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ORIGINAL ARTICLE

The Correlation of Preoperative Serum Thyroglobulin between Benign and Papillary Thyroid Carcinoma

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SUMMARY

Background: **Papillary thyroid carcinoma (PTC) is the most common thyroid cancer, accounting for about 85 - 90%. Thyroglobulin (Tg) can be produced by normal thyroid follicular epithelial cells and well-differentiated malignant thyroid tumor cells. In our study, we investigated the correlation of preoperative serum Tg between benign thyroid tumors and PTC patients.**
Methods: **The data of 1,074 patients were retrospectively collected, including benign thyroid tumor group (517 cases) and PTC group (557 cases). Preoperative serum Tg and other thyroid function indicators were detected by chemiluminescence immunoassay (CLIA). Serum levels were compared between patients with benign thyroid tumors and PTC using SPSS 22.0.**
Results: **In patients with PTC, the levels of serum Tg were significantly lower than those in patients with benign thyroid tumors (p = 0.000). In both groups, no significant difference of serum Tg was observed between the genders, but there were significant differences of serum Tg among the different ages and tumor sizes. The results of Spearman correlation analysis showed that serum Tg positively correlated with tumor sizes and negatively correlated with serum thyroglobulin antibody (TgAb) in the two groups. Through the binary regression analysis, the independent predictors of PTC included the sex, tumor sizes, and serum TgAb of patients (p = 0.000, 0.000, and 0.020, respectively). For the PTC patients, serum Tg was markedly higher in the cervical lymph node metastasis (10.84 ng/mL), compared with no metastasis (8.41 ng/mL), with p = 0.017.**
Conclusions: **Serum Tg in the PTC group was significantly lower than in the benign thyroid tumor group; however, serum Tg was not useful as an independent predictor of PTC patients. For the PTC patients, high preoperative serum Tg predicts the cervical lymph node metastasis.**
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KEYWORDS

papillary thyroid carcinoma, benign thyroid tumor, thyroglobulin

INTRODUCTION

Thyroid cancer is a malignant tumor originating from the thyroid follicular epithelium or follicular epithelial cells, and it is also the most common malignancy in the head and neck region [1]. In recent years, the incidence of thyroid cancer has gradually increased on a global scale [2]. Among these, papillary thyroid carcinoma

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(PTC) is the most common, accounting for approximately 85 - 90% of all thyroid cancers [3].

Thyroglobulin (Tg) is a thyroid follicular cell-secreted glycoprotein stored in the follicular lumen [4]. Tg has tissue specificity and is highly expressed in metastatic lymph nodes, well-differentiated thyroid carcinomas, and normal thyroid tissues [5,6]. So, serum Tg levels can be currently measured in the evaluation of papillary thyroid neoplasms for distinguishing between benign or malignant [7-10]. Additionally, Tg level is valuable in predicting the central lymph node metastasis or metastatic recurrence after total thyroidectomy in well-differentiated thyroid carcinomas [11,12]. Now, Tg measurement is a sensitive biochemical method in determining persistent tumors and is used routinely in the follow-up of PTC [13].

However, according to the European and American Thyroid Associations, preoperative Tg testing is insensitive and non-specific for thyroid cancer [14,15]. Meanwhile, the 2017 Chinese Expert Consensus on the Clinical Application of Serum Markers in Thyroid Cancer did also not recommend using Tg to differentiate between benign and malignant thyroid tumors.

Therefore, our study aimed to investigate the correlation of preoperative serum Tg between patients who underwent thyroidectomy for benign thyroid tumors and PTC.

MATERIALS AND METHODS

Patients and sample collection

Data were collected from 1,074 patients with thyroid tumors admitted to Beijing Tongren Hospital, Capital Medical University, from January 2021 through August 2023. Inclusion criteria were as follows: 1) complete clinical data; 2) no special treatments (e.g. radiotherapy, chemotherapy, hormone replacement therapy, etc.); 3) postoperative pathology confirming benign thyroid tumor or PTC; and 4) clear pathological staging. Exclusion criteria were as follows: 1) concurrent other cancers; 2) concurrent liver diseases; 3) concurrent kidney diseases; 4) concurrent other infectious diseases; and 5) concurrent cardiovascular system diseases. The tumor lymph node metastasis (TNM) staging followed the 8th edition classification system of the American Joint Committee on Cancer.

