sharp rise over the past 30 years (1). To define treatment and evaluate the prognosis of patients, the American Joint Committee on Cancer (AJCC) released a new tumor-node-metastasis (TNM) system, which was based on long-term follow-up surveillance and survival diversities from population studies (2, 3). The American Thyroid Association (ATA) (4) and the British Thyroid Association (BTA) (5) regarded it as a guideline for classifying patients at the initial presentation, determining the cancer-specific survival and best initial treatment. In fact, the actual goal of DTC management is to predict recurrence, but we should also pay attention to its long-term CSS.

Age is considered as the most important prognostic factor and has been combined with the anatomic tumor extent to stage DTC since 1983 (6, 7). Although many studies (8–10) have indicated that distant metastasis has the highest hazard ratio of DTC, the TNM system still adopted age as the most important and initial dichotomous variable in the postoperative staging system over the last 40 years, rather than distant metastasis. The division by age resulted in a poor correlation between the risk of death and stage: patients with stage II disease could have a low, intermediate, or even high risk of death (11).

As knowledge of cancer biology evolves, diagnostic tools and treatment modalities have been improved constantly (3). Although the TNM staging system has been widely applied in clinic, there are still studies that query the predictive effectiveness on an individual level (10, 12–15). For example, for a 54-year-old patient with T4bN1bM1, the TNM stage should be set as stage II, and for a 56-year-old patient with T1aN1aM0, the TNM stage is also stage II. If the postoperative stage of the patient is T4aN0M0, it can even be set as stage III. This is obviously unreasonable. The balance between age and distant metastasis is controversial. A model combined with multiple factors should be built.

Recently, decision tree methodology has become popular in medical research (16–18). An example of the medical use of the decision tree is to diagnose a disease according to the symptoms, in which the categories defined by the decision tree can be different clinical subtypes or a disease, or the prognosis of different patients (19). Therefore, we aimed to use a statistically sophisticated methodology to identify cancer-specific survival (CSS) in individual patients with DTC to define more accurate staging groups than previous versions.

Materials and methods

Data source

Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database due to its large sample size. The SEER Program of the National Cancer Institute (20) is a dependable national cancer registry that is widely used within the USA. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering an estimated 26% of the US population. The mortality rate data reported by SEER are provided by the National Cancer Institute, updated annually, and provided as a public service in print and electronic formats.

Patients

All included patients had undergone initial surgery and been diagnosed with papillary thyroid carcinoma (PTC) or follicular thyroid carcinoma (FTC) by postoperative pathology between 2004 and 2020. They were identified using the histopathology codes of the International Classification of Disease for Oncology, third edition (ICD-O-3): 8050/3, 8260/3, 8340/3, 8341/3, 8342/3, 8343/3, 8344/3, 8330/3, 8331/3, 8332/3, and 8335/3. The exclusion criteria were as follows: (1) unknown age or race; (2) unclear/missing surgical information; (3) incomplete/missing information regarding tumor size, tumor extension, lymph node metastasis, or distant metastasis; and (4) the SEER cause-specific death classification was "N/A not first tumor". Because there are very few cases of distant metastasis in our center, we did not use the information from our center. All patients with missing data were excluded. Patients were divided into a training cohort (2004-2015) and a validation cohort (2016-2020). Given that the SEER database provides anonymous and public access to its data after obtaining permission, the Institutional Review Committee was not required to scrutinize this study.

General patient information was extracted from the database, including age at diagnosis, gender, histological type, and tumor size. It is worth noting that our data were somewhat different from those previously. Tumor size was divided into three subgroups (≤1 cm, 1–4 cm, and >4cm and extrathyroidal extension (ETE) had four subgroups (no, only strap muscles, T4a and T4b). CSS was defined as the time from initial surgery to the last censoring or death caused by DTC (21, 22).

Statistical analysis

All categorical variables were reported as frequency and proportion. CSS was estimated using the Kaplan–Meier method. The effect of potential predictors was estimated using Cox regression, and results were reported as a hazard ratio (HR) with a 95% confidence interval (CI). The validity of the model was examined with the area under the receiver operating characteristic curve (AUC), proportions of variance explained (PVEs), and the Akaike information criterion (AIC). AUC was displayed in the output window. The value of the AUC ranges from 0 to 1, with values closer to 1 indicating a stronger discriminative ability of the model. A mathematical formula of PVE = 1 - exp(-G^2/n) was used to determine PVE, where 'G^2' was the maximum likelihood ratio determined by the chi-square test and Cox regression analyses, and 'n' was the total number of cases in the present study. PVEs (%) range from 0 to 100; larger numbers suggest a better predictability (23, 24). The AIC was defined as follows: AIC =-2 log maximum likelihood + 2 *(the number of parameters in the model). A smaller AIC value indicated a better goodness-of-fit (25).

Decision tree

Decision tree methodology is a commonly used data mining method that is used in many applications as a powerful solution to classification and prediction problems. The method divides a data group into branch segments, and constructs an inverted tree model including root nodes, internal nodes, and leaf nodes. The Gini index is used to measure the change in "purity" of a variable after node splitting. When merging variables, the model seeks a splitting method that minimizes the Gini index. If two or more variables produce similar purity after splitting, they may be merged. It is a fast and effective method and can provide good decision support (26). The goal of a classification tree is to separate the observations belonging to one category from those belonging to another category as far as possible through a series of binary data segmentations (27).

Several algorithms have been introduced to construct decision trees, such as classification and regression trees (CARTs). The CART algorithm is one of the most commonly used methods of constructing decision trees. It was applied to our training cohort to divide the patients into several groups. We then combined adjacent groups based on their statistical properties and clinical experience to obtain the new staging system. Contrasts between adjacent stage groups were evaluated by Cox regression analysis, adjusting for baseline factors. The methodology is a built-in computational feature in SPSS, requiring no additional algorithms.

Validation cohort

The new TNM groupings and the 8th AJCC TNM staging system were applied to the validation cohort to examine CSS estimates. The estimates obtained using the new TNM groupings were compared with those obtained using the 8th AJCC TNM staging system. All statistical calculations were performed using IBM SPSS software (version 23.0) and R, version 3.1.0 (R Project).

Results

Training cohort

A total of 52,917 patients with DTC were included in the training cohort. Demographic and clinical patient characteristics are shown in Table 1. Of these, 40,848 (77.2%) were women. In the pre analysis, we firstly included age as a continuous variable, and we found that the cohort was divided into 17 subgroups, which made the system unsuitable for clinical work. Additionally, it was found that the current staging system does not perform better than the 8th AJCC TNM staging system; therefore, we still regarded it as a binary variable (<55 and ≥55). Most of the patients (96.9%) had PTC, and 18,148 (34.3%) had a tumor less than 1 cm in size. Overall, 88.7% of our cohort had no extrathyroidal extension after the initial surgery. The invasion of strap muscles and posterior neck compartments (T4a & T4b) were 7.1% and 4.2%, respectively. The incidence of cervical lymph node metastasis was 39.1% and 1.2% (654 patients)

TABLE 1 Baseline clinicopathological characteristics of patients in the training cohort.

	Case no. (%) (n=52,917)
Gender	
Female	40,848 (77.2)
Male	12,069 (22.8)
Age (years)	
<55	36,038 (68.1)
≥55	16,879 (31.9)
Histology	
PTC	51,278 (96.9)
FTC	1,639 (3.1)
Foci	
Solitary	27,866 (52.6)
Multifocal	25,051 (47.4)
Tumor size (cm)	
≤1	18,148 (34.3)
1~4	30,251 (57.2)
>4	4,518 (8.5)
ETE	
no	46,958 (88.7)
Strap muscles	3,749 (7.1)
T4a	1,569 (3.0)
T4b	641 (1.2)
N component	
N0	32,240 (60.9)
N1a	14,064 (26.6)
N1b	6,613 (12.5)
Distant metastases	
N0 M0	52,263 (98.8)
Yes M1	654 (1.2)
TNM-8 stage	
I	45,332 (85.7)
II	6,199 (11.7)
III	704 (1.3)
IVA	287 (0.5)
IVB	395 (0.7)
Extent of surgery	
LTT	3,989 (7.5)
TT	48,928 (92.5)

(Continued)

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TABLE 1 Continued

	Case no. (%) (n=52,917)
CSS	
Alive/other causes	51,922 (98.1)
Dead	995 (1.9)
Follow up (years)	7.3

had distant metastasis. The proportions of patients at the 8th edition stages I, II, III, IVA, and IVB were 85.7% (n=45,332), 11.7% (n=6,199), 1.3% (n=704), 0.5% (n=287), and 0.7% (n=395), respectively. The mean follow-up duration until censoring or death was 7.3 years. The proportion of cancer-specific deaths in the training cohort was 1.9% (n=995).

To determine the prognostic factors affecting DTC and the relevant factors suitable for inclusion in decision tree analysis, Cox proportional hazard regression analysis for variables associated with CSS was performed (eTable 1 in Supplementary Table 1). In univariate and multivariate analyses, except for foci (p=0.32), all variables were statistically significantly associated with CSS. All variables were risk factors, except for being female (HR=0.76). To confirm that there were enough patients in each leaf node of the next decision tree analysis module, we combined clinical experiences and the statistics index. Therefore, we finally decided to include these six variables in the initial analysis of the decision tree model (age at diagnosis, tumor size, histology type, ETE, and N and M categories), which can be closer to clinical applications rather than statistical applications.

With the decision tree methodology for the training cohort, M categories had the highest priority, followed by age, ETE, size, and N categories. Histology type had nearly no effect on the decision tree methodology; therefore, it was not shown in the final rules. It is worth noting that (1) in the ETE group, no ETE and only strap muscles were combined into one group and T4a and T4b were combined into one group. We recorded them as T4 later on. (2) In the tumor diameter group, the ≤1cm and 1–4 cm groups were combined into one group and recorded as the ≤4 cm group. Based on the existing interactions between predictor variables, 11 rules were extracted from the decision tree classification corresponding to 11 leaf nodes. These rules are shown in eTable 2 in the Supplementary Table 1. Then, we identified four TNM groups with a similar within-group CSS: stage I was divided into stage IA (M0, age <55, no or only strap muscles, regardless of tumor size and N), stage IB (M0, age ≥55, no or only strap muscles, ≤4 cm or >4 cm with N0; age <55, T4), stage II (M0, age ≥55, no or only strap muscles, >4 cm with N1; M0, age ≥55, T4, ≤4 cm; M1, age <55, T4 stage III (M0, age ≥55, T4, >4 cm; M1, age ≥55, no or only strap muscles, ≤ 4 cm), and stage IV (M1, age ≥55, no or only strap muscles, >4 cm; M1, age ≥55, T4) (Table 2). They differed from each other with distinct CSS rates. The differences in the number of patients in each stage are shown in Figure 1. More patients were classified as stage I, and the number of stage IV patients decreased.

Hazard ratios for the risk of cancer-specific survival and 5-year CSS for the TNM-8 and new TNM stage are displayed in Table 3 and Figure 2. According to our algorithm, differences in survival appeared to be more discriminate in the new TNM groups than the current 8th TNM staging system. In TNM-8, 5-year CSS for DTC was 99.6% for stage I, 96.5% for stage II, 86.0% for stage III, 78.4% for stage IVA, and 66.6% for stage IVB. While in the new system, CSS was 99.8% for stage IA, 98.6% for stage IB, 90.5% for stage II, 77.0% for stage III, and 54.3% for stage IV. The distinction in CSS among different groups has become more significant. The results in Table 4 demonstrated that the new system could discriminate more accurately than TNM-8. The new system has a higher PVE (5.04%), higher AUC (0.844), and lower AIC (18331.906) than TNM-8 (a PVE of 4.11%, an AUC of 0.819 and an AIC of 18,692.282). Therefore, we assumed that the new staging system revealed a higher efficiency

Validation cohort

The validation cohort had a similar population of patients with DTC from SEER (2016–2020). A total of 48,896 patients were

TABLE 2 New TNM stage derived by decision tree analysis.

Group	M	ETE	Age	Tumor size	N
IA	M0	No or only strap muscles	<55	Any	Any
IB	M0	No or only strap muscles	≥55	≤4 cm	Any
				>4 cm	N0
		T4	<55	Any	Any
II	M0	No or only strap muscles	≥55	>4 cm	N1
		T4		≤4 cm	Any
	M1	Any	<55	Any	Any
III	M0	T4	≥55	>4 cm	Any
	M1	No or only strap muscles		≤4 cm	
IV	M1	No or only strap muscles	≥55	>4 cm	Any
		T4		Any	

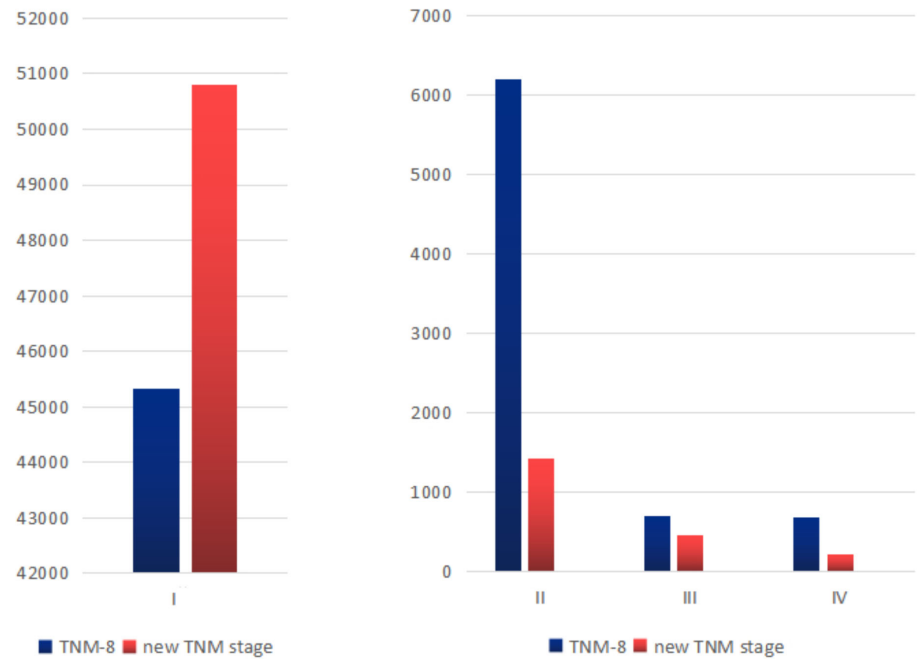

FIGURE 1
Stage distribution for the TNM-8 stage and new TNM stage in the training cohort.

finally included in validation analysis. The new TNM system showed a 5-year CSS of 99.9% for stage IA, 99.4% for stage IB, 95.1% for stage II, 84.3% for stage III, and 74.2% for stage IV. For the TNM-8 system, the 5-year CSS was 99.8% for stage I, 98.2% for stage II, 92.6% for stage III, 81.1% for stage IVA, and 80.1% for stage IVB. The 5-year CSS for the two systems is shown in Figure 3. The evaluation of discrimination comparison is shown in Table 4. These patterns were consistently observed in the training cohort and supported the better discrimination ability of the new system. Accordingly, 5,485 (11.2%) patients were down-staged to stage I. Overall, the new system outperforms the 8th AJCC TNM staging system in all metrics, both in the modeling and validation groups.

Discussion

The large cohort study examined the appropriateness of the 8th TNM staging system in estimating survival and identifying

TABLE 3 Hazard ratios for the risk of cancer-specific survival for the TNM-8 stage and new TNM stage for the SEER cohort.

	No. of patients (%)	No. of deaths (%)	5-year CSS (%)	HR (95% CI)	*P*-value
TNM-8					
I	45,332 (85.7)	270 (0.6)	99.6	Reference	
II	6,199 (11.7)	329 (5.3)	96.5	9.96 (8.48–11.70)	
III	704 (1.3)	144 (20.5)	86.0	40.72 (33.26–49.85)	<0.01
IVA	287 (0.5)	83 (28.9)	78.4	60.90 (47.61–77.89)	
IVB	395 (0.7)	169 (42.8)	66.6	114.73 (94.53–139.24)	
New TNM					
IA	34,788 (65.7)	127 (0.4)	99.8	Reference	
IB	16,003 (30.2)	357 (2.2)	98.6	6.62 (5.41–8.11)	
II	1,435 (2.7)	242 (16.9)	90.5	53.51 (43.16–66.33)	<0.01
III	470 (0.5)	143 (30.4)	77.0	119.81 (94.29–152.25)	
IV	221 (0.4)	126 (57)	54.3	292.84 (228.50–375.30)	

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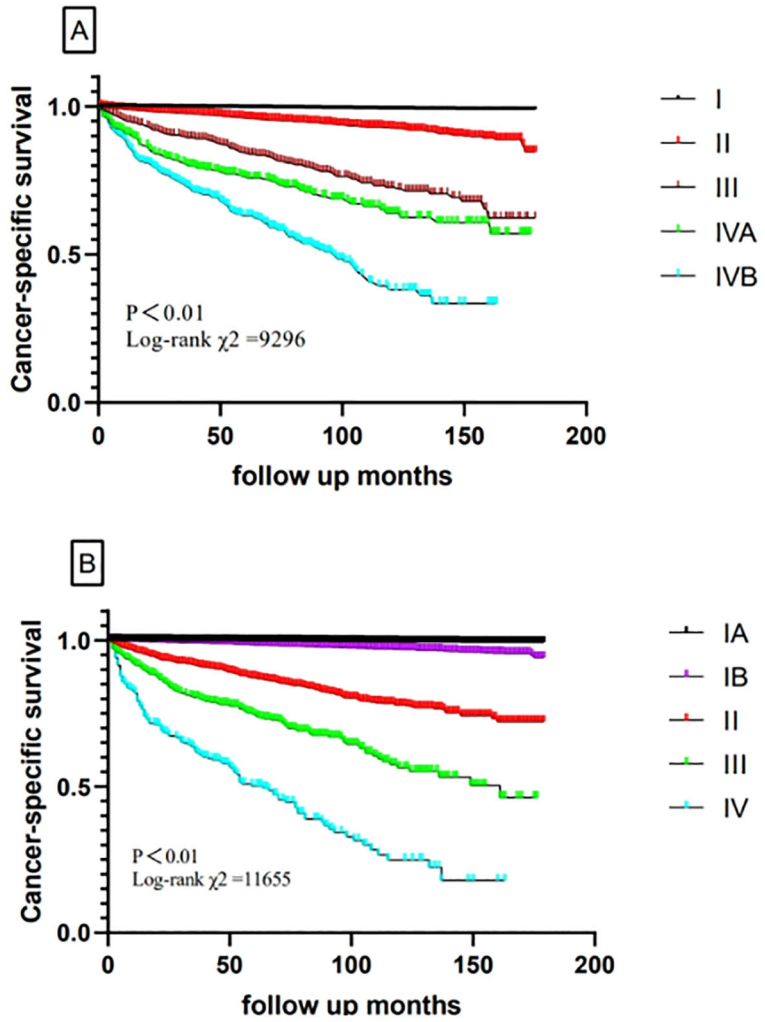

FIGURE 2
Comparison of cancer-specific survival based on the TNM-8 stage and new TNM stage in the training cohort (**A**, TNM-8; **B**, new TNM stage).

homogeneous survival groups in DTC patients. It also provided possible revisions to sharpen the estimates of prognosis. Using decision tree methodology, the M category had the highest priority, followed by age, ETE, tumor size, and N categories. Then, we identified four TNM groups (I, II, III, and IV) on the basis of within-group similarities in survival. This approach has been shown to produce accurate predictions. The new groups revealed a higher efficiency than the TNM-8 system, both in the training cohort and validation cohort. After applying the new staging system, nearly two-thirds of patients shifted from stages I-IV to stages IA-III. Based on the SEER cohort, it could better provide accurate predictions and treatment options for DTC patients.

When facing patients with newly diagnosed DTC, the primary task of clinical doctors is to use the available basic prognostic information to make personalized judgments on survival outcomes and make tailored decisions regarding the most effective treatment plan. Therefore, the importance of creating reliable grouping rules to classify patients into some predefined categories is remarkable. Clinical decision rules are designed to help clinicians make

TABLE 4 Comparison between multivariate Cox regression models in the two staging systems.

	Training cohort			Validation cohort		
	AUC	AIC	PVE (%)	AUC	AIC	PVE (%)
TNM-8	0.819	18,692.282	4.11	0.814	5,886.380	3.28
New-TNM	0.844	18,331.906	5.04	0.846	5,706.544	4.00

AUC, area under Roc curve; AIC, Akaike information criterion; PVE, proportions of variance explained.

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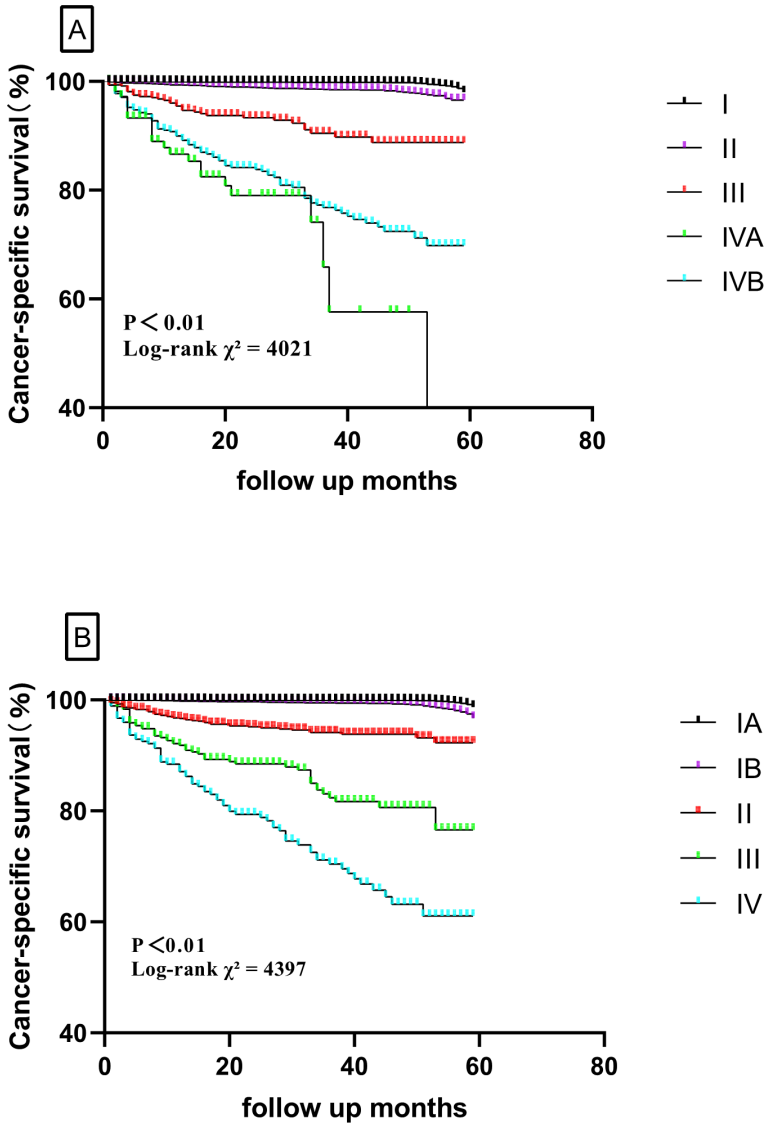

FIGURE 3
Comparison of cancer-specific survival based on the TNM-8 stage and new TNM stage in the validation cohort (**A**, TNM-8; **B**, new TNM stage).

diagnosis and treatment decisions (28–31). Although the TNM categories were accepted as descriptors of disease extent, the prediction efficiency of long-term CSS in guiding the clinical treatment of DTC patients was still unsatisfactory.

The decision tree method is a powerful statistical tool for medical research (32, 33). Decision trees have several advantages, such as being able to be applied to any data structure, especially discrete, continuous, or mixed data, and explaining prediction rules in a simple way, providing good accuracy to highly non-linear prediction problems, performing stepwise variable selection, reducing complexity, and so on.

Although the TNM staging system is constantly updated, the 8th edition still has some limitations. Many studies (8–10) have indicated that distant metastasis has the highest hazard ratio for DTC. We indicated that the M category was the most important and initial factor for defining the stages. In addition, in the previous T stage, the diameter of the tumor was not considered for patients with extrathyroidal extension, which was controversial. Previous studies (9, 34, 35) have mentioned that the size of the tumor was also a factor affecting patients in the T3b category, so the tumor diameter should also be considered for these patients. For the two cutoff diameters in our study, 4 cm was accepted by all experts, and we chose 1 cm instead of 2 cm because the topic of active surveillance(AS) (36–38) is controversial at present, and the subtype of papillary thyroid microcarcinoma (PTMC) is removed in the 5th edition of the WHO Classification of Endocrine and Neuroendocrine Tumors (39). Therefore, 1 cm was included in the study as another cutoff point. The results also showed that <1 cm could be combined with 1–4 cm, and there was a survival difference when 4 cm was the cutoff diameter in patients with ETE. Therefore, the tumor diameter was also taken as a factor in the new stage. Furthermore, for the histology type, we did not obtain positive

results, which was consistent with the AJCC stage. Nevertheless, many studies (9) have shown that although FTC and PTC are both follicular cell-derived, FTC is more frequent in distant metastasis and predicts a worse prognosis. However, we considered that the difference in histology type disappeared because of the integration of relevant prognostic factors. Finally, the role of lymph node metastasis was further weakened in our staging system and was only slightly reflected in Rules 3 and 4, which were similar to some prognostic scoring systems; the reason for this might be due to the fact that lymph node metastasis (LNM) was more related to recurrence rather than CSS.

The results of the present study demonstrated that our new stage was more suitable for the postoperative staging of DTC. According to the 8th AJCC TNM staging system, 1.2% and 1.3% of patients were classified as having stage IV and III disease; however, according to the new TNM stage, only 0.4% and 0.5% of the patients remained in stage IV and III. This has better benefits in avoiding overtreatment or relieving patients' emotional stress. We should underline that cancer staging should be based on an accurate correlation with survival, maximizing the similarity of survival within groups and the difference of survival between groups. Although the improvements in AUC, PVE, and AIC are not sufficiently obvious, any system updates should follow the principle of gradual improvement. We proposed a system based on the framework of the TNM-8 system, wishing to provide some support for future amelioration.

The most significant clinical implication of our study is the refinement of the prognostic model for DTC, utilizing a more precise algorithm. We have re-evaluated the risk factors based on their impact on prognosis, resulting in a more rational and efficient system that holds greater significance for the precise and individualized treatment of patients. Furthermore, for DTC, which generally has a favorable prognosis, we also emphasized the importance of patients' mental health in addition to surgical treatment. The new system reclassifies previously higher-stage patients to lower stages based on our more accurate algorithm, which corresponds to a lighter psychological burden for patients. This multifaceted approach to treatment is an area that we, as surgeons, need to enhance in the future. In clinical settings, we will highlight the potential for improved decision-making regarding follow-up strategies and therapeutic interventions. We will also suggest steps for incorporating this new system into clinical practice, including training for healthcare providers and updates to clinical guidelines to ensure a smooth transition.

Strengths and limitations

The strengths of this study include its large sample size, the sufficient number of death events, and the application of decision tree methodology. The decision tree model is a non-parametric approach without distributional assumptions that simplifies complex relationships between input variables and is easy to understand and interpret. Any future information about prognostic indicators in DTC could be incorporated with minor changes, making our new staging system adaptable. However, there are also limitations. One potential problem is that the follow-up duration was not long enough; therefore, there might be bias in the results. A longer follow-up period is required in the future. In addition, the outcome is only "alive" or "dead" in the SEER database; biochemical and genetic factors and cancer recurrence were not available. To date, a definition of the genetic events leading to the development of cancer is possible in the vast majority of DTC patients. The translation of biological knowledge into clinical practice represents the next target to be achieved. The prognostication may be empowered in the near future by non-tissue molecular prognosticators, including circulating BRAFV600E, miRNAs, germline VEGF-A SNPs, and so on (40, 41). A great effort is required to overcome the technical issues.

Conclusion

The new system for DTC appeared to be more accurate in distinguishing stages according to the risk of mortality and provided more accurate risk stratifications and potential treatment selections.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

LH: Writing – original draft. JX: Writing – original draft, Data curation, Conceptualization. HZ: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1419125/full#supplementary-material

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Current status of the prediction for radio-iodine refractory thyroid cancer: a narrative review

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It is well established that patients with the most differentiated thyroid cancers have a good prognosis, whereas when the disease develops into radio-iodine refractory thyroid cancer (RAIR) their prognosis is poor and the 10-year survival rate is low. At present, the therapeutic methods for RAIR are limited and have low efficacy. As a consequence, several models have been developed for predicting RAIR. The aim of this review was to describe recent developments regarding the factors that influence and predict the occurrence of RAIR. Many variables including demographic characteristics, tumor clinicopathology, serology changes, disease characteristics, and PET/CT results have been shown to be independent factors that influence the development of RAIR. The cut-off value derived from multivariate prediction models therefore effectively predicts the onset of RAIR. However, the current models for predicting RAIR were obtained through retrospective studies, and the prospective prediction studies are needed in the future to confirm their validity.

KEYWORDS

radio-iodine refractory, differentiated thyroid cancer, prediction, radioactive iodine therapy, PET/CT

Introduction

The global incidence of thyroid cancer, the most common malignancy in the endocrine system, has continued to rise in recent years (1). The majority of thyroid cancers originate from follicular epithelial cells, with differentiated thyroid cancer (DTC) accounting for about 90% of lesions. DTC retains some of the physiological functions of thyroid follicular epithelial cells, such as the expression of the sodium iodine transporter (NIS) and the capacity to uptake iodine. As a consequence of these actions, most DTCs are sensitive to

radioactive iodine (RAI) and can be cured by surgery, radioactive iodine therapy, and thyroid hormone suppression, with a 20-year survival rate of > 95% (2). However, following the development of the disease, the expression of the NIS in some recurrent or metastatic lesions is decreased or the targeting of the NIS to the cell membrane is diminished (3). This results in decreased uptake of RAI by the lesions, resulting in rapid progression of radio-iodine refractory thyroid cancer (RAIR-DTC), with a 10-year survival rate of < 10% (4–6).

At present, localized, targeted, or redifferentiation therapies are mainly recommended for the treatment of RAIR-DTC. The primary objective of localized treatment is to relieve local compression symptoms. The tyrosine kinase inhibitors (TKIs) drugs approved by the FDA to treat progressive RAIR-DTC have been studied extensively in recent years and the results of clinical trials have been impressive. However, these TKIs mainly target receptors for vascular endothelial growth factor but not the special RAIR drugs, and therefore need to be used continuously. The side effects of these drugs also reduce the quality-of life of patients and increase the risk of death (5). RAIR-DTC often occurs in case of thyroid dedifferentiation, so a potential treatment option is to induce the lesions to restore radioactive iodine uptake after redifferentiation (7, 8). However, the majority of drugs currently being tested for induction of redifferentiation are in the research stage or have been shown to have limited clinical value (4, 9, 10). Predictions in published literature are that the incidence and crude death rate of thyroid cancer will continue to rise in the future (11). In view of this apparent lack of effective treatment, some studies have investigated how to predict the occurrence of RAIR-DTC. In this paper, we review studies on how to predict RAIR-DTC, and examine the factors involved in cancer development and feasible methods for forecasting this development. The original and review literature were searched in the Pubmed and Wanfang databases using the search terms “iodine refractory differentiated thyroid cancer” and “prediction”. The references in the relevant articles were also searched to identify any other relevant articles.

The value of demographic characteristics

Several studies have identified the cut-off age for predicting RAIR-DTC, with one study reporting the cut-off point was ≥ 55 years old (12), while other studies used >45 (13), >48 (14), or >55 years when the thyroglobulin antibody (TgAb) was positive and >40 years when TgAb was negative (15). Although a meta-analysis of 13 studies (16) showed that age was not an influential factor in the development of RAIR-DTC, the authors considered that this result may have been due to age-matching in the majority of the studies and therefore suggested that young age may be a protective factor. It is speculated that age is a possible predictive factor for RAIR-DTC, but the influence of age may be related to the fact that elderly people are more likely to have an advanced tumor grade and stage (17). Whether or not age influences the development and prognosis of RAIR-DTC, patients with tumor are generally significantly older than those without RAIR-DTC (18) that the probability of developing RAIR is up to 4.5 times greater in patients older than 46 years (19). Elderly patients have a poor prognosis due to a number of factors, such as clinic-pathologic factors and selection of therapy (17). Therefore, the possible predictive value of age on RAIR should be taken into account when choosing therapeutic options for elderly patients.

The incidence of thyroid cancer in females is higher than that in males, while for DTC, the prognosis of males is worse than that of females (17). In one study, the proportion of males in the RAIR patient group was higher than that in the non-RAIR group, with logistic regression analysis showing that male gender was a predictive factor for RAIR (18). However, a study by WL (20) showed that the ratio of females in the RAIR group was higher than that of males, although this difference was not statistically significant. Meanwhile, other studies also reported that gender was not a factor in the occurrence of RAIR-DTC (12, 14, 15). Considering the small number of RAIR-DTC cases in the literature (18), a study on a large number of patients should be carried out in the future to verify whether sex is a predictive factor.

White race ethnicity has been shown to be associated with a reduced odds ratio of RAIR disease (19). A study on the germline genetic landscape of African American and Caucasian patients showed some RAIR risk haplotypes occurred only in African American patients with >80% of African ancestry (21). These results indicate that race/ethnicity may be a factor in RAIR.

In addition, smoking and body mass index (BMI) ≥24 kg/m2 (12) were reported to increase the incidence of RAIR-DTC, Although most of the above studies were a retrospective design, the demographic characteristics may have influenced the course of RAIR, and prospective studies are therefore required in the future to analyze the predictive value of these demographic factors in the occurrence of RAIR-DTC.

The value of clinicopathological features

Papillary carcinoma is the most common subtype in thyroid cancers, and also in most patients with RAIR-DTC (12, 20, 22). Multivariate analysis confirmed that follicular thyroid cancer (12) was one of the independent factors that predicted the prevalence of RAIR-DTC. Binary logistic regression analysis showed that a high-risk histological subtype was one of the independent risk factors for RAIR-DTC (20), while a meta-analysis (16) also showed high-risk pathological subtypes significantly increased the risk of RAIR-DTC.

Abbreviations: DTC, differentiated thyroid cancer; NIS, sodium iodine transporter; RAI, radioactive iodine; RAIR, radio-iodine refractory thyroid cancer; TKI: tyrosine kinase inhibitor; BMI, body mass index; MAPK, mitogen activated protein kinase; TSH, Thyroid Stimulating Hormone; Tg, Thyroglobulin; TgAb, Thyroglobulin Antibody; TPO, thyroid peroxidase; AXL, anexelekto; ^{18}F-FDG, Fluorine 18(18F) fluorodeoxyglucose; SUV, Standardized uptake value; PET/CT, Positron Emission Tomography/Computed Tomography; ROC, receiver operating characteristic; LDL-Ch/TCh, low density lipoproteincholesterol-total cholesterol ratio; WBC, white blood cell; ATA, American Thyroid Association.

In addition to the pathological classification, other clinicopathological characteristics of the tumor can also predict the development of RAIR-DTC. The probability of RAIR is increased significantly by the occurrence of vascular invasion (23) and extrathyroid invasion (12, 15, 16). As the primary tumor size is either >10 mm or >20 mm the risk of RIAR is increased significantly (12), with a maximum tumor diameter ≥12.5mm shown to be an independent risk factor for RAIR (20). In addition to the pT stages, the risk of RAIR is also increased in the pN or pM stages (12). The specificity of RAIR predicted by the combination of distant metastasis, high-risk histological subtype and maximum tumor diameter ≥12.5 mm was 98% (20). Therefore, it can be seen that the risk of developing RAIR-DTC increases gradually with the progression of the tumor. From this perspective, vigorous treatments for DTC patients should be carried out in order to determine whether this reduces the chance of developing RAIR. However, other studies reached different conclusions. For example, when the groups were divided according to TgAb positive or negative, tumor size, multiple focal points, TNM stage, lung metastasis size and lymph node metastasis size this did not increase the risk of RAIR in the TgAb negative group (15). Aamna et al. (24) also demonstrated there was no correlation between TNM stage and the occurrence of RAIR, while there was no significant correlation between tumor size and RAIR in a meta-analysis (16). Taken together, these studies indicate that it is controversial to perform a total thyroidectomy or lobectomy in low-risk thyroid cancer patients, and therefore we consider that it would be of value to clarify whether there is a correlation between TNM stage and RAIR in surgical protocols.