Prior to surgery, fasting peripheral venous blood samples of 3 mL were collected from all patients and immediately centrifuged at 3,000 rpm for 10 minutes. Clinical biochemical and thyroid function indicators were promptly analyzed.

Ethical statement

The clinical study protocol was designed and implemented following the relevant provisions of the Helsinki Declaration on the protection of the rights and interests of subjects, and the experiments were authorized by the academic ethics committee of Beijing Tongren Hospital Affiliated to Capital Medical University (lot: TRE CKY2021-131). All procedures were strictly implemented according to the code of ethics.

Detection of clinical biochemical and thyroid function indicators

Beckman AU5811 biochemical analyzer and its corresponding reagents (Beckman Coulter Inc., Brea, CA, USA) were used to measure serum glucose (GLU), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine (CRE). Additionally, on the Beckman AU5811 instrument, the Kyowa Medex Co., Ltd. reagents from Japan were employed to determine triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c).

Beckman DXI800 chemiluminescent immunoassay analyzer and its associated reagents were utilized for the detection of thyroid function indicators, including total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), thyroglobulin (Tg), thyroglobulin antibody (TgAb), and thyroid peroxidase antibody (TPOAb).

Data analysis and statistical analysis

The statistical analysis was conducted using SPSS 22.0 software, and graphing was performed using GraphPad Prism 8.0 software. Normally distributed metric data were expressed as $\bar{x} \pm$ standard deviation (SD). Differences between two groups were compared using independent sample *t*-tests, while differences among three groups were assessed using one-way analysis of variance (ANOVA). For skewed distribution measurement data, the median (interquartile range) [M (P25, P75)] was used. The Mann-Whitney U test was employed to compare differences between two groups, and Kruskal-Wallis H test was employed to compare differences among three groups. Count data were presented as cases or percentages, and intergroup comparisons were made using the chi-squared test. A significance level of $p < 0.05$ was considered statistically significant.

The following factors were included in the Spearman correlation and binary statistical analysis: the gender and age of the patients, tumor sizes of the thyroid gland, and the levels of serum Tg and TgAb. The variables that showed statistical correlation ($p < 0.05$) by logistic regression analysis were considered as independent predictive factors of PTC. Receiver operating characteristic (ROC) curve was used to analyze the diagnostic value of Tg in PTC with lymph node metastasis (LNM), and the area under the ROC curve (AUC) was analyzed using GraphPad Prism.

RESULTS

Patient characteristics

A total of 1,074 patients (age range: 18 to 86 years, median age: 46 years) were included, with 517 in the benign thyroid tumor group and 557 in the PTC group based on the postoperative pathological results. Among the 517 patients in the benign thyroid tumor group, 18 cases were benign papillary hyperplasia, 44 cases were thyroid adenoma, and 455 cases were nodular goiter. Their general characteristics are shown in Table 1.

Firstly, there was no significant difference in the sexes and ages between the benign and the PTC group. The ratio of women to men were 3.01 and 2.69 in the two groups, respectively. However, the tumor sizes of benign thyroid tumors were significantly bigger than those of malignant tumors. The majority of tumor diameters in PTC patients were generally smaller than 2 cm (77.20%), while the tumor diameters of benign thyroid tumors were mostly more than 2 cm (57.45%). For the PTC patients, tumor staging revealed 475 cases (85.28%) in stages 1 - 2 and 82 cases (14.72%) in stages 3 - 4. Lymph node metastasis was absent in 337 cases (60.50%) and present in 220 cases (39.50%).

Secondly, because the median age of benign tumor group was older than that of the PTC group, the levels of serum GLU and lipoproteins in the benign thyroid tumor group were slightly higher than those in the PTC group. However, no significant difference was observed in the clinical biochemistry (GLU, liver function, kidney function, and lipoproteins) between the two groups ($p > 0.05$).