BRAFV600E is the most effective activator of the mitogen activated protein kinase (MAPK) bypass which plays a key role in the regulation of cell growth and proliferation (25). It is controversial whether there is a correlation between BRAFV600E and RAIR. Some studies have reported that BRAFV600E is an independent predictive factor for RAIR (13), independent of the setting of TgAb positivity or negativity (15), and that the BRAFV600E mutation is related closely to the occurrence of RAIR in papillary carcinoma (22). However, the study by Shobab reported that the prevalence of BRAFV600E mutation in RAIR patients was lower than that in general DTC patients (19). Based on the result that lower iodine avidity was observed in BRAFV600E-mutated lymph node metastases, we speculate that BRAFV600E may affect the occurrence of RAIR. In addition to BRAFV600E gene mutation, TERT mutation has also been shown to be an independent factor for predicting RAIR and significantly increases the risk of RAIR (16, 26). Compared with DTC with only BRAF gene mutation, patients with DTC and TERT mutation accompanied by distant metastasis are more likely to develop RAIR during initial iodine therapy, which indicates that TERT mutation predicts the occurrence of RAIR earlier than that of BRAFV600E mutation (27). In contrast, the incidence of lower iodine avidity in cases of lymph node metastatic DTC was less with the TERT mutation than that observed in the BRAFV600E group (28). Regardless of which mutation is more likely to be associated with the development of RAIR, the ratio of RAIR occurrence was reported to be significantly higher with the coexistence of the BRAFV600E and TERT mutations (26).

Expression of several proteins such as thyroid peroxidase (TPO) has been shown to have a significant correlation with iodine avidity in the thyroid (28), with iodine avidity decreasing with decreased expression of TPO. Consistent with this, the absence of TPO expression in the thyroid cancer lesions showed by immunohistochemical analysis predicts the failure of iodine therapy and the occurrence of RAIR (29). When the proportion of thyroglobulin (Tg) positive cells in metastatic lesions is < 56%, it effectively monitors the occurrence of RAIR. The expression level of anexelekto (AXL), a tyrosine kinase receptor, has also been shown to be a predictor of RAIR and significantly reduces the expression of NIS and RAI uptake (30). These results confirm that the occurrence of RAIR can be predicted based on the expression of these proteins in thyroid lesions thereby guiding effective individual treatment after surgery.

Taken together, these results suggest that the clinicopathological characteristics of thyroid lesions deserve attention, which may allow treatment plans to be adjusted in the early clinical stage.

Predictive value of serological markers

The prognosis of patients with thyroid cancer after surgery and radioactive iodine therapy can be assessed by monitoring Tg levels when the TgAb is negative in the clinic. Based on the finding of a retrospective study that showed preoperative serum Tg was significantly higher in patients with repeated iodine therapy than in those who did not receive this therapy or only received one iodine administration of iodine, an increase in serum Tg could be used as an independent predictor of RAIR (31). It has been suggested that if Tg changes greatly during follow-up, the possibility of RAIR should be considered, especially when the level doubles within a short period of time (< one year) (5). Some studies used ROC curve analysis to determine the cut-off value for changes in Tg levels that predicted RAIR. In pulmonary metastatic DTC patients, the cut-off value for detecting RAIR was 0.544 for stimulated Tg ratio before the first and second RAI therapy and 0.564 for a suppressed Tg ratio before and after the second RAI therapy (13). Based on the ratio of stimulating or inhibiting Tg between two RAI therapies, 57% and 81% were shown to be the cut-off values for predicting RAIR-DTC, respectively (32). When TgAb was positive, the TgAb level was 14.8 times higher than the upper limit level, or when the TgAb level decreased by < 46.4% between two RAI treatments this indicated the occurrence of RAIR (15). These studies showed that predicting RAIR was feasible using the changes in Tg or TgAb levels, especially when the Tg levels increased significantly in a short period of time or alternatively when the TgAb level did not decrease significantly between the two RAI treatments.

It has also been reported in the literature that conventional blood biomarkers can also be used to predict early-stage RAIR. The low density lipoprotein cholesterol-to-total cholesterol ratio (LDL-Ch/Tch) correlated positively with the incidence of RAIR, while the white blood cell (WBC) count at surgery was shown to be inversely

associated with RAIR (33). However, it is important to note that the level of these two indices may be influenced by other factors. Therefore, the predictive value of conventional blood biomarkers in RAIR-DTC needs to be verified.

Predictive value of positron emission tomography/computed tomography imaging

The definition of RAIR in the 2015 American Thyroid Association (ATA) thyroid cancer guidelines focused on the uptake of RAI in thyroid cancer-related lesions (34). It was shown that more than 90% of recurrences or metastatic DTC with negative radioiodine uptake could take up Fluorine 18(18F) fluorodeoxyglucose (^{18}F-FDG) (35). When ^{18}F-FDG was taken up by DTC metastases, this indicated that the lesions were not sensitive to iodine therapy, with the degree of ^{18}F-FDG uptake correlating negatively with the iodine therapeutic effect. This suggested that ^{18}F-FDG imaging predicted the occurrence of RAIR (36, 37). Regardless of the degree of RAI uptake, lesions with ^{18}F-FDG uptake are an independent predictor of the occurrence of RAIR, and of great value in the diagnosis and prediction of prognosis of RAIR (14, 37, 38). The diagnostic efficacy of RAIR was highest when the ratio of the maximum standardized uptake value (SUVmax) of the lesion and the standardized uptake value (SUV) of the liver was 3.01 (39). In view of these findings, the possibility of RAIR should be considered when thyroid cancer-related non-primary lesions show ^{18}F-FDG avidity. At this point, clinicians should consider treatment options other than iodine therapy when the lesion is FDG positive either with or without the presence of iodine uptake.

With the advent of new novel molecular probes, some have been used to detect the lesions in RAIR, such as fibroblast activation protein inhibitor (FAPI) (40, 41) and prostate specific membrane antigen (PSMA) (42). A study by Martina (43) also showed that the expression of PSMA correlated strongly with the aggressiveness of DTC. In addition, several other articles reported that lesions in RAIR patients exhibited higher FAPI uptake. However, there is no evidence for the relationship between FAPI uptake in thyroid lesions and the risk of developing RAIR. It is hoped in the future that some new molecular probes can be used to predict RAIR at an earlier stage than that achieved by ^{18}F-FDG.

Predictive value of radio iodine therapy characteristics

One of the definitions for RAIR in the European Thyroid Association Guidelines (44) is reaching a cumulative radioactive activity of iodine > 22.2 GBq. A retrospective study also showed that the cumulative radioactive iodine dose and treatment times of RAIR patients were increased significantly compared with those in non-RAIR patients (19, 33). Therefore, when the frequency of radioactive iodine treatment and cumulative dose of radioactive iodine are used as variables, the frequency of radioactive iodine treatment ≥ 3 times is a predictor of RAIR, and the specificity and sensitivity of the occurrence of RAIR is increased significantly (18). The recurrence between the operation and iodine-131 treatment was also reported to have a good ability to predict RAIR (14). An interval between the initial diagnosis and the diagnosis of RAIR metastatic disease < 3 years has also been shown to predict poor survival (22). In conclusion, the rate of RAIR increases with the increase of iodine therapy. Given the indications for iodine therapy, it may be more likely that the risk of RAIR increases in cases with more severe forms of cancer.

Multi-parameter model

Information on the patient was assigned to multiple variables and the predictive potential of these variables analyzed using a parametric model. Table 1 lists the studies that used a nomogram model to predict RAIR. Of the five studies, the independent predictors of RAIR in three were mainly the clinicopathological

TABLE 1 Key data of studies that used a nomogram model to predict the development of RAIR.

Authors, Reference	Article category	Study Design	Numbers of RAIR case	Independent predictors of RAIR	Scoring	Cut-off value
Li G, et al (12)	Original	Retrospective	120	Smoking, tumor type, extra-thyroid extension, lymph node metastasis number, lymph node metastasis rate, pN	24	7
Meng C, et al. (32)	Original	Retrospective	71	Δs-Tg/Δs-TSH<1.50, age upon diagnosis	0.95	0.722
Liu Y, et al. (14)	Original	Retrospective	223	Age at diagnosis (≥48 years), recurrence between the operation and iodine-131 treatment, site of metastasis, uptake of ^{18}F-FDG	52	10
Schubert L, et al. (23)	Original	Retrospective	159	age at diagnosis ≥ 55yr, vascular invasion, synchronous cervical, pulmonary and bone metastases at the initial work-up, cervical and pulmonary recurrence during follow-up	10	8.9
Liu H, et al. (33)	Original	Retrospective	12	LDL-Ch/TCh ratio, WBC levels	20 × LDL-Ch/TCh - 0.6 × WBC	8.34

Δs-Tg, s-Tg1/s-Tg2; Δs-TSH, s-TSH1/s-TSH2; ^{18}F-FDG, Fluorine 18(18F) fluorodeoxyglucose; LDL-Ch, low density lipoprotein cholesterol; Tch, total cholesterol; WBC, white blood cell.

characteristics of the patients. There were some differences in the risk factors and cut-off values in these three models, due possibly to differences in the inclusion criteria for patients, such as the number of iodine treatments or the proportion of FTC. The sensitivity, specificity, and area under the curve (AUC) of these scoring systems were: 77.7%, 81.2%, 0.795 (12), 76%, 93%, 0.898 (14) and 86%, 92% and 0.95 (23), respectively. Of the three models, the model of Li et al (12) is suitable for postoperative use, with the prediction period being slightly earlier than that of the other two models (14, 23), and the AUC being slightly lower than that reported for the other two models which are suitable for use after follow-up or in patients who have undergone ^{18}F-FDG examinations. However, regardless of their differences, the three models are easy to operate.

The other two models mainly focused on serological markers. The study of Meng et al. (32) used a prediction model combining changes of the stimulated Tg between the first and second RAI treatments with the age at diagnosis, with the model having a specificity of 0.830, sensitivity of 0.755, and AUC of 0.830. It was obvious that this model was suitable for patients who needed repeated RAI treatment. Another prediction model for RAIR (33) used preoperative serological indicators with a low LDL-Ch/TCh and WBC count and was reported to have a sensitivity, specificity, and AUC of 0.833, 0.875, and 0.861 respectively. This model greatly advanced the prediction time of RAIR and could be carried out before the operation and was very easy to perform. However, there are many factors influencing these serological indicators and therefore the practicability of this model needs to be further investigated.

Taken together, these current multi-parameter model studies confirm that the multi-parameter model analysis is effective for predicting RAIR. However, all the above studies were a retrospective design and therefore prospective studies are needed to confirm the predictive value of these models.

This paper reviewed and summarized the relevant factors that predicted the development of RAIR thereby providing the basis for effective clinical treatment. A limitation of the paper was that most of the references were for retrospective studies, with a lower number of studies reporting the use of multi-parameter prediction models. Therefore, a larger number of prospective studies are needed in the future to confirm the clinical value of relevant predictors.

Conclusions

Current studies have shown that the occurrence of RAIR can be predicted by analyzing the clinicopathological characteristics of thyroid cancer lesions and that more attention should be paid to these characteristics. RAIR should be taken into account when the lesions are positive in ^{18}F-FDG images or when Tg levels increase significantly over a short period of time. The multi-parameter model which combines the information of multiple patients has a good predictive efficacy, is easy to carry out and could be used to identify the risk of developing RAIR thereby assisting in the development of effective treatment measures.

Author contributions

YW: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization. XL: Writing – review & editing, Methodology, Investigation, Formal analysis. HL: Writing – review & editing, Visualization, Validation, Supervision, Resources, Funding acquisition.

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Conflict of interest

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Comparison between gas insufflation and gasless techniques for endoscopic transaxillary thyroidectomy

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Objective: This study aimed to compare clinical outcomes and prognosis of endoscopic thyroidectomy via axillary approach using insufflation and gasless methods.

Methods: Retrospective analysis included patients undergoing endoscopic thyroidectomy at our institution from June 2022 to October 2023. Patients were categorized into insufflation and gasless groups. Analysis compared surgical time, blood loss, drainage volume, tube removal time, hospital stay, complications, pain score, and incision satisfaction.

Results: 73 patients (48 insufflation, 25 gasless) were analyzed. Insufflation technique showed significantly superior outcomes: shorter surgery duration, reduced drainage volume, earlier tube removal, shorter hospital stay, and higher incision satisfaction (all $P < 0.05$). Postoperative pain (VAS) was lower in insufflation group on first day, but no significant difference on seventh day. No significant differences in blood loss or complications were observed.

Conclusion: Insufflation technique offers advantages over gasless method including shorter operation time, reduced drainage, earlier tube removal, and shorter hospital stays, with comparable outcomes in pain and incision satisfaction.

KEYWORDS

remote approach thyroid surgery, thyroidectomy, endoscopic, transaxillary, gas insufflation, gasless, thyroid tumor

Introduction

Papillary thyroid carcinoma (PTC) is a prevalent endocrine malignancy worldwide. Recent studies have shown a rise in the global incidence of thyroid cancer over the past twenty years (1). The primary treatment for thyroid cancer is surgery, but conventional open thyroidectomy (COT) often results in visible scarring on the neck, making it less

preferred. Particularly for young women and Asian patients with a predisposition to scarring, the presence of any neck scars is deemed unacceptable for cosmetic reasons (2).

Various minimally invasive and remote surgical techniques have been developed to address cosmetic concerns, such as laparoscopy and robotics, allowing for intricate procedures through smaller incisions (3, 4). Endoscopic technology has a certain priority in terms of aesthetic effect and postoperative quality of life, so it is generally considered as a cosmetic advantage of benign tumors, follicular adenomas and other surgical methods (5, 6). However, as a new treatment method for patients with malignant tumors, the safety and radical treatment of surgical methods should be confirmed. The safety and radical effectiveness of endoscopic or laparoscopic surgery in the treatment of malignancies in other organs has been demonstrated, with no difference in recurrence rates and survival between traditional open surgery and endoscopic or laparoscopic surgery (7). However, many researchers are skeptical about the feasibility of endoscopic thyroid surgery for radical treatment of malignant tumors (8). In a report on the effectiveness of minimally invasive video-assisted thyroidectomy (MIVAT) in PTC, the results are very similar to traditional surgery in terms of integrity, and its authors argue that endoscopic surgery is superior to open surgery when there is local aggression (9).

Transaxillary approach endoscopic thyroid surgery is one of the most widely used methods (10–13), it hides the incision in the natural fold of the axillary skin, has better cosmetic results than other methods, and is more feasible in the identification of the recurrent laryngeal nerve and the parathyroid gland, as well as the manipulation of the upper pole of the thyroid (14). In transaxillary endoscopic thyroidectomy, inflatable or airless techniques are used to maintain operating space. The aeration technique, which requires a carbon dioxide gas catheter to maintain a constant air pressure, was first invented by Ikeda in 2000. He used a continuous CO2 gas injection method to create a workspace, but at first the working space was relatively small, and the operating field of view was easily disturbed by smoke from the use of ultrasound knives. Saline irrigation and aspiration can also cause the collapse of surgical space (15). Therefore, to address this problem, a gasless endoscopic surgery method using an external retractor via a transaxillary approach has been developed (16). The gasless technique uses an external retractor to lift the chest flap and neck muscles without the problem of gas-related complications. With the introduction of robotic surgery, the airless technique has become more prevalent to assist in the operation of surgical robots (17, 18). The inflatable technique remains popular among laparoscopic surgeons. Each method has its own advantages and drawbacks, and the selection of technique should be based on individual patient needs and surgical goals.

Patients and methods

In order to compare the two surgical methods, the main subjects included in this study were PTC patients. In 2006, Lombardi et al. reported the safety and efficacy of endoscopic thyroidectomy and selective neck dissection in the treatment of low-risk papillary thyroid microcarcinoma (19). For endoscopic thyroidectomy as a treatment for thyroid cancer, the selection criteria of tumor patients are the most important. As a result, we have some limitations in our criteria for inclusion of patients. This is because we are concerned about the limitations and safety of endoscopic thyroidectomy. “Low-risk” PTC, represented by small thyroid nodules with a good prognosis, is considered a suitable indication for endoscopic thyroidectomy. In addition, PTC is commonly seen in younger people, who are often concerned about the cosmetic effects of surgery.

Patients

The clinical data of patients who underwent endoscopic transaxillary lobectomy for PTC at our hospital from June 2022 to October 2023 were retrospectively reviewed. The two surgical methods in our hospital have been carried out for many years, and the technology is relatively mature. Different surgical methods are selected according to the patients’ own wishes, and the patients are divided into inflatable group and non-inflatable group according to different surgical methods. Among them, the experimental group was inflatable group, a total of 48 cases, and the control group was non-inflatable group, a total of 23 cases. The age of the patients ranged from 18 to 60 years, with an average age of 40 years. All endoscopic procedures were successfully performed without the need for conversion to open surgery. Informed consent was obtained from each patient, who also signed a written consent form. All surgeries were conducted by a skilled surgeon.

Inclusion and exclusion criteria: Inclusion criteria included having a single tumor limited to one thyroid lobe, with a maximum tumor diameter of ≤2cm as measured by ultrasound. Preoperative fine needle aspiration biopsy (FNAB) confirmed the diagnosis of PTC. Patients had no evidence of lymph node metastasis, no bleeding disorders, and had high cosmetic expectations for neck appearance. Exclusion criteria comprised patients with a body mass index exceeding 35 kg/m2 or having overdeveloped neck muscles, FNAB results indicating poorly differentiated pathologic types with evidence of external thyroid invasion or distant metastasis, a history of prior neck or axillary surgery, or radiotherapy, and comorbidities such as significant heart, lung, brain, or other systemic diseases that precluded general anesthesia.

Operative methods

Preoperative preparation included standard examinations such as thyroid function testing, neck X-ray, and laryngoscopy to assess tracheal compression, vocal cord function, and recurrent laryngeal nerve function. The skin was prepared and surgical markings were made prior to the operation. The extent of thyroidectomy was determined based on the guidelines of the American Thyroid Association (20), taking into consideration the specific patient population. In this study, unilateral lobectomy with isthmus and

prophylactic unilateral central region dissection were the chosen surgical approaches.

Inflation group

After intubation, the patient is placed in the supine position. Shoulders are elevated, and the head is slightly turned to the healthy side to slightly extend the neck. The affected arm is extended 90°, fully exposing the axilla. The operative field is routinely sterilized and draped. A 1 cm incision is made along the midline of the axilla on the affected side, and a skin retractor is used to expand the subcutaneous tissue around the incision. A Trocar is inserted and a rigid endoscope is guided, with CO2 being injected and maintained at 6mmHg pressure. Two additional 5mm incisions are made in the same axilla and two more Trocars are inserted, guiding the left and right side operating instruments. The pectoralis major muscle is identified and dissection is performed along the pectoralis major muscle and the subcutaneous soft tissue between the muscle and the anterior chest wall. The SCM is identified and the space is further dissected along the SCM clavicle and coracoid bone notch, freeing the sternocleidomastoid muscle and the anterior neck muscle group. A laparoscopic thyroid hook is used to elevate the anterior neck muscles with an endoscopic thyroid retractor. The thyroid gland tissue is exposed. During the dissection, the side hole inserted into the endoscope Trocar is opened to discharge smoke and improve visibility, and the endoscope lens can be soaked in hot water if necessary, so that the endoscope lens is easier to keep clean and clear, and the time of repeated wiping of the lens during the operation is shortened.

Using fine dissection instruments and forceps, the gland is dissected between the true and false capsules in the endoscope. The gland superior pole is freed, and the thyroid superior artery is separated. The ultrasonic shears are held close to the gland and the superior pole is transected, lifting the superior pole towards the abdominal side. The recurrent laryngeal nerve is identified and confirmed, and its dorsal side is dissected with the ultrasonic shears, and the thyroid middle vein is identified and transected with the ultrasonic shears. The separation continued to the lower pole, and the pathological thyroid tissue, including tumors, was completely removed. The thyroid isthmus was separated in front of the trachea by separation forceps and cut off by ultrasonic knife. The intraoperative recurrent laryngeal nerve monitoring instrument detected the nerve signal throughout the operation. During the operation, the parathyroid gland was distinguished and protected, and its blood supply was retained. If it could not be retained *in situ*, it could be removed and cut up, dissolved in saline, and implanted between the sternocleidomastoid muscle or forearm muscle. The lymph nodes were separated in front of the trachea, the thymus was exposed and preserved, and the lateral lymph nodes were separated along the muscle and carotid sheath. The central lymph nodes were lifted, the recurrent laryngeal nerve was exposed and separated, and the esophagus and nerve were protected. The central lymph nodes were cleaned.

The removed thyroid and lymph nodes were put into a tissue specimen bag, and were taken out through the axillary incision for pathological examination. The wound was washed, completely stopped bleeding, and the parathyroid blood supply and the integrity of the recurrent laryngeal nerve were checked again. A negative pressure drainage tube was inserted into the wound and taken out through the axillary incision. Finally, all surgical incisions were sutured layer by layer.

Non-inflation group

The patient's position was similar to that of the inflation operation. A 4-5cm long incision was made at the axillary fold, and the subcutaneous tissue was separated from the surface of the pectoralis major fascia with a long-handled electric knife. The flap was pulled up with a special retractor and inserted into the endoscopy and ultrasound knife. Then a 0.5 cm incision was made next to the incision, and Trocar was inserted into the endoscopic grasper or separation forceps.

First, we exposed the SCM anatomical tunnel to the anterior neck area. Secondly, the space between the sternal bone and the clavicle head of SCM was found under endoscopy, the space was separated from the cricoid cartilage to the clavicle, the position of the retractor was adjusted, and the space was separated from the sternohyoid muscle and sternothyroid muscle to the depth after the chest bone was lifted, and then the space of the retractor was fully dissociated between the sternothyroid muscle and the thyroid gland, and the position of the retractor was adjusted again. The free anterior cervical band muscle and the SCM chest bone were pulled upward and fixed on the traction scaffold to fully expose the thyroid gland and complete the establishment of surgical space.

The surgical procedures and precautions of thyroidectomy were basically the same as those of the inflatable method.

Outcomes measured

Demographic data and thyroid nodule characteristics were recorded. The perioperative conditions of the two groups were analyzed. The intraoperative conditions included the total operation time (from skin incision to closure) and the estimated intraoperative blood loss. The postoperative data also analyzed the postoperative drainage flow, drainage tube removal time, hospital stay, postoperative complications, pain score and cosmetic effect. Among them, postoperative complications mainly included superior laryngeal nerve injury, recurrent laryngeal nerve injury, hypocalcemia, incision infection, and incision edema. For postoperative pain control, oral non-opioid analgesics are prescribed by the attending physician and administered immediately after surgery. The standard visual Analogue Scale (VAS) was used to assess pain on the first and seventh days after surgery on a scale of 0 to 10, with 0 indicating no pain, 10 indicating severe pain, and the middle part indicating varying degrees of pain. The beauty score was evaluated by Digital Evaluation Scale (NRS), and the satisfaction was evaluated by integers ranging from 0 to 10. The higher the score, the better the beauty effect. All clinical outcomes were compared between the two groups.

The incidence of postoperative complications was recorded. In all cases, laryngeal sensation and vocal cord movement were

routinely observed by the surgeon within 1 week after surgery. The patient's postoperative tone drop and drinking water choking were recorded as upper laryngeal nerve injury, and those who did not recover after symptomatic treatment for more than 6 months were considered to be permanent upper laryngeal nerve injury. Vocal cord paralysis and hoarseness caused by temporary recurrent nerve injury usually return to normal within 3 to 6 months after surgery, and vocal cord paralysis lasting 6 months is considered to be permanent recurrent nerve injury. Transient hypocalcemia usually appears within 72 hours after surgery. The clinical manifestations are numbness or hand, hand and mouth around the patient, which can be relieved within 4 to 5 days. Hypoparathyroidism more than 6 months is defined as permanent hypocalcemia.

Statistical analysis

Data were imported into SPSS26.0 statistical software for statistical analysis. Descriptive statistics are used to summarize the characteristics of the research object. Measurement data is expressed as mean with standard deviation or median with interquartile spacing, and counting data is expressed as rate (%). The T-test is used to compare the mean of continuous data between two groups, using a chi-square test for correlations between categorical variables. $P < 0.05$ indicated that the difference was statistically significant.

Results

Patient characteristics

The patients included in the study were PTC patients who underwent transaxillary endoscopic lobectomy in our hospital from June 2022 to October 2023. There were 73 cases, 48 of which were aerated and the other 25 were non-aerated. The clinical characteristics of the patients are shown in Table 1. There were no significant differences in demographics, body mass index (BMI), and thyroid lesion characteristics between the two groups.

Clinical results

The operative time of aerated group was significantly shorter than that of non-aerated group (59.2 ± 3.8 min Vs. 72.3 ± 3.2 min; P <0.001), and there was no significant difference in intraoperative blood loss between the two groups (Table 2). In addition, the postoperative drainage volume in aerated group was significantly lower than that in non-aerated group [95.0 (90.0,100.0) mL vs. 130 (125,137.5) mL; P < 0.001], and the drainage tube removal time was lower than that of the control group [3.0 (3.0,3.0) days vs. 4.0 (4.0,4.0) days; P < 0.001]. Similarly, the total hospital stay in the aerated group was significantly less than that in the aerated group [3.0 (3.0,3.0) days vs. 5.0 (4.0,5.0) days; P < 0.001]. In terms of pain, there were significant differences in VAS scores between the two groups on day 1 after surgery [5.0 (5.0,5.0) vs. 6.0 (6.0,6.0); P < 0.001], but there was no significant difference in VAS scores on day 7 after surgery. In addition, complication rates were not comparable between the two groups. Finally, the NRS score of the aerated group was higher than that of the non-aerated group [8.0 (7.0,8.0) vs. 6.0 (6.0,7.0); P < 0.001], and the difference was statistically significant (Table 3).

No deaths were observed during the study period, and there were no serious complications, including postoperative heavy bleeding, permanent voice changes, or gas-related complications. Both groups of patients had a pathological diagnosis of well-differentiated papillary carcinoma, limited to the thyroid gland, and no lymph node metastasis was found in the central area lymph nodes after surgery, thus no completion thyroidectomies or secondary neck dissection were required.

Discussion

In recent years, with the increase of life pressure and the change of dietary habits, the incidence of thyroid diseases, especially thyroid micro-papillary carcinoma (PTMC, meaning the papillary carcinoma with the largest diameter < 1cm) has been increasing year by year under the increasingly popular diagnostic technology (21). Traditional open thyroid surgery requires incision of the cervical white line during the operation, which will lead to adhesion of the neck skin. Some patients feel strange neck sensation and swallowing discomfort after the operation, and there are obvious disadvantages of neck scars, causing psychological trauma to the patients. With the development of minimally invasive and "remote" surgical methods, endoscopic thyroidectomy has gradually become accepted by most patients and surgeons. In recent years, many reports have reported the experience of endoscopic thyroid surgery for low-risk PTMC (19, 22). Endoscopic surgery has a smaller wound, and the location of

TABLE 1 Patient characteristics of gasless and gas insufflation transaxillary endoscopic thyroid lobectomy.

	Gas insufflation (n=48)	Gasless (n=25)	P value
Age (mean±SD)	39.9±10.5	38.9±6.8	0.605
Gender			0.933
Male(%)	20.8	20	
Female(%)	79.2	80	
Body mass index (mean±SD)	21.1±1.4	20.7±1.3	0.214
Size of nodule (cm) (mean±SD)	1.1±0.4	1.2±0.4	0.543

TABLE 2 Operative period data of gasless and gas insufflation transaxillary endoscopic thyroid lobectomy.

	Gas insufflation (n=48)	Gasless (n=25)	P value
Operative time (min) (mean±SD)	59.2±3.8	72.3±3.2	<0.001
Estimated blood loss (mL) (mean±SD)	19.7±1.8	20.3±1.4	0.192

the wound can be moved to the cosmetic area (23). Different incision sites were used, including the chest wall, armpit, breast, and submandibular area (14, 15, 24–26). For transaxillary endoscopic thyroidectomy, there are two ways to maintain the work space: carbon dioxide injection and mechanical retractor lifting procedures, both of which are commonly used by surgeons. We hypothesized that these different mechanisms for maintaining operational space during surgery would lead to different clinical outcomes.

In order to make the comparison between surgical techniques as accurate as possible, the PTC patients selected for endoscopic thyroidectomy through axillary approach were not only similar in basic clinical features, but also had no significant differences in thyroid nodule size. In addition, all surgeries are performed by an experienced surgeon.

In our study, the aeration group showed significant benefits of the aeration technique in terms of total time to surgery, postoperative pain, and aesthetic satisfaction 3 months after surgery. Analysis of the reasons showed that in the non-inflatable group, due to the larger flap area separated during the establishment of surgical space, and the need to timely adjust the position of the retractor, the time was longer. Indeed, non-aeration technology has the advantages of large surgical space, not affected by gas expansion, and can avoid the occurrence of complications such as gas embolism and hypercapnia (27). However, the aesthetic results of aerated surgery are better (28), compared to non-aerated techniques, the injected CO2 can create relatively less operating space for soft tissue stripping, the postoperative discomfort in the thoracic area is less (29), and it also prevents wound contraction. Therefore, aeration has better incision satisfaction and less postoperative pain than airless surgery (30). In addition, it is reported that the occurrence of high carbonization and its severity depend on the aeration pressure of CO2, which should not exceed 16 mmHg in order to avoid complications (31). According to the study of Ochiai et al. (32), the optimal CO2 pressure is 6mmHg, which will greatly reduce the occurrence of gas-related complications. Our approach to this problem was to use a separation rod to widen the surrounding subcutaneous space, and after blunt separation of subcutaneous tissue, the inflation pressure of 6mmHg was sufficient to maintain the surgical space, but also low enough to avoid absorbing large amounts of carbon dioxide through the subcutaneous tissue. It is worth mentioning that our study results showed that the VAS results of the two groups were comparable on the 1st day after surgery, but there was no statistical difference on the 7th day after surgery. This was due to the similar degree of anatomy and the same postoperative analgesia regimen in the two groups, and the good analgesia regimen resulted in the good control of postoperative pain in the two groups. In this study, there was no statistically significant difference in the estimated intraoperative blood loss ($P > 0.05$), which was due to the surgeons' understanding of the anatomical level and surgical proficiency, regardless of the operation space maintenance technique.

In terms of postoperative related indexes, the postoperative drainage flow, drainage tube removal time and hospitalization days in the aeration group were significantly less than those in the non-aeration group. This may be due to the different mechanisms by which different workspace maintenance techniques exert pressure on soft tissue resistance during surgery (33). In the non-inflatable group, when external pulling equipment was used to maintain the surgical space, the pressure was directly acted on a specific soft tissue, and the stress on the soft tissue increased with the increase of the operative time. This not only produced a lot of drainage fluid, but also led to a longer hospital stay. However, in CO2 aeration technology, this pressure diffuses into the soft tissue surrounding the operating space, minimizing pressure on specific areas of the soft tissue. In addition, other factors such as the proficiency of surgical assistants and individual differences of patients may be the factors that determine the poor prognosis of the airless group.

There was no significant difference in the incidence of postoperative complications between the two groups (all P >

TABLE 3 Postoperative period data of gasless and gas insufflation transaxillary endoscopic thyroid lobectomy.

	Gas insufflation (n=48)	Gasless (n=25)	P value
Postoperative drainage volume [median (IQR)]	95.0(90.0,100.0)	130(125,137.5)	<0.001
Drainage tube removal time (days) [median (IQR)]	3.0(3.0,3.0)	4.0(4.0,4.0)	<0.001
Hospital stay (days) [median (IQR)]	3.0(3.0,3.0)	5.0(4.0,5.0)	<0.001
Postoperative day 1 VAS score[median (IQR)]	5.0(5.0,5.0)	6.0(6.0,6.0)	<0.001
Postoperative day 7 VAS score[median (IQR)]	2.0(2.0,3.0)	2.0(2.0,3.0)	0.596
Postoperative satisfaction with incision at 3 months[median (IQR)]	8.0(7.0,8.0)	6.0(6.0,7.0)	<0.001

0.05). In the aeration group, 1 case (2.08%) had water choking, 2 cases (4.17%) had hoarseness and 1 case (2.08%) had hypocalcemia. In the airless group, 1 case (4.00%), 1 case (4.00%) of hoarseness and 1 case (4.00%) of hypocalcemia occurred after operation. No tone drop, incision infection or edema were observed in both groups. Postoperative injury of recurrent laryngeal nerve and internal branch of superior laryngeal nerve was found in both groups. Postoperative injury of recurrent laryngeal nerve and internal branch of superior laryngeal nerve occurred in both groups, which may be caused by thermal injury caused by ultrasound activated scalpel during gland resection or excessive nerve pulling during operation (34). In this study, parathyroid glands were preserved *in situ* in both groups during the operation, and there was 1 case of hypocalcemia in each group after the operation, which was related to hypoparathyroidism. Some authors suggest that a single functional parathyroid is sufficient to maintain normal glandular activity. On the other hand, some authors believe that at least three parathyroids are needed to restore normal function (35). In AlqahtaniSM's study (36), the occurrence of hypocalcemia in patients after unilateral thyroidectomy may be related to low preoperative calcium levels, parathyroid tissue loss, and postoperative decreased parathyroid hormone levels. The function of the above complications can be recovered after symptomatic treatment.

In summary, aeration technology has better clinical results than airless technology, but there are still some limitations worth noting. First, the patients we studied were followed for a short period of time after surgery because PTC can recurs even 20-30 years after thyroidectomy. However, two-thirds of recurrences typically occur in the first decade after the initial surgery, and especially in the first five years, the period of highest risk (37). In addition, the quality of life of cancer patients may gradually improve after surgery (38). In addition, we did not conduct statistical analysis of preoperative quality of life in the two groups. Second, differences in the abilities of surgeons for each surgical technique are difficult to eliminate, which can affect differences in outcomes. Finally, this study is a single-center, small-sample case study, and there are some limitations in the number of patients included and the criteria, which limit the reliability of the research results.

Conclusion

Compared with the non-inflatable group, the inflatable group had a shorter surgical time, less acute postoperative pain, and better incision satisfaction. And because of gas injection, the inflatable group provided significantly better clinical outcomes in terms of postoperative drainage flow, drainage removal time, and length of hospital stay. There was no significant difference in the estimated intraoperative blood loss and the incidence of postoperative complications. Therefore, aeration via axillary approach complete endoscopic thyroid surgery has more advantages than non-aeration method and is worth popularizing.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Research Subcommittee of the Medical Ethics Committee of Zhongshan Hospital, Affiliated to Xiamen University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/ next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LL: Conceptualization, Formal analysis, Investigation, Software, Writing – original draft, Writing – review & editing. SC: Methodology, Writing – review & editing. YL: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tumor differentiation-dependent conditional survival of patients with operable thyroid cancer

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Objective: Little is known about the changing risk profile of death and conditional survival in patients with operable thyroid cancer. This study aimed to investigate the annual hazard rate of cancer death, actuarial disease-specific survival (DSS), and conditional DSS in patients with thyroid cancer and explore the effects of tumor differentiation.