Thirdly, about the thyroid function tests, there was no significant difference between the two groups in TT3, TT4, FT3, FT4, TSH, and TPOAb. However, the benign thyroid tumor group exhibited significantly higher levels of serum Tg and lower levels of serum TgAb compared with the PTC group (Table 1). Serum Tg of benign thyroid tumor group was 17.43 (6.46 - 60.03) ng/mL, while serum Tg of PTC group was only 9.02 (3.62 - 20.01) ng/mL. In contrast, the majority of serum TgAb in the two groups were in relatively low levels. The median of serum TgAb in benign thyroid tumor group was 0.2 IU/mL, lower than that in PTC group (0.5 IU/mL).

The levels of serum Tg between the genders and among the different ages and tumor sizes in the benign and PTC patients

As shown in Figure 1A, in the benign thyroid group, the levels of serum Tg did not differ between the genders. Similarly, in the PTC group, serum Tg of males was slightly higher than that of females, but there was also no significant difference between the genders.

In our study, we divided the patients of each group into three subgroups: ≤ 40 years, 40 - 60 years, and > 60 years. In the benign thyroid patients, serum Tg of the three age groups were 12.35, 16.28, and 48.86 ng/mL, respectively. And in the PTC patients, serum Tg of the three age groups were 7.87, 8.40, and 10.07 ng/mL, respectively. These results indicated that serum Tg elevated with age in both patient groups. Through the Kruskal-Wallis H test, there was significant difference among the three age groups (Figure 1B).

Additionally, in the benign thyroid tumor patients, serum Tg of the two tumor size groups (≤ 2 cm and > 2 cm) were 7.94 and 38.32 ng/mL, respectively. And in the PTC patients, serum Tg of the two tumor sizes groups were 7.40 and 22.21 ng/mL, respectively. The result of Mann-Whitney U test showed that there were significant differences of serum Tg between the two tumor sizes in the benign and the PTC groups. These results demonstrated that serum Tg increased with the tumor sizes, whether in the benign or PTC patients. Furthermore, it should be noticed that when the tumor size was ≤ 2 cm, the levels of serum Tg did not differ between the benign and PTC groups ($p = 0.136$, > 0.05), but when the tumor size was > 2 cm, the serum Tg of benign group was significantly higher than that of PTC group ($p = 0.042$, < 0.05) (Figure 1C). This is most likely associated with the tumor sizes. Approximately 57.45% of tumor diameters in the benign tumor group were > 2 cm and the maximum of them could even be 10 cm. Conversely, only 22.80% of tumor diameters in the PTC group were > 2 cm and few of them reached more than 4 cm.

The correlation analysis of serum Tg with age, tumor sizes, and serum TgAb in the benign and PTC groups

To analysis serum Tg-related factors in the benign and PTC patients, we evaluated the correlation between serum Tg and the age, tumor sizes, and serum TgAb in the two groups. The results of Spearman correlation analysis demonstrated that there was a positive correlation between serum Tg and tumor sizes in both the benign and PTC patients ($r = 0.536$ and 0.344, respectively). In contrast, serum Tg was negatively correlated with serum TgAb in both groups ($r = -0.393$ and -0.577, respectively). Between the serum Tg and age, a positive correlation presented in the benign group ($r = 0.259$, $p = 0.000$), but they were not correlated in the PTC group ($r = 0.061$, $p = 0.152$) (as shown in Table 2).

Evaluation of the independent predictors of the PTC group through the logistic regression analysis

Through the binary regression analysis, we evaluated the independent predictors of PTC (including the sex and age of patients, tumor sizes of the thyroid gland, and serum Tg and TgAb of patients). The results revealed that the gender, tumor sizes, and serum TgAb were the independent predictors of PTC group ($p = 0.000$, 0.000, and 0.020, respectively). And serum Tg was not an independent predictor of PTC patients ($p = 0.097$) (as shown in Table 3).

Table 1. General characteristics of patients with benign thyroid tumor and with PTC.