Methods: Patients diagnosed with thyroid cancer (N = 132,354) between 2004 and 2019 were identified from the Surveillance, Epidemiology, and End Results database. The hazard function was used to estimate the annual hazard rate of death. The Kaplan-Meier method and log-rank test were used for the calculation and between-group comparison of actuarial DSS, respectively. The life table was used to estimate the conditional DSS.

Results: A total of 1896 (1.4%) patients died due to thyroid cancer during the follow-up period. Patients with ATC (68.9%, 313/454) were more likely to die than those with PDTC (19.4%, 171/883) or DTC (1.1%, 1412/131017). For the entire cohort, patients with DTC and PDTC had excellent and relatively stable one-year conditional survival, respectively; patients with ATC had the worst one-year conditional survival, but they achieved the greatest improvements. The worst one-year conditional survival and the most obvious improvement were seen in patients with ATC regardless of any SEER Summary Stage.

Conclusion: Prognosis improved over time in a tumor differentiation-dependent manner in patients with operable thyroid cancer after diagnosis. This information provides more precise dynamic evaluations of the long-term prognosis of thyroid cancer survivors and paramount clinical implications for individualized treatment and surveillance.

KEYWORDS

thyroid cancer, surgery, tumor differentiation, prognosis, hazard, conditional survival

Introduction

Thyroid cancer is the most common endocrine malignancy (1) and has significantly increased worldwide over the past few decades (2, 3). Based on the degree of tumor differentiation, thyroid cancers are categorized as differentiated thyroid cancer (DTC), poorly-differentiated thyroid cancer (PDTC)/differentiated high-grade thyroid cancer (DHGTC) and anaplastic thyroid cancer (ATC). DHGTC is considered as a distinct pathological entity in the latest World Health Organization (WHO) histologic classification of thyroid neoplasms released in 2022 (4). DTC, which encompasses papillary cancer, follicular cancer and oncocytic cancer (previously known as Hürthle cell cancer), accounts for approximately 90% of all diagnosed thyroid cancers and generally has a slow progression and good prognosis with a 10-year survival rate of more than 90% (5, 6). PDTC and ATC, although rare, are the most clinically aggressive thyroid cancers. Patients with PDTC has a 10-year survival rates of 34-50%, while very few patients with ATC can survive longer than 1 year (7, 8). The clinical outcome of DHGTC is similar to PDTC, showing an intermediate prognosis between DTC without high-grade features and ATC (9).

Curative surgery is the cornerstone of the treatment for patients with thyroid cancer. Patients with thyroid cancer of different tumor differentiation might want to be informed about a realistic view of life expectancy after surgery. The survival rates of patients with thyroid cancer after surgery are known, but the death hazard is not constant and the likelihood of survival could change over time during follow-up. Thus, the time-dependent risk of death and survival probability for a patient who has already survived a long time after surgery remains to be further studied.

Traditional survival estimates mainly focus on survival rates at a given time and cannot provide accurate and dynamic prognostic evaluations over time. Time-dependent survival analysis, such as annual death hazard and conditional survival, can reflect real-time changes in death risk or survival at a specific time point and provide a more accurate and dynamic outlook of prognosis. The annual death hazard illustrates the absolute hazard of death at any instant among the remaining at-risk individuals (10). The conditional survival represents the probability of surviving certain additional years for patients who have lived for a designated period (11). These dynamic prognostic data provide important clinical implications for personalized treatment and surveillance. Furthermore, little evidence known about the prognostic factor of subtype and histological grade, since the prognostic impact has always been distinguished between DTC vs. ATC. The AJCC/UICC TNM, QTNM, AGES, MACIS and AMES systems consider the histological type (differentiated vs anaplastic), AGES also considers the tumor grade. A nomogram with excellent performance was developed for predicting the probability of death for patients with thyroid cancer based on a competing risks model and histological subtype was also considered as an important clinical predictive factor (13). All of these indicate the importance of histological subtype and grade in the prognosis of thyroid cancer. Thus, this study aimed to investigate the annual hazard rate of cancer death, actuarial disease-specific survival (DSS), and conditional DSS in thyroid cancer patients, and further explore the effects of tumor differentiation using the Surveillance, Epidemiology, and End Results (SEER) database.

Materials and methods

Patient were selected between 2004 and 2019 from the SEER database, which was maintained by the National Cancer Institute of the USA. It currently covers and publishes cancer incidence and survival data of approximately 34.6% of the US population across 18 regions. Patients diagnosed with DTC, PDTC or ATC were identified as per the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histological codes. The exclusion criteria were as follows: i) not undergoing thyroidectomy, ii) more than one type of primary malignancy, iii) unknown SEER combined summary stage, iv) patients with DHGTC and v) zero days of follow-up. The following information was extracted: age at diagnosis, sex, race/ethnicity, and the combined summary stage (2004+). This database contains anonymized patient information and is publicly accessible. Informed consent and approval from the institutional review boards were not required. The work has been reported in line with the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) reporting guidelines (12).

Statistical analysis

The DSS was measured from the time of diagnosis to death due to PTC as the primary endpoint of this study. The maximum likelihood estimate from the piecewise exponential model was used to evaluate the annual hazard rate, and the kernel-smoothing method was used to display the graphics. The Kaplan-Meier method and log-rank test were used for the calculation and between-group comparison of actuarial DSS, respectively. The conditional survival was defined as the probability of surviving additional y years, given that a patient has already lived for x years, and can be stated as follows: $CS(x|y) = S(x+y)/S(x)$, where $S(x)$ represents overall survival at x years. The conditional survival was computed from the life table survival data. A 2-tailed P value < 0.05 was considered statistically significant. All analyses were conducted using Stata software (version 16.0; Stata Corporation Ltd., College Station, TX, USA).

Results

Patient characteristics

Baseline characteristics of the study cohort are summarized in Table 1. A total of 132,354 patients undergoing surgery for thyroid cancer were enrolled for analysis. Overall, 131,017 (99.0%) patients had DTC. Only 883 (0.7%) and 454 (0.3%) patients had PDTC and ATC, respectively. The median age at diagnosis was 47 years (interquartile range, 36-58 years). The lower the degree of tumor

TABLE 1 Baseline characteristics of patients with operable thyroid cancers.

Characteristics	DTC n= 131,017, n (%)	PDTC n=883, n (%)	ATC n=454, n (%)	Total n=132,354, n (%)
Age (median, years)	47 (36-58)	55 (42-66)	67 (59-75)	47 (36-58)
Sex				
Female	101,918 (77.8)	560 (63.4)	268 (59.0)	102,746 (77.6)
Male	29,099 (22.2)	323 (36.6)	186 (41.0)	29,608 (22.4)
Race/ethnicity				
White	104,838 (80.0)	672 (76.1)	369 (81.3)	105,879 (80.0)
Black	8,259 (6.3)	84 (9.5)	35 (7.7)	8,378 (6.3)
Others/unknown	17,920 (13.7)	127 (14.4)	50 (11.0)	18,097 (13.7)
Tumor stage				
Localized	90,090 (68.8)	383 (43.4)	48 (10.6)	90,521 (68.4)
Regional	37,931 (29.0)	334 (37.8)	140 (30.8)	38,405 (29.0)
Distant metastasis	2,996 (2.3)	166 (14.5)	266 (58.6)	3,428 (2.6)

DTC, differentiated thyroid cancer; PDTC, poorly differentiated thyroid cancer; ATC, anaplastic thyroid cancer; Tumor stage was categorized according to SEER Combined Summary Stage (2004+).

differentiation, the older the patients (47 years for DTC, 55 years for PDTC and 67 years for ATC). Females and white predominated regardless of type of thyroid cancer. Localized disease (68.8%) was common in DTC, while distant metastasis (58.6%) was common in ATC. PDTC lied between DTC and ATC. The median follow-up duration was 74 months (interquartile range, 35-121 months).

Death hazard analysis

A total of 1896 (1.4%) patients died due to thyroid cancer during the follow-up period. Patients with ATC (68.9%, 313/454) were more likely to die than those with PDTC (19.4%, 171/883) or DTC (1.1%, 1412/131017). For the entire study population, the annual hazard curve of cancer mortality of patients with ATC showed a downward trend from fast to slow without an obvious peak, while that of patients with PDTC or DTC showed two almost parallel lines. The death hazard rate of patients with ATC was obviously higher than that of patients with PDTC or DTC. The pattern of death hazard of patients with different tumor differentiation was almost similar to that of the entire study population regardless of any SEER Summary Stage (Figure 1).

Traditional actuarial DSS

The 1- and 10-year DSS rates were 36.81% ± 2.42% and 19.82% ± 2.33% for ATC, 94.95% ± 0.78% and 74.92% ± 1.96% for PDTC, and 99.76% ± 0.20% and 98.47% ± 0.25% for DTC, respectively. The prognosis of patients with ATC was worst, followed by PDTC and DTC. Moreover, regardless of any SEER Summary Stage, patients with ATC had worse DSS compared to those with PDTC or DTC. The higher the SEER Summary Stage, the closer the prognosis of PDTC was to ATC (Figure 2).

Conditional DSS

For the entire cohort, patients with DTC and PDTC had excellent and relatively stable one-year conditional survival, respectively; patients with ATC had the worst one-year conditional survival, but they achieved the greatest improvements. For patients with different SEER Summary Stages, patients with distant disease had the worst one-year conditional survival, but obtained the most significant improvement. The worst one-year conditional survival and the most obvious improvement were seen in patients with ATC regardless of any SEER Summary Stage (Figure 3).

Discussion

In this study, we identified tumor differentiation has a significant impact on the prognosis of patients with operable thyroid cancer. For the entire study population, the death hazard rate of patients with ATC was obviously higher than that of patients with PDTC or DTC, showing a downward trend from fast to slow without an obvious peak. The prognosis of patients with ATC was worst, followed by PDTC and DTC. Patients with DTC and PDTC had excellent and relatively stable one-year conditional survival, respectively; patients with ATC had the worst one-year conditional survival, but they achieved the greatest improvements. Moreover, we achieved the same results when conducting stratified analysis based on the SEER Summary Stage. In brief, we demonstrated that

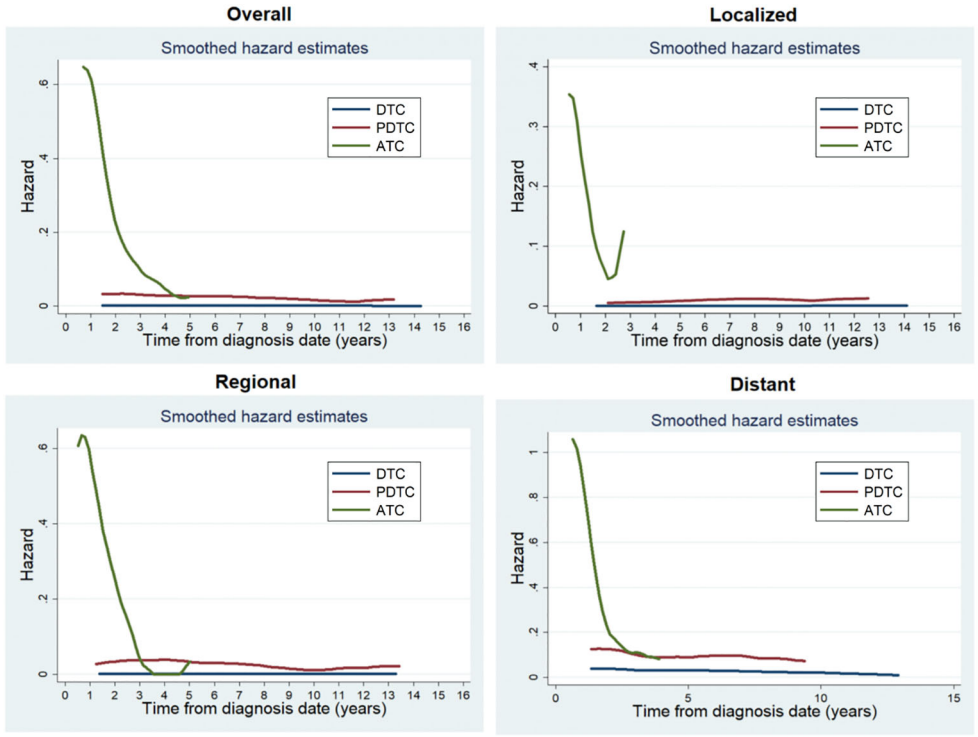

FIGURE 1
Annual hazard rates of cancer death of patients with different tumor differentiation for the entire cohort and at different SEER Summary Stages.

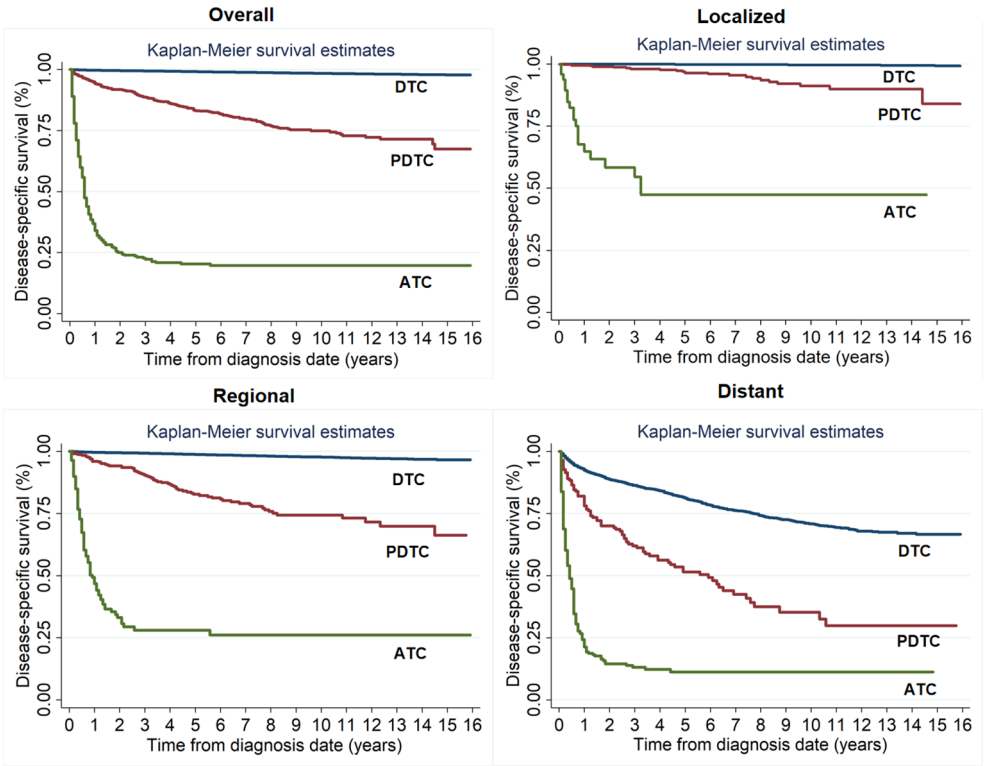

FIGURE 2
Kaplan-Meier survival estimates for actuarial disease-specific survival of patients with different tumor differentiation for the entire cohort and at different SEER Summary Stages.

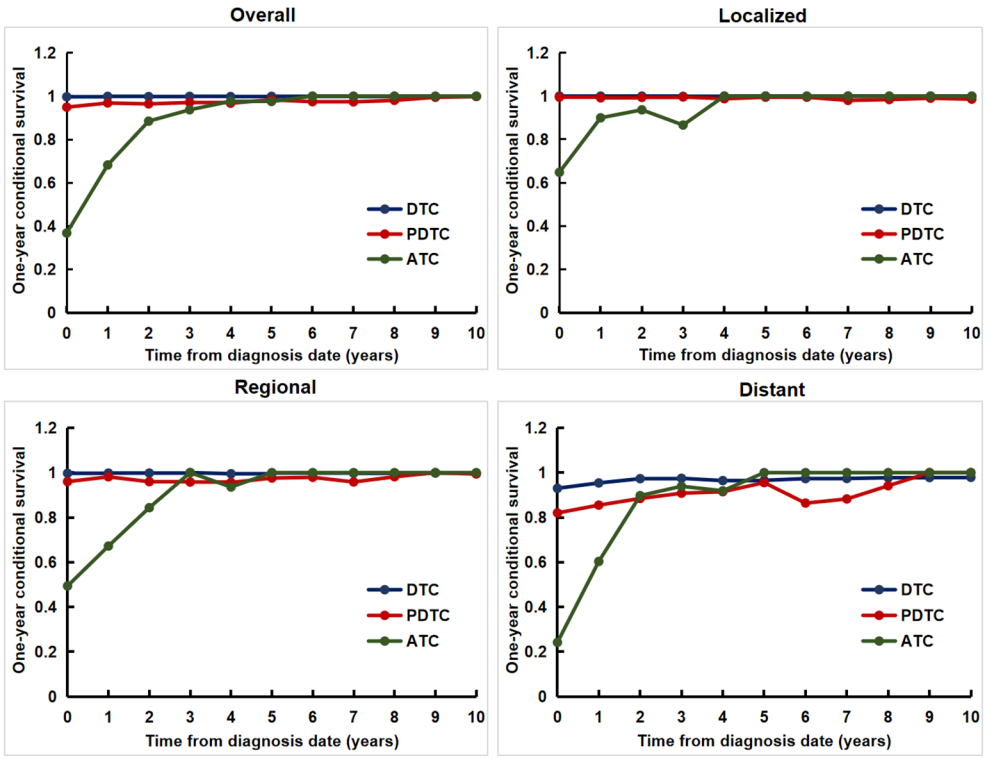

FIGURE 3
The one-year conditional disease-specific survival for patients with different tumor differentiation for the entire cohort and at different SEER Summary Stages.

improved survival probability was strongly dependent on tumor of the prognosis irrespective of where they are in any SEER Summary Stage. Our study is the first large population-based study comparing dynamic outcomes in thyroid cancer patients with different tumor differentiation treated with surgery.

Surgical resection remains the cornerstone of treatment for patients with thyroid cancer and this explains the improved outcome of patients who received surgery in our study. Previous studies have reported on the survival outcomes of patients with different tumor differentiation (6, 14). The prognosis of patients with DTC is usually good with the postoperative 10-year survival rate exceeding 90% (6, 14). However, PDTC and ATC have much worse outcomes. Lee et al. analyze the temporal changes of the long-term outcomes of 184 patients who were diagnosed with ATC or PDTC with 38.9 months. They found that the 5-year DSS rate was significantly higher in PTDC than ATC among all patients (65.8% vs.14.3%) and also in patients with resectable tumors (71.4% vs. 26.5%) (15). A recent epidemiological study from Denmark using a national cancer registry also reported that the 5-year survival rates were 91.1% and 79.9% in PTC and FTC, respectively, 63.6% in PDTC and 12.2% in ATC (16). We have achieved similar results. Not only that, our study clearly demonstrated dynamic prognostic changes of thyroid cancer patients with different tumor differentiation.

In previous studies dynamic evaluation of prognosis for malignant tumors have mainly been conducted based on SEER stage, TNM, or clinical pathological characteristics (17–20). Wang et al. found that gastric cancer patients with a higher stage from the SEER database had lower 5-year conditional survival, but the greatest increase in conditional survival occurred as more time elapsed from diagnosis (17). Shin et al. estimated the 5-year conditional survival of patients with ovarian cancer between 1997 and 2016 using data from the Korean Central Cancer Registry and found that the 5-year conditional survival improved over time, and the largest improvements were noted in patients with poorer initial prognostic factors (e.g., higher cancer stage) (18). Wang et al. investigate the CS and dynamic failure hazard in non-metastatic nasopharyngeal cancer receiving intensity-modulated radiotherapy and found that survival prognosis of non-metastatic non-metastatic nasopharyngeal cancer evolves over time with distinct dynamic patterns across TNM stages (19). Ploussard et al. evaluated the changes in the 5-year conditional survival rates of 8,141 patients treated with radical cystectomy for bladder cancer at 15 international academic centers between 1979 and 2012, and found that the 5-year conditional survival improved mainly for surviving patients with advanced-stage disease (20). These results suggest that the prognosis improved over time, and the largest improvements were noted in patients with higher stage or poorer initial prognostic factors. Our results indicated that the prognosis improved over time in a tumor differentiation-dependent manner among patients with thyroid cancer. The most obvious improvements were found in patients with ATC.

The strengths of our study include its large cohort with a sufficient sample size, nationally representative population, and

long-term follow-up. However, this study had several limitations. First, treatment information was limited, and it is possible that changes in treatment regimens during the study period. Second, the study is subject to U.S. population, and the findings may not be generalizable to other populations. Third, data on tumor recurrence were not available, and we were unable to assess recurrence-free survival.

Conclusion

This nationwide study described the hazard rate of cancer death, traditional actuarial DSS, and conditional DSS of patients with operable thyroid cancer of different tumor differentiation, providing a dynamic prognostic evaluation for these patients. Understanding the hazard rate and the conditional survival of thyroid cancer is key to creating more tailored treatment plans and surveillance.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: All data used in this study can be freely accessed from the SEER program (https://seer.cancer.gov/).

Ethics statement

The requirement of ethical approval was waived by the Institutional Review Board of the First Hospital of China Medical University for the studies involving humans because this database contains anonymized patient information and is publicly accessible. Informed consent and approval from the institutional review boards were not required. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board also waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this database contains anonymized patient information and is publicly accessible. Informed consent and approval from the institutional review boards were not required.

Author contributions

R-nY: Conceptualization, Formal analysis, Data curation, Writing – original draft. Z-qZ: Conceptualization, Data curation, Formal analysis, Writing – original draft. PZ: Conceptualization, Formal analysis, Writing – review & editing. HZ: Conceptualization, Formal analysis, Writing – review & editing. H-IQ: Conceptualization, Formal analysis, Writing – review & editing, Supervision. W-wD: Conceptualization, Formal analysis, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Correlation analysis of Hashimoto's thyroiditis with papillary thyroid carcinoma occurrence and its central lymph node metastasis: a single center experience

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Purpose: This study investigates the clinicopathological characteristics of papillary thyroid carcinoma (PTC) with coexisting Hashimoto's thyroiditis (HT) and further explores the risk factors for central lymph node metastasis (CLNM) in PTC.

Method: A retrospective analysis was conducted on 415 PTC patients who underwent surgical treatment for thyroid cancer at the First Affiliated Hospital of Anhui University of Chinese Medicine from 2016 to 2022. Clinicopathological features were compared between PTC patients with and without HT. Univariate and multivariate logistic regression were used to analyze the risk factors of CLNM.

Result: The PTC+HT group had a higher proportion of female patients (85.5%) than the PTC group (P<0.05). Univariate analysis revealed no statistically significant difference between the two groups in eight aspects (all P>0.05). Multivariate analysis showed that HT was positively associated with the total number of central lymph node (CLN) dissected, Thyroid-stimulating hormone (TSH), Thyroid peroxidase antibody (TPOAb), and Thyroglobulin antibodies (TgAb), while identified as a protective factor against invasion with an odds ratio of 0.422 (95%CI 0.209-0.853, P=0.016). Through univariate and multivariate logistic regression, we proved that tumor position, Capsule + Extrathyroidal extension (ETE), multifocal tumors, and the total number of CLN dissected were independent risk factors for CLNM. Multiple linear regression analysis told us that invasion (β= 0.093, p=0.048) had a positively predictive impact on CLN positive rate.

Conclusion: Female PTC patients are more prone to concurrent HT, which elevates the levels of TSH, TPOAb, and TgAb. HT not only promotes the longitudinal growth of nodules and PTC development, but also reduces the risk of invasion and CLNM. Therefore, we posit that the impact of HT on PTC

patients is a "double-edged sword". Isthmus, Capsule + ETE, multifocality, age < 55 years old, and male are high-risk factors for CLNM in PTC, while HT is regarded as a protective factor. Capsule + ETE is the primary risk factor affecting the CLN positive rate.

KEYWORDS

papillary thyroid carcinoma, Hashimoto's thyroiditis, central lymph node metastasis, multivariate analysis, risk factors

Introduction

Thyroid carcinoma is the predominant malignant disease affecting the endocrine system, characterized by a favorable prognosis and high overall survival rate, particularly in cases of papillary thyroid carcinoma (PTC) (1). However, with the continuous improvement of diagnostic tools ——such as fine needle aspiration, high-resolution ultrasound, thyroid-specific antibody testing, and genetic testing——the morbidity of thyroid cancer has increased dramatically in recent years (2). Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis, is the most prevalent autoimmune thyroid disease and the primary cause of hypothyroidism in iodine-sufficient regions worldwide (3). Studies show that approximately one-third of individuals diagnosed with PTC also have HT, and this prevalence is increasing rapidly (4–6).

Since Rudolf Virchow initially posited the link between chronic inflammation and cancer development in 1863, a growing number of studies have substantiated that chronic inflammation can contribute to cancer progression, such as inflammatory bowel disease with colon cancer, chronic viral hepatitis with liver cancer, as well as chronic gastritis induced by Helicobacter pylori infection with gastric cancer (7–13). The association between HT and PTC was first described by Dailey et al. (14) in 1955. Subsequently, much research has been conducted on this topic, but a consensus has yet to be reached. So, does the presence of HT increase the risk of developing PTC? And does HT contribute to the occurrence of lymph node metastasis in PTC? Many studies have confirmed that HT can promote the occurrence of PTC, and male, age ≤45 years, and tumor diameter > 1cm are risk factors for CLNM in PTC patients (5, 15, 16). However, there is some disagreement about whether HT increases the risk of CLNM in PTC patients (17, 18). Therefore, based on the analysis of the clinical characteristics of PTC patients with HT, this study will further focus on the impact of HT on the risk rate of CLNM in PTC patients. We performed a retrospective analysis of clinical and pathological data from 415 patients who underwent surgery for PTC, with a focus on the clinical characteristics of PTC in combination with HT.

Materials and methods

Patients

This study comprehensively evaluated all patients who underwent thyroidectomy for PTC at the Second Department of General Surgery, First Affiliated Hospital of Anhui University of Chinese Medicine, from January 2016 to December 2022.

Inclusion criteria: (1) First-time surgical intervention for thyroid cancer; (2) Postoperative pathological diagnosis confirming PTC; (3) No prior occurrence of thyroid or cervical lymph node disorders; (4) No history of other malignant tumors; (5) Availability of complete clinical and pathological data.

Exclusion criteria: (1) Metastatic thyroid cancer; (2) Postoperative pathology showing other types of thyroid cancer, such as follicular or medullary carcinoma; (3) Previously diagnosed as thyroid or cervical lymph node diseases; (4) History of other malignant tumors or current coexistence of other malignancies; (5) Incomplete clinical or pathological data.

After screening, a total of 415 cases were selected for inclusion in this study. Based on postoperative pathological examinations, the patients were categorized into two groups: the PTC with HT group (PTC+HT) and the PTC without HT group (PTC). The ethical review for this project was approved and registered by the Medical Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine.

Preoperative examination

The blood samples from all patients were consistently analyzed at the Test Center of the First Affiliated Hospital of Anhui University of Chinese Medicine. The testing parameters included serum Thyroid-stimulating hormone (TSH), serum Free triiodothyronine (FT3), serum Free thyroxine (FT4), Thyroglobulin antibodies (TgAb), and Thyroid peroxidase antibody (TPOAb). All preoperative thyroid color ultrasound examinations were conducted by physicians at the Ultrasound Center of the First Affiliated Hospital of Anhui University of Chinese Medicine.

Surgical methods

All patients underwent either unilateral or bilateral thyroidectomy, accompanied by isthmus and ipsilateral central lymph node dissection. In cases where biopsy cytology or intraoperative frozen section revealed lateral lymph node metastasis, functional lateral lymph node dissection was performed simultaneously. All surgeries were executed in an open situation by highly qualified surgeons in our department. No serious postoperative complications were observed in any of the patients after surgery. The cervical lymph node zoning and extent of lymph node dissection in each region strictly adhered to the guidelines established by the American Thyroid Association (19).

Pathological diagnosis

The pathological examination results of all patients were uniformly reported by the pathology department of our hospital. Each pathology report offered a detailed description of the tumor, covering its position, maximum diameter, invasion of the thyroid capsule, number of lesions, lymph node zoning and counts, as well as lymph node metastasis. The pathological staging followed the 2017 8th edition of the American Joint Committee on Cancer (AJCC) Staging Guidelines for Differentiated Thyroid Cancer (20). All patients were diagnosed with PTC in their pathological reports.

Diagnostic criteria and grouping

The evaluation of thyroid capsule invasion was not solely reliant on subjective observation. Rather, it was a synthesis of the surgeon's notes in the operative records and the final pathology reports. In instances where there was a discrepancy, the pathological results were prioritized. The diagnostic criteria for HT were as follows: postoperative pathology showed that thyroid tissue appeared enlarged, grayish, and firm, thyroid cells in some patients displayed enlarged and thickened, leading to distinctive Hürthle cells. Additionally, the stroma was heavily infiltrated by hematopoietic monocytes, predominantly lymphocytes alongside some plasma cells, while lymphoid follicles and active germinal centers were formed. Patients whose pathological reports matched the above description were categorized into the PTC+HT group. The remaining patients were placed in the PTC group.

Observed index

Retrospective data analysis was used to compare the clinicopathological characteristics between the two groups. The clinicopathologic features mainly encompassed age, gender, position, maximum tumor diameter, presence of microcarcinoma, presence of calcification, anteroposterior to transverse diameter ratio (A/T), invasion, number of lesions, number of central lymph node (CLN) dissected, number of central lymph node metastasis (CLNM), pathological stage, preoperative thyroid function indicators (including FT3, FT4, TT3, TT4, TSH, TPOAb, TgAb), etc. Both capsular invasion and extrathyroidal extension (ETE) indicated invasion.

Statistical analysis

The data were processed using SPSS statistical software and R language software. Measurement data were presented as mean and standard deviation. For normally distributed data, t-test and ANOVA were employed for comparative analysis. Categorical data were represented as percentages (%), compared by χ^2 test and rank-sum test. Non-parametric tests were used for ordinal and non-normally distributed data. Multivariate linear regression was applied to assess continuous variables, while logistic regression was utilized for binary dependent variables. The predictive value of those factors was measured through the area under the receiver operating characteristic (ROC) curve. $P<0.05$ was deemed statistically significant in all tests.

Results

Basic clinicopathological features of HT group and PTC+HT group

A cohort of 415 patients diagnosed with PTC was selected in this study, comprising 96 males and 319 females, resulting in a male-to-female ratio of approximately 1:3. The age distribution of the patients ranged from 15 to 78 years, with a mean age of 45.23 ± 12.090 years and a median age of 46 years. Among these patients, 319 cases were younger than 55 years, whereas 96 cases were 55 years or older.

According to the presence or absence of HT, the subjects were divided into two groups. The PTC group comprised 298 patients, including 79 males (26.5%) and 219 females (73.5%), with a mean age of 45.70 ± 12.586 years. In contrast, the PTC+HT group included 117 patients, consisting of 17 males (14.5%) and 100 females (85.5%), with a mean age of 44.05 ± 10.681 years. While the mean age in the PTC group was slightly higher than that in the PTC +HT group, the difference did not reach statistical significance ($P>0.05$). Simultaneously, a higher proportion of patients under 55 years old was observed in the PTC+HT group (82.1%) compared to the PTC group (74.8%), though this disparity was also not statistically significant($P>0.05$). However, the percentage of female patients was higher in the PTC+HT group (85.5%) compared to the PTC group ($P<0.05$). Analysis of the pathological examination results revealed no statistically significant differences between the two groups across eight factors: position, maximum tumor diameter, presence of microcarcinoma, presence of calcification, invasion, number of lesions, number of positive central lymph node, and pathological staging (all $P>0.05$). Furthermore, upon dividing the maximum tumor diameter into two groups with a 20mm boundary, no statistically significant difference was observed between the two groups ($P>0.05$). Conversely, the proportion of A/T >1 in the PTC+HT group (59.8%) was higher than that in the

PTC group (44.6%), showing a statistically significant difference (P<0.05). The total number of central lymph node dissected in the PTC+HT group (7.62 ± 5.898) was markedly higher than that in the PTC group (P<0.00). Similarly, the PTC+HT group had a greater percentage of central lymph node with a positive rate compared to the PTC group (P=0.007). The laboratory examination results revealed that the mean values of FT3 before operation in the PTC +HT group were slightly lower than that in the PTC group (P<0.05). The preoperative mean values of TSH, TPOAb, and TgAb all exhibited an increase in the PTC+HT group compared to the PTC group (P<0.05), with the latter two indicating a more pronounced rise. Nevertheless, there were no notable differences in the mean values of FT3, TT3, and TT4 between the two groups before operation (P>0.05). (Table 1)

Multivariate analysis of the effect of coexistent HT in PTC patients

All potential variables related with HT were added to the Logistic regression model. Multivariate analysis displayed that HT was positively associated with the total number of CLN dissected (OR=1.186, 95%CI 1.100-1.280, P<0.001), TSH (OR=1.260, 95%CI 1.043-1.521, P=0.016), TPOAb (OR=1.007, 95%CI 1.004-1.010, P<0.001) and TgAb (OR=1.003, 95%CI 1.001-1.004, P<0.001). Nevertheless, HTemerged as a protective factor against invasion, with an odds ratio (OR) of 0.422, (95%CI 0.209-0.853, P=0.016) (Table 2). After stratifying adjustments for age and maximum tumor diameter, we obtained the same outcomes as above.

Univariate analysis predictive risk factors of CLNM in PTC patients

Univariate analysis found that age (P<0.001), gender (P=0.016), position (P=0.023), microcarcinoma (P<0.001), calcification (P=0.006), invasion (P<0.001), focality (P=0.019) and the total number of CLN dissected (P<0.001) were all associated with CLNM in PTC patients. Compared with the non-CLNM group, the CLNM group had a higher proportion of male (29.4%), isthmus (20.6%), calcification presence (63.5%), Capsule +ETE (38.2%), multifocal (34.7%) and maximum tumor diameter≥20mm (18.2%), all of which had a positive effect on CLNM. On the contrary, age≥55 years old and microcarcinoma presence were both negatively related with CLNM (Table 3).

Multivariate analysis predictive risk factors of CLNM in PTC patients

Our multivariate Logistic analysis revealed that position(Right, OR=1.920, 95%CI 1.166-3.164; Bilateral, OR=9.393, 95%CI 0.607-145.408; Isthmus, OR=1.066, 95%CI 0.451-2.522; P=0.033), Capsule + ETE (OR=2.246, 95%CI 1.363-3.700, P=0.001), multifocal (OR=1.999, 95%CI 1.029-3.885, P=0.041) and the total number of CLN dissected (OR=1.143, 95%CI 1.083-1.206, P<0.001) were defined as independent risk factors for CLNM. Conversely, age≥55years old (OR=0.358, 95%CI 0.201-0.637, P<0.001), female (OR=0.433, 95%CI 0.257-0.730, P=0.002), microcarcinoma (OR=0.329, 95%CI 0.205-0.528, P<0.001) and HT (OR=0.412, 95%CI 0.234-0.727, P=0.002) were protective factors for CLNM (Table 4).

Receiver operating characteristic (ROC) curves were drawn to predict the risk of CLNM in PTC patients by using the significant factors respectively (Figure 1). The respective values for the area under the curve (AUC) of age stratification, gender, position, microcarcinoma, invasion, number of lesions, the total number of CLN dissected and HT were respectively 0.439, 0.447, 0.576, 0.389, 0.595, 0.555, 0.656 and 0.456 (all P<0.1). On this basis, we use these 8 factors to build a prediction model and plot its ROC curve. The AUC of this model was 0.759, which was higher than the previous individual factors (Figure 2). Therefore, it demonstrates that the prediction model has a higher diagnostic value. To visualize the model, different versions of the nomogram were plotted to better illustrate the problem (Figures 3, 4). The calibration curve revealed good predictive accuracy between the actual probability and predicted probability (Figure 5). To determine the net benefit of the nomogram, we built a decision curve analysis (DCA) (Figure 6). The curve indicated that the nomogram could be useful when the threshold probability was between 0.15 and 0.75. In the prediction model, the DCA's net benefit was substantially higher.