Parameters	Benign thyroid tumor (n = 517) (median, interquartile range)	PTC (n = 557) (median, interquartile range)	p-value
Gender			
Male	**129**	**151**	**0.444**
Female	**388**	**406**	
Age (years)			
≤ 40	**201**	**234**	**0.221**
40 - 60	**212**	**233**	
> 60	**104**	**90**	
Tumor diameter			
≤ 2cm	**220**	**430**	**0.000**
> 2cm	**297**	**127**	
Tumor stage			
T1 - T2	**-**	**475**	
T3 - T4	**-**	**82**	
Lymph node metastasis			
N0	**-**	**337**	
N1	**-**	**220**	
Clinical biochemistry			
GLU (mmol/L)	**5.30 (4.90 - 5.90)**	**5.21 (4.84 - 5.78)**	**0.230**
BUN (mmol/L)	**4.8 (4.0 - 5.7)**	**4.7 (3.9 - 5.6)**	**0.672**
CRE (umol/L)	**61 (54 - 70)**	**61 (53 - 72)**	**0.660**
ALT (U/L)	**17 (12 - 25)**	**18 (13 - 26)**	**0.325**
AST (U/L)	**20 (17 - 24)**	**20 (17 - 24)**	**0.503**
Triglyceride (mmol/L)	**1.17 (0.77 - 1.69)**	**1.15 (0.75 - 1.67)**	**0.469**
TC (mmol/L)	**4.80 (4.12 - 5.43)**	**4.72 (4.08 - 5.36)**	**0.345**
LDL-c (mmol/L)	**2.95 (2.43 - 3.59)**	**2.90 (2.41 - 3.56)**	**0.311**
HDL-c (mmol/L)	**1.30 (1.09 - 1.60)**	**1.34 (1.12 - 1.65)**	**0.209**
Thyroid function indicators			
TT3 (nmol/L)	**1.64 (1.46 - 1.84)**	**1.67 (1.46 - 1.84)**	**0.628**
TT4 (nmol/L)	**116.3 (104.0 - 131.8)**	**116.9 (103.8 - 132.7)**	**0.921**
FT3 (pmol/L)	**5.34 (4.95 - 5.80)**	**5.43 (4.99 - 5.89)**	**0.131**
FT4 (pmol/L)	**11.25 (10.06 - 12.42)**	**11.01 (9.92 - 12.37)**	**0.231**
TSH (mIU/L)	**1.55 (0.97 - 2.40)**	**1.59 (1.05 - 2.47)**	**0.233**
Thyroglobulin (ng/mL)	**17.43 (6.46 - 60.03)**	**9.02 (3.62 - 20.01)**	**0.000**
TgAb (IU/mL)	**0.2 (0.2 - 0.3)**	**0.5 (0.2 - 1.2)**	**0.019**
TPOAb (IU/mL)	**0.8 (0.4 - 3.5)**	**0.9 (0.4 - 4.4)**	**0.229**

GLU - glucose, BUN - blood urea nitrogen, CRE - creatinine, ALT - alanine aminotransferase, AST - aspartate aminotransferase, TC - total cholesterol, LDL-c - low-density lipoprotein cholesterol, HDL-c - high-density lipoprotein cholesterol. n refers to number of patients in group.

The correlation of serum Tg and TgAb in the benign thyroid tumor and PTC patients

The reference interval of serum TgAb was 0 - 4 IU/mL, using the Beckman DXI800 analyzer and its associated reagents. So, a relative TgAb value > 4 IU/mL was considered positive. Both in the benign and PTC patients, we found that the prevalence of TgAb positivity in PTC patients was significantly higher than that in the benign thyroid tumor patients (chi-squared 8.420, p = 0.004), as shown in Table 4.

As shown in Figure 2, serum Tg of TgAb-positive patients was markedly decreased compared to in the

Table 2. The correlation of serum Tg and age, tumor sizes, and TgAb in benign and PTC groups.

Indicators	Benign (n = 517)		PTC (n = 557)	
	r	p	r	p
Age	0.259	0.000 **	0.061	0.152
Tumor sizes	0.536	0.000 **	0.344	0.000 **
TgAb	-0.393	0.000 **	-0.577	0.000 **

*** p < 0.05, ** p < 0.01.**

Table 3. The independent risk factors for malignancy in PTC.