Multivariate linear regression analysis of risk factors of CLN positive rate in PTC patients

Based on multiple linear regression analysis, a new regression equation was established for predicting the risk of CLN positive rate in patients with PTC, which had statistical significance (F=5.750, P<0.001). Among them, age (β=-0.229, P<0.001), female gender (β=- 0.161, P=0.001), and microcarcinoma (β=- 0.244, P=0.001) exhibited negatively predictive effects; while invasion (β= 0.093, p=0.048) showed a positively predictive effect. Together, these variables collectively accounted for 16.3% of the variation in the CLN positive rate (Table 5).

Discussion

Thyroid carcinoma is the most prevalent endocrine malignancy with soaring morbidity worldwide. As of 2018, it ranked ninth among all cancers globally (21). There are four common pathological types of thyroid carcinoma, with PTC being the most frequent type, accounting for approximately 80% of cases and generally having a favorable overall survival rate (22, 23). Nonetheless, Lim et al. (24) discovered that both morbidity and mortality of PTC have been gradually ramping up in recent years. The underlying reasons of this trend remain unclear. Currently, the academic community is actively investigating potential risk factors in hopes of addressing this issue.

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TABLE 1 Comparison of clinicopathological characteristic in PTC patients according to with or without HT.

Group	PTC (n=298)	PTC+HT (n=117)	t/U/χ^2 value	P
Age	45.70 ± 12.586	44.05 ± 10.681	16088	0.221
<55	223 (74.8%)	96 (82.1%)	2.073	0.150
≥55	75 (25.2%)	21 (17.9%)		
Gender				
Male	79 (26.5%)	17 (14.5%)	6.124	0.013
Female	219 (73.5%)	100 (85.5%)		
Position				
Left	119 (39.9%)	42 (10.1%)	4.713	0.180
Right	135 (45.3%)	50 (12.0%)		
Bilateral	41 (13.8%)	25 (6.0%)		
Isthmus	3 (1.0%)	0 (0%)		
Maximum tumor diameter (mm)	10.66 ± 7.888	9.31 ± 5.871	16339	0.318
<20	256 (85.9%)	107 (91.5%)	1.880	0.170
≥20	42 (14.1%)	10 (8.5%)		
Microcarcinoma				
No	113 (37.9%)	35 (29.9%)	2.010	0.156
Yes	185 (62.1%)	82 (70.1%)		
Calcification				
No	132 (44.3%)	54 (46.2%)	0.054	0.816
Yes	166 (55.7%)	63 (53.8%)		
A/T >1				
No	165 (55.4%)	47 (40.2%)	7.170	0.007
Yes	133 (44.6%)	70 (59.8%)		
Invasion				
No	210 (70.5%)	93 (79.5%)	3.024	0.082
Capsule + ETE	88 (29.5%)	24 (20.5%)		
Number of lesions				
Unifocality	222 (74.5%)	76 (65%)	3.320	0.068
Multifocality	76 (25.5%)	41 (35%)		
The total number of CLN dissected	4.27 ± 3.709	7.62 ± 5.898	11581	0.000
Number of positive CLN	1.19 ± 2.072	1.00 ± 2.316	15566.5	0.056
CLN positive rate (%)	24.96 ± 34.983	13.92 ± 27.887	14786	0.007
Staging				
I	247 (82.9%)	104 (88.9%)	3.626	0.297
II	16 (5.4%)	6 (5.1%)		
III	23 (7.7%)	6 (5.1%)		
IV	12 (4.0%)	1 (0.9%)		
FT3 (pmol/L)	4.37 ± 1.03	4.14 ± 0.64	14994	0.027

(Continued)

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TABLE 1 Continued

Group	PTC (n=298)	PTC+HT (n=117)	t/U/χ^2 value	P
FT4 (pmol/L)	12.86 ± 2.08	12.36 ± 2.11	15487	0.077
TT3 (nmol/L)	1.46 ± 0.32	4.42 ± 30.65	16525	0.409
TT4 (nmol/L)	94.41 ± 19.40	93.18 ± 29.43	16278	0.293
TSH (mIU/L)	1.98 ± 1.38	3.09 ± 3.98	12760	0.000
TPOAb (IU/ml)	17.55 ± 86.67	180.85 ± 263.00	5314.5	0.000
TgAb (IU/ml)	30.31 ± 124.52	163.93 ± 254.22	4549.5	0.000

TABLE 2 Multivariate Logistic regression analysis the effect of coexistent HT in PTC patients.

Variables	Subgroup	Unadjusted			Subgroup	Adjusted		
		OR	95% CI	P		OR	95% CI	P
Age		0.990	0.965-1.015	0.426	<55	1		
					≥55	0.669	0.328-1.367	0.270
Gender	Male	1			Male	1		
	Female	1.256	0.572-2.761	0.570	Female	1.251	0.570-2.745	0.577
Position	Left	1		0.842	Left	1		0.837
	Right	1.108	0.594-2.067	0.747	Right	1.125	0.601-2.103	0.713
	Bilateral	0.000	0.000-.	0.999	Bilateral	0.000	0.000-.	0.999
	Isthmus	0.682	0.244-1.911	0.467	Isthmus	0.686	0.244-1.923	0.473
Maximum tumor diameter (mm)		0.985	0.918-1.055	0.660	<20	1	0.174-1.851	0.348
					≥20	0.568		
Microcarcinoma	No	1			No	1		
	Yes	0.896	0.320-2.510	0.834	Yes	0.890	0.419-1.889	0.762
Calcification	No	1			No	1		
	Yes	0.671	0.378-1.189	0.171	Yes	0.648	0.365-1.152	0.139
A/T >1	No	1			No	1		
	Yes	1.658	0.903-3.047	0.103	Yes	1.651	0.900-3.030	0.105
Invasion	No	1			No	1		
	Capsule + ETE	0.422	0.209-0.853	0.016	Capsule + ETE	0.411	0.202-0.834	0.014
Number of lesions	Unifocality	1			Unifocality	1		
	Multifocality	1.501	0.667-3.380	0.326	Multifocality	1.491	0.666-3.337	0.331
The total number of CLN dissected		1.186	1.100-1.280	0.000		1.182	1.094-1.276	0.000
Number of positive CLN		0.869	0.695-1.087	0.218		0.884	0.708-1.104	0.277
CLN positive rate (%)		0.720	0.159-3.264	0.670		0.691	0.153-3.126	0.632
FT3		0.593	0.338-1.040	0.068		0.587	0.336-1.025	0.061
FT4		1.044	0.798-1.367	0.752		1.044	0.799-1.364	0.753
TT3		1.204	0.498-2.912	0.681		1.198	0.523-2.745	0.669

(Continued)

TABLE 2 Continued

Variables	Subgroup	Unadjusted			Subgroup	Adjusted		
		OR	95% CI	P		OR	95% CI	P
TT4		0.997	0.972-1.023	0.822		0.998	0.973-1.023	0.851
TSH		1.260	1.043-1.521	0.016		1.259	1.043-1.520	0.016
TPOAb		1.007	1.004-1.010	0.000		1.007	1.004-1.010	0.000
TgAb		1.003	1.001-1.004	0.000		1.003	1.001-1.004	0.000

TABLE 3 Univariate analysis of the clinicopathological factors associated with CLN in PTC patients.

Group	without CLNM (n=245)	with CLNM (n=170)	t/U/χ^2 value	P
Age	48.10 ± 11.312	41.11 ± 12.011	13841	0.000
<55	176 (71.8%)	143 (84.1%)	7.836	0.005
≥55	69 (28.2%)	27 (15.9%)		
Gender				
Male	46 (18.8%)	50 (29.4%)	5.801	0.016
Female	199 (81.2%)	120 (70.6%)		
Position				
Left	107 (43.7%)	54 (31.8%)	8.762	0.023
Right	106 (43.3%)	79 (46.5%)		
Bilateral	31 (0.4%)	2 (1.2%)		
Isthmus	1 (12.7%)	35 (20.6%)		
Maximum tumor diameter (mm)	9.13 ± 7.088	11.94 ± 7.530	15244.	0.318
<20	224 (91.4%)	139 (81.8%)	7.693	0.006
≥20	21 (8.6%)	31 (18.2%)		
Microcarcinoma				
No	65 (26.5%)	83 (48.8%)	20.777	0.000
Yes	180 (73.5%)	87 (51.2%)		
Calcification				
No	124 (50.6%)	62 (36.5%)	7.554	0.006
Yes	121 (49.4%)	108 (63.5%)		
A/T >1				
No	127 (51.8%)	85 (50.0%)	0.072	0.789
Yes	118 (48.2%)	85 (50.0%)		
Invasion				
No	198 (80.8%)	105 (61.8%)	17.533	0.000
Capsule + ETE	47 (19.2%)	65 (38.2%)		
Focality				
Unifocality	187 (76.3%)	111 (65.3%)	5.501	0.019
Multifocality	58 (23.7%)	59 (34.7%)		
The total number of CLN dissected	4.39 ± 4.566	6.40 ± 4.597	14329	0.000

(Continued)

TABLE 3 Continued

Group	without CLNM (n=245)	with CLNM (n=170)	t/U/χ^2 value	P
FT3 (pmol/L)	4.29 ± 1.08	4.32 ± 0.69	19594.5	0.306
FT4 (pmol/L)	12.76 ± 2.02	12.67 ± 2.21	20754.5	0.953
TT3 (nmol/L)	2.80 ± 21.15	1.56 ± 1.57	20451.5	0.756
TT4 (nmol/L)	94.40 ± 23.98	93.58 ± 20.63	20187.5	0.596
TSH (mIU/L)	2.33 ± 2.91	2.25 ± 1.60	20138.5	0.568
TPOAb (IU/ml)	71.52 ± 193.88	52.151 ± 139.44	20333	0.682
TgAb (IU/ml)	61.07 ± 170.79	77.94 ± 195.45	20773	0.965
HT				
No	167 (68.2%)	131 (77.1%)	3.496	0.062
Yes	78 (31.8%)	39 (22.9%)		

HT, as a complex autoimmune thyroid disease, is characterized by diffuse lymphocytic infiltration (especially T cells) and follicular destruction leading to progressive atrophy and fibrosis of thyroid tissue, even to progressive damage, which is clinically manifested as obvious hypothyroidism (25). Some studies believe that its pathogenesis may be the combination of genetic susceptibility and environmental factors, resulting in the loss of immune tolerance, and subsequent autoimmune attack on thyroid tissue, ultimately the disease appears (26–28).

The relationship between PTC and HT has been the focus of extensive research. Investigations have sought to determine whether special clinicopathological features or prognostic implications arise when they coexist. Since the association between HT and PTC was first described in 1955 (14), numerous studies have confirmed that HT elevates the risk of developing PTC (29, 30). As Danis et al. (31)found, among 469 patients who underwent thyroidectomy, 54.9% were diagnosed with both PTC and HT, 33.1% with HT alone, and the remaining 12% with PTC alone (P<0.001).

This paper aims to analyze the clinical and pathological characteristics of PTC patients combined with HT through a retrospective study, and on this basis, further delves into the risk factors affecting central lymph node metastasis in PTC patients. We have obtained some novel insights and perspectives.

TABLE 4 Multivariate analysis of the clinicopathological factors associated with CLNM in PTC patients.

Variables	Subgroup	OR	95% CI	P
Age	<55	1		0.000
	≥55	0.358	0.201-0.637	
Gender	Male	1		0.002
	Female	0.433	0.257-0.730	
Position	Left	1		0.033
	Right	1.920	1.166-3.164	
	Bilateral	9.393	0.607-145.408	
	Isthmus	1.066	0.451-2.522	
Microcarcinoma	No	1		0.000
	Yes	0.329	0.205-0.528	
Invasion	No	1		0.001
	Capsule + ETE	2.246	1.363-3.700	
Number of lesions	Unifocal	1		0.041
	Multifocal	1.999	1.029-3.885	
The total number of CLN dissected		1.143	1.083-1.206	0.000
HT	No	1		0.002
	Yes	0.412	0.234-0.727	

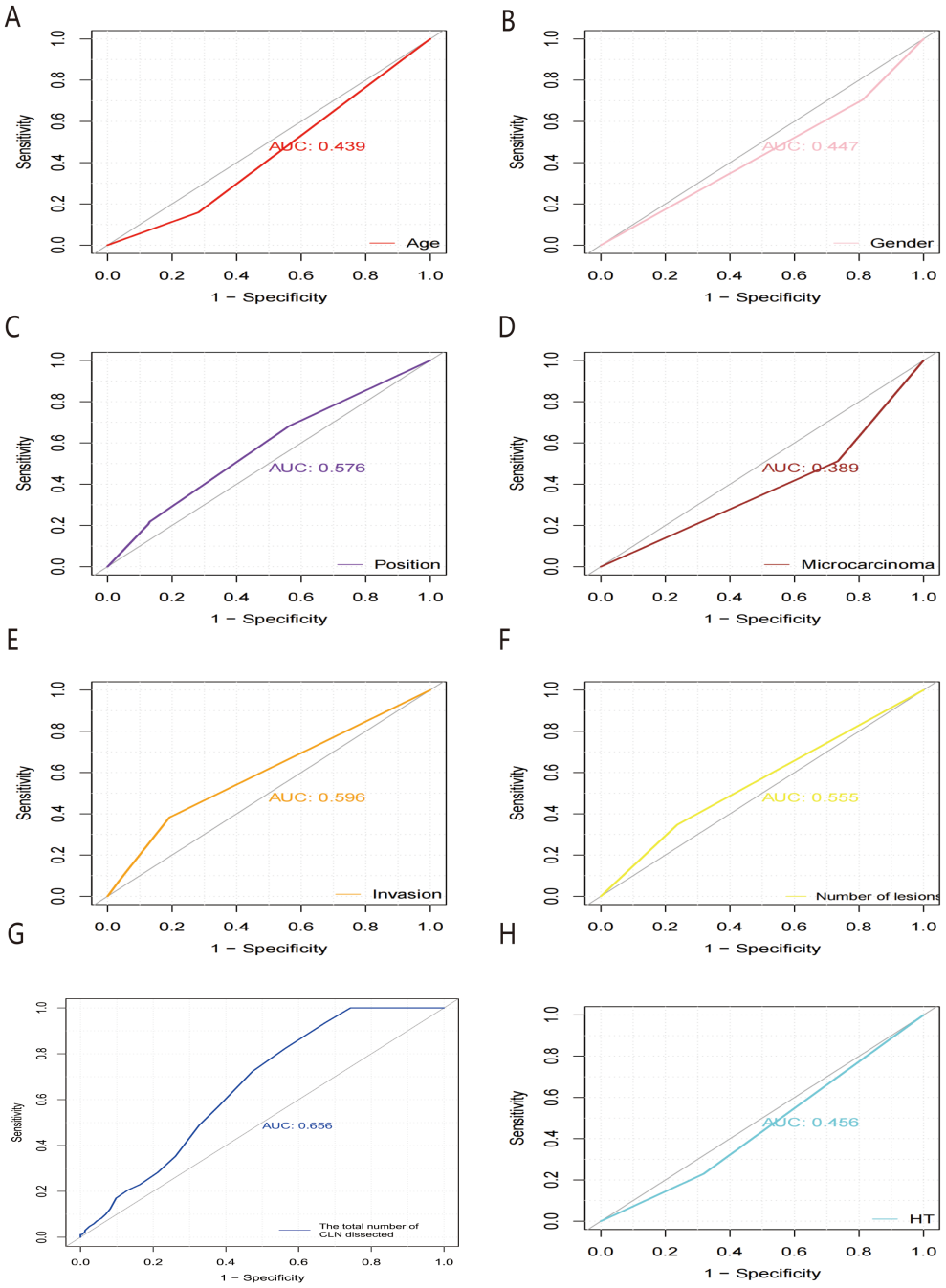

FIGURE 1
ROC curves of predicting the risk of CLNM in PTC patients by HT **(A)**, microcarcinoma **(B)**, the total number of CLN dissected **(C)**, position **(D)**, number of lesions **(E)**, gender **(F)**, invasion **(G)** and age stratification **(H)**, respectively. ROC, receiver operating characteristic; AUC, area under the ROC curve.

Firstly, this study found that the PTC+HT group had a higher proportion of female patients than the PTC group (P<0.05), indicating that female PTC patients are more likely to have coexisting HT. Similar results were gained by Heo et al. (32) through a retrospective analysis of case data. Cappellacci et al. (33) also believed that PTC patients with concurrent HT had a younger age of onset (P=0.4131) and a greater female predominance compared to those without HT (P<0.0001). In addition, our study revealed the proportion of A/T > 1 in the PTC+HT group (59.8%) was higher than that in the PTC group (44.6%), and there was a statistical difference between them (P=0.007). This result suggests that patients with concurrent HT are more prone to experience longitudinal growth of nodules, thereby increasing the risk of PTC.

Secondly, our investigation revealed that the mean values of preoperative TSH, TPOAb, and TgAb in the PTC+HT group were higher than those in the PTC group, and the latter two were more significant, with statistical significance (all P<0.001). Multivariate

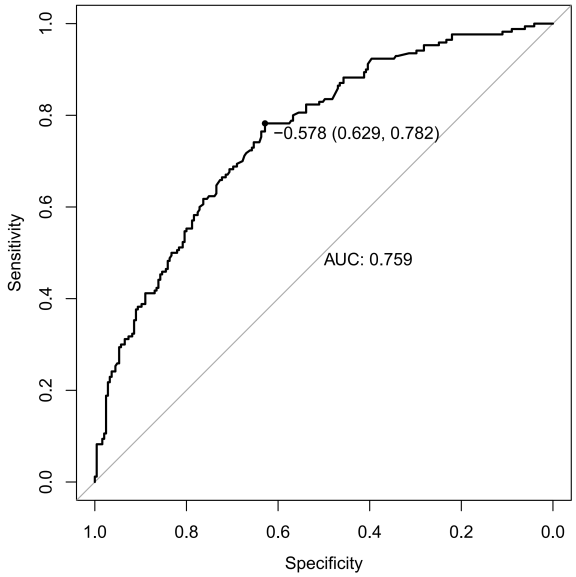

FIGURE 2
ROC curves of predicting the risk of CLNM in PTC patients by the model. ROC, receiver operating characteristic; AUC, area under the ROC curve.