Factor	B	S.E.	Wald	df	Sig.	Exp (B) 95% CI
Gender	1.064	0.173	37.651	1	0.000 **	2.064 - 4.073
Tumor sizes	1.854	0.178	108.576	1	0.000 **	4.506 - 9.053
Age ≤ 40 years			0.120	2	0.942	
40 - 60 years	-0.073	0.221	0.109	1	0.742	0.603 - 1.433
> 60 years	-0.035	0.215	0.026	1	0.872	0.633 - 1.474
Serum Tg (ng/mL)	-0.001	0.001	2.762	1	0.097	0.997 - 1.000
Serum TgAb (IU/mL)	0.001	0.000	5.419	1	0.020 *	1.000 - 1.001

*** p < 0.05, ** p < 0.001.**

Table 4. The prevalence of serum TgAb positivity in the benign thyroid tumor and PTC patients.

Parameters	Benign (n = 517)	PTC (n = 557)	p-value
Combined with "TgAb positive"	72	115	0.004
Combined with "TgAb negative"	445	442	

n - refers to number of patients in group.

TgAb-negative patients in the two groups, which was consistent with the result of Table 2. On the other hand, whether in the TgAb-positive or in the TgAb-negative patients, serum Tg of benign thyroid tumor group was significantly higher than those of PTC group.

The levels of serum Tg and lymph node metastasis (LNM) in the PTC patients

Next, we investigated the correlation of preoperative serum Tg and LNM in PTC patients. Among the 557 PTC patients, there were 220 cases (39.50%) with cervical LNM and 337 cases (60.50%) without LNM. The results demonstrated that serum Tg of PTC with LNM patients were 10.84 (3.32 - 30.10) ng/mL, significantly higher than those without LNM [8.41 (3.77 - 14.76) ng/mL (p = 0.017, < 0.05)] (Figure 3). To further study the diagnostic efficacy of Tg in PTC with LNM, the ROC curve was used for analysis. The results demonstrated that the AUC of Tg for the diagnosis of PTC with LNM was 0.560 (95% CI: 0.509 - 0.611), p = 0.017. And the cutoff value of Tg was 14.86 ng/mL, with 42.47% sensitivity (95% CI: 36.10 - 49.09) and 75.37% specificity (95% CI: 70.50 - 79.67) (Figure 4).

DISCUSSION

In all age groups, except for the childhood group, thyroid cancers are three times more common in women than in men [16]. The incidence of thyroid cancer in-