Logistic regression analysis further provided additional confirmation that HT was positively correlated with TSH, TPOAb, and TgAb. These results told us that the coexistence of HT can cause blood TSH, TPOAb, and TgAb to rise in PCT patients. Currently, it is an indisputable fact that the occurrence of thyroid cancer is related to elevated TSH levels in the blood. TSH, as a growth factor, can regulate the proliferation and function of thyroid cells under normal circumstances. When TSH exceeds the upper limit of the normal range, it is positively correlated with the malignant transformation rate of nodular goiter. Many studies have verified this view (34, 35).

However, the presence of HT in PTC patients could trigger the body's autoimmune response mechanism, leading to the production of autoantibodies that specifically target thyroid antigens by immune cells. These autoantibodies mainly act on Thyroid peroxidase (TPO) and Thyroglobulin (Tg), resulting in atrophy and destruction of thyroid cells, even causing hypothyroidism. At this time, there is a decline in the production of thyroid

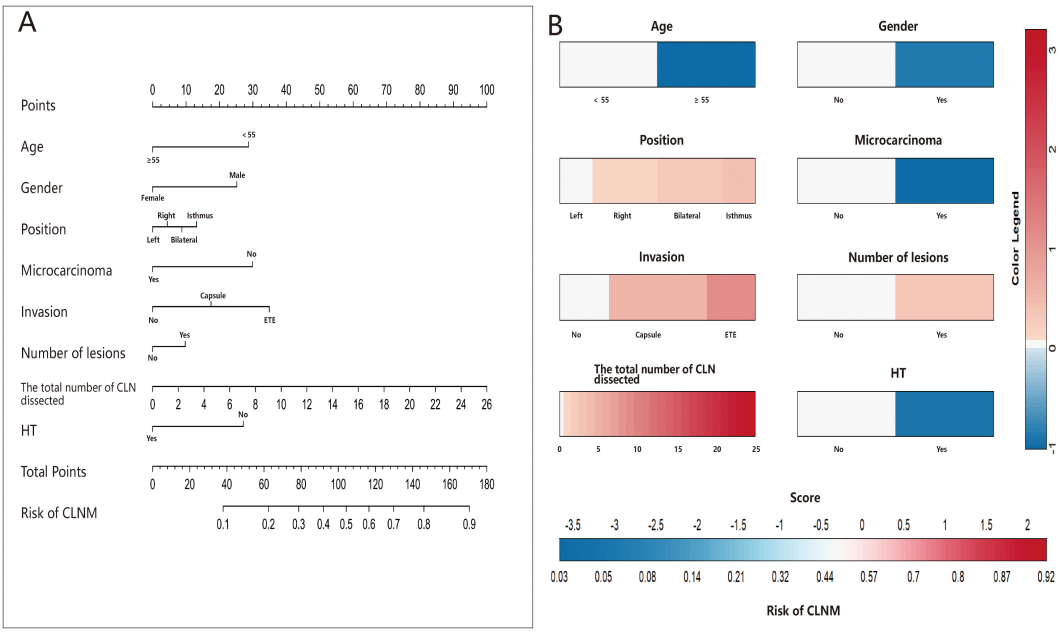

FIGURE 3
Nomograms **(A, B)** of the prediction model for the risk of CLNM in PTC patients.

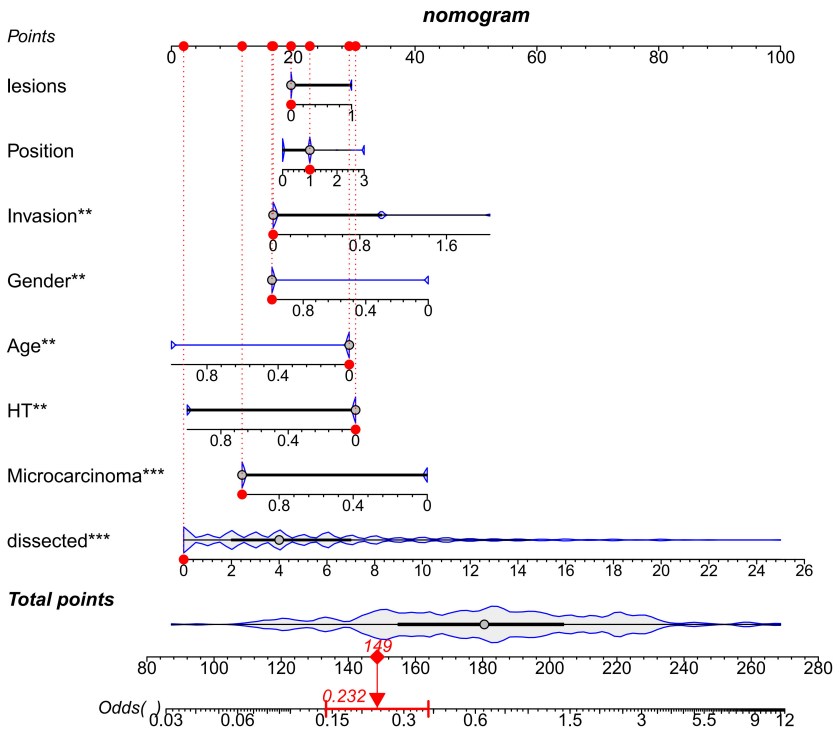

FIGURE 4
Dynamic Nomogram of the prediction model for the risk of CLNM in PTC patients.

hormones, which motivates the body to stimulate the pituitary gland to accelerate the secretion of TSH through the feedback regulation mechanism of the endocrine system, thus elevating the concentration of serum TSH (36, 37). Therefore, coexisting HT can promote the release of TSH, TPOAb, and TgAb in PCT patients, engendering an increase of their respective components in serum. Through research, Sakiz et al. (38) also observed that the TSH concentration in PTC patients with coexisting HT was significantly higher than that in patients without HT (1.71mIU/L vs 1.28 mIU/L, P=0.001).

Once again, through univariate analysis, the result found that the total number of CLN dissected in the PTC+HT group was higher than that in the PTC group, but the positive rate of CLN in the PTC+HT group was lower than that in the PTC group (P=0.000,

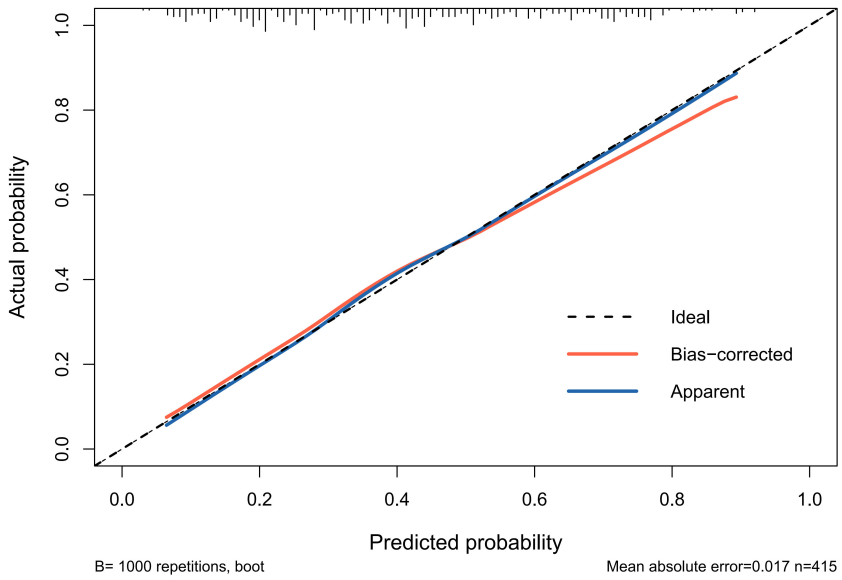

FIGURE 5
Calibration curve of the prediction model for the risk of CLNM in PTC patients.

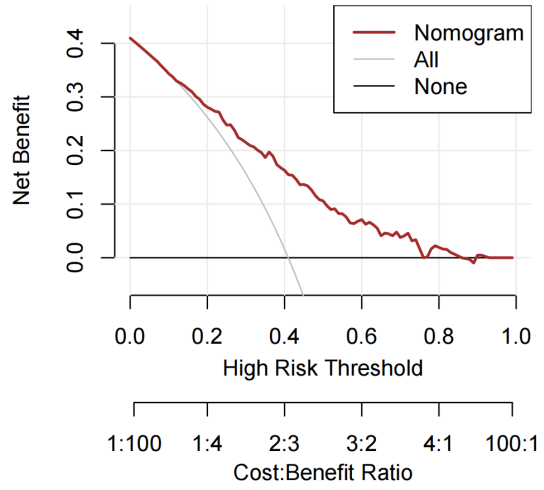

FIGURE 6
Decision curve analysis of the prediction model for the risk of CLNM in PTC patients.

P=0.007). Meanwhile, multivariate logistic regression analysis was used to validate that HT was positively associated with the total number of CLN dissected but negatively correlated with invasion. These findings show that PTC patients with HT are more prone to experience lymph node enlargement, yet ultimately the malignancy rate of the central lymph node is lower, which also reduces the invasiveness of PTC. Therefore, it is believed that HT not only increases the risk of developing PTC but also prevents further deterioration of PTC disease.

Hence, the growing evidence also illustrates that the chronic inflammatory process of HT confers a protective effect on PTC progression. Likewise, a retrospective cohort study from a large medical center in China confirmed that papillary thyroid microcarcinoma (PTMC) patients with coexisting HT have a significantly lower incidence of lymph node metastasis in the central neck (40.9% vs 56.2%, P<0.001) and lateral neck (11.6% vs 14.2%, P=0.016), which indicated that patients with HT had fewer aggressive features and better prognosis (39). However, there are some studies with controversial conclusions. For example, Zeng et al. (18) uncovered that among PTC patients, those with coexisting HT have a higher incidence of central lymph node metastasis compared to non-HT patients (39.2% vs 31.4%, P=0.043). A retrospective cohort study also showed HT was an independent risk factor in predicting CLNM in PTC patients (40).

Thus far, only a handful of studies have investigated the impact of HT on CLNM in PTC. In our study, we compared the data between the non-CLNM group and the CLNM group using univariate analysis, then verified that age, gender, position, microcarcinoma, calcification, invasion, focality, and the total number of CLN dissected were all associated with CLNM in PTC patients, all of which were statistically significant. Additionally, we also acquired a captivating outcome. Although the data showed that the PCT patients with HT in the CLNM group were significantly less than those in the non-CLNM group, indicating that the combination of HT might decrease the occurrence of CLNM in PCT patients, unfortunately, this difference did not reach statistical significance. Our data showed the PCT patients with HT in the CLNM group were significantly fewer than those in the non-CLNM

TABLE 5 Multivariate Linear Regression Analysis about Risk Factors of CLN Positive Rate in PTC Patients.

Variables	B	β	t	95% CI	P	F	Adjusted R^2
Age	-0.006	-0.229	-4.953	-0.009~-0.004	0.000	5.750	0.163
Gender	-0.128	-0.161	-3.448	-0.201~-0.055	0.001		
Position	0.006	0.017	0.298	-0.031~0.043	0.766		
Maximum tumor diameter (mm)	0.001	0.023	0.312	-0.005~0.007	0.755		
Microcarcinoma	-0.170	-0.244	-3.374	-0.269~-0.071	0.001		
Calcification	0.014	0.022	0.459	-0.048~0.076	0.647		
A/T>1	-0.022	-0.032	-0.671	-0.085~0.042	0.503		
Invasion	0.070	0.093	1.981	0.001~0.140	0.048		
Number of lesions	0.051	0.069	1.190	-0.033~0.135	0.235		
FT3	0.006	0.016	0.302	-0.032~0.044	0.763		
FT4	-0.011	-0.070	-0.930	-0.035~0.013	0.353		
TT3	-0.001	-0.044	-0.941	-0.003~0.001	0.347		
TT4	4.073E-5	0.003	0.038	-0.002~0.002	0.970		
TSH	-0.003	-0.022	-0.399	-0.018~0.012	0.690		
TPOAb	-9.824E-5	-0.051	-0.997	0.000~0.000	0.319		
TgAb	-8.258E-6	-0.004	-0.089	0.000~0.000	0.929		
HT	-0.068	-0.091	-1.694	-0.146~0.011	0.091		

group, indicating that the combination of HT may reduce the occurrence of CLNM in PCT patients. Unfortunately, this difference did not reach statistical significance.

Furthermore, we conducted a multivariate logistic regression analysis, which manifested that position, Capsule + ETE, multifocality, and the total number of CLN dissected were independent risk factors for CLNM. Conversely, age ≥ 55 years old, female, microcarcinoma, and HT were identified as protective factors against CLNM. These results are consistent with the previous comparison between the HT Group and PTC+HT Group, providing additional evidence that HT is more susceptible to causing lymph node enlargement in PTC, but not true lymph node metastasis. Through a study of 444 PTC patients, Wang et al. (41) concluded that the autoimmune response of HT seems to reduce the occurrence of CLNM in PTC patients. Meanwhile, age<55 years and tumor size ≥10mm are identified as independent risk factors for CLNM. Building upon these results, Battistella et al. (42) further discovered that the PTC-HT group had smaller tumor size, lower invasiveness, and fewer lymph node metastasis, simultaneously with a higher rate of early tumor diagnosis. Moreover, we have also identified the risk factors that are prone to induce CLNM in PTC: Isthmus, Capsule + ETE, multifocality, age<55 years old, and male gender. Some studies have also yielded similar results. For instance, Liu et al. (43) conducted a clinical data analysis of 966 patients and verified that male, age<45 years old, tumor size>1.0cm, ETE, and microcalcification were independent risk factors for CLNM. Even, some researchers put these high-risk factors together to establish a model that might serve as a more comprehensive theoretical basis for clinical assessment of the risk of CLNM (44). We also constructed a similar prediction model based on the above independent factors to judge the probability of CLNM occurrence. The results showed that the model has a high diagnostic value and certain generalization significance.

Finally, we performed a multiple linear regression analysis, incorporating all potential factors related to the CLN positive rate. The results stated that age, female, and microcarcinoma exhibited negative predictive effects, whereas invasion showed a positive predictive effect. Combining the previous logistic regression analysis results on the risk factors of CLNM, we believe that age<55 years old, male, position, Capsule+ETE, and multifocality are all potential risk factors for CLNM. However, among these factors, the presence of Capsule + ETE is the most influential one that can ultimately affect the rate of CLNM transfer. Therefore, the stronger the invasiveness of carcinoma in PTC patients, the higher the likelihood of CLNM occurrence, eventually leading to a higher ratio of CLNM.

Conclusion

In summary, our experimental conclusion is that female PTC patients are more prone to concurrent HT, which elevates the levels of TSH, TPOAb, and TgAb in the blood of PTC patients. HT not only promotes the longitudinal growth of nodules and PTC development, but also reduces the risk of invasion and CLNM. Therefore, we posit that the impact of HT on PTC patients is a “double-edged sword”. Isthmus, Capsule + ETE, multifocality, age < 55 years old, and male are high-risk factors for CLNM in PTC, while HT is regarded as a protective factor. Capsule + ETE is the primary risk factor affecting the CLN positive rate. Our results are consistent with the results of most similar studies, and our data confirm that HT reduces the risk of CLNM. According to our conclusions, we suggest that patients with clinically diagnosed HT should actively monitor and manage the levels of TSH, TPOAb, and TgAb, reducing or avoiding the conversion to PTC. Additionally, if the aforementioned high-risk factors are absent in preoperative ultrasound and clinical data analysis, there is no need for extensive prophylactic central lymph node dissection during surgery when HT is combined with PTC. We hope that the conclusions of this study will offer valuable insights and guidance to clinicians.

Limitations

Nevertheless, in light of this study primarily involving single-center data analysis, there may be certain limitations that could lead to biases in the final research conclusions. In the future, we will continue to make efforts to carry out some studies on large sample sizes, multiple centers, and molecular genetics, leveraging the experiences and achievements of previous researchers, to gain a deeper understanding about the pathological transformation mechanisms of how HT affects the patients of PTC and bring more benefits to thyroid disease patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by First Affiliated Hospital of Anhui University of Chinese Medicine ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants’ legal guardians/next of kin.

Author contributions

KS: Conceptualization, Data curation, Investigation, Software, Writing – original draft. XW: Project administration, Writing – review & editing. DC: Supervision, Validation, Writing – review & editing. CM: Funding acquisition, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1420998/full#supplementary-material

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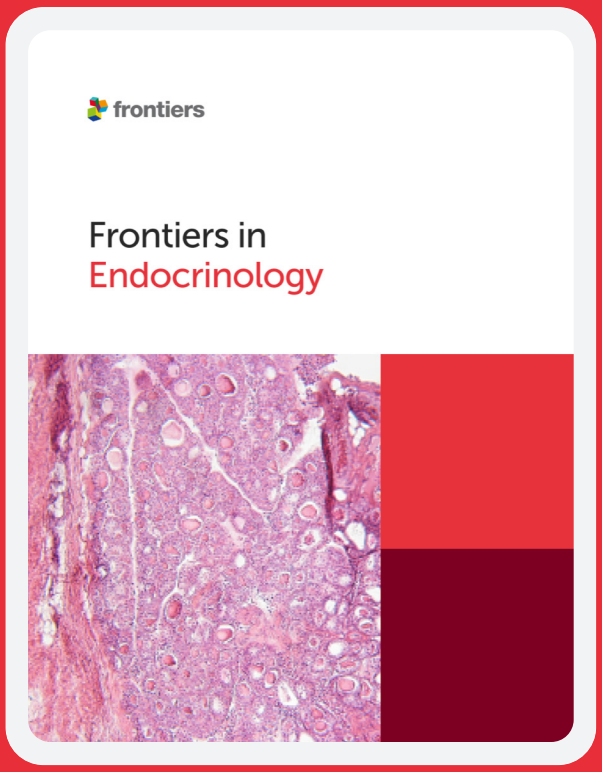

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