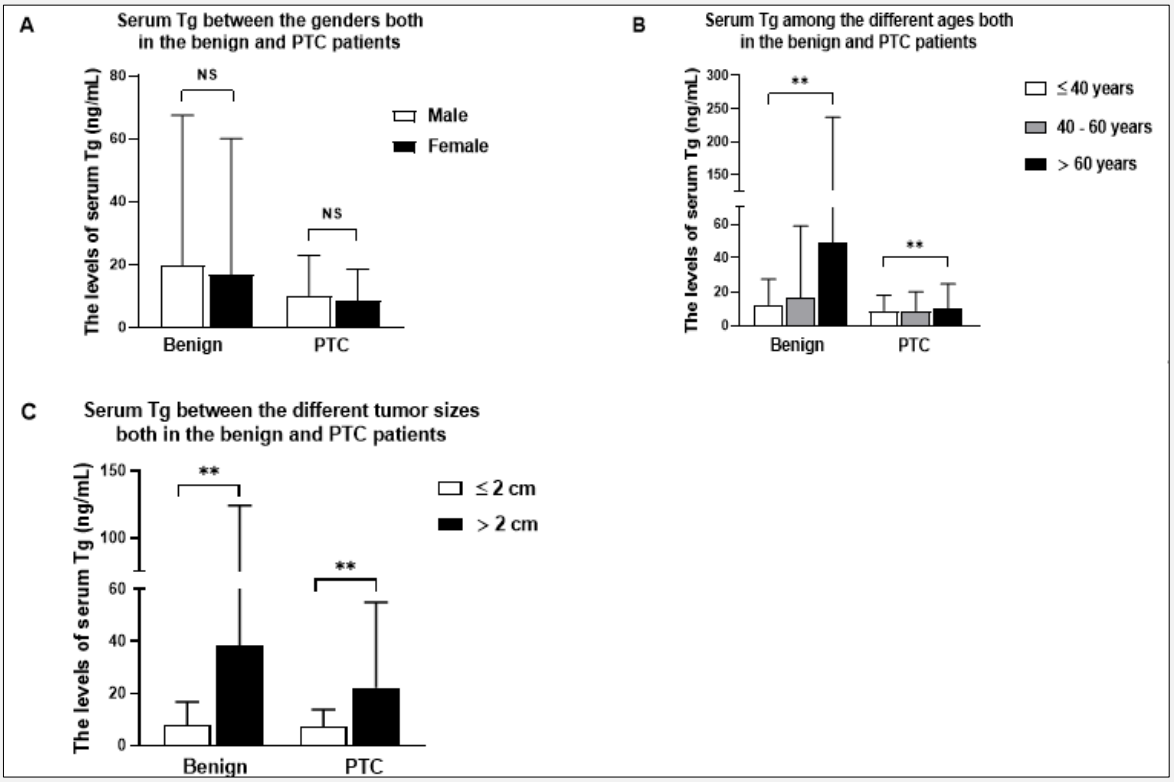

Figure 1. The levels of serum Tg between the genders and among the different ages and tumor sizes in the two groups.

A) Serum Tg between the genders, both in the benign and PTC patients. B) Serum Tg among the different ages, both in the benign and PTC patients. C) Serum Tg between the different tumor sizes, both in the benign and PTC patients.

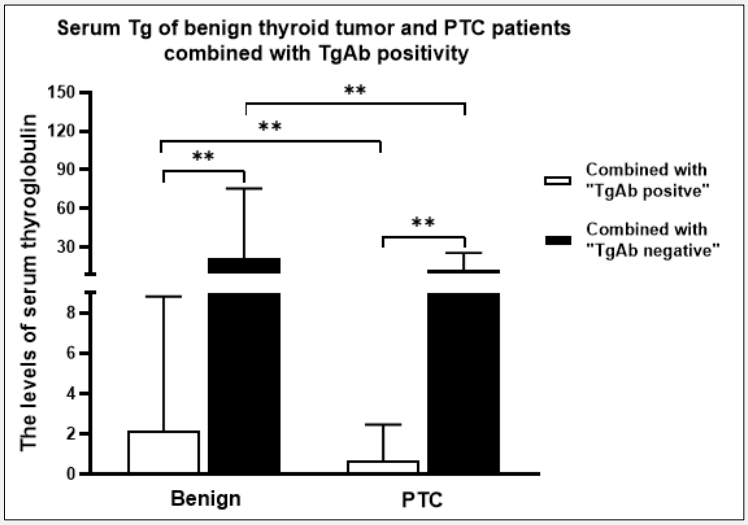

Figure 2. Serum Tg of benign thyroid tumor and PTC patients combined with TgAb positivity. * p < 0.05, ** p < 0.01.

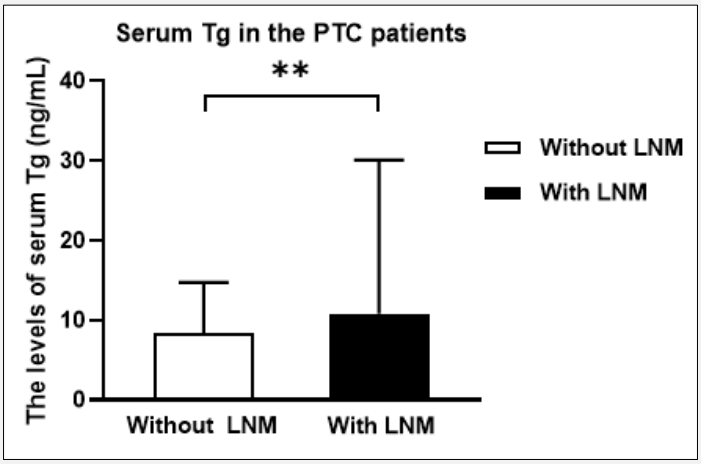

Figure 3. Serum Tg and lymph node metastasis (LNM) in the PTC patients.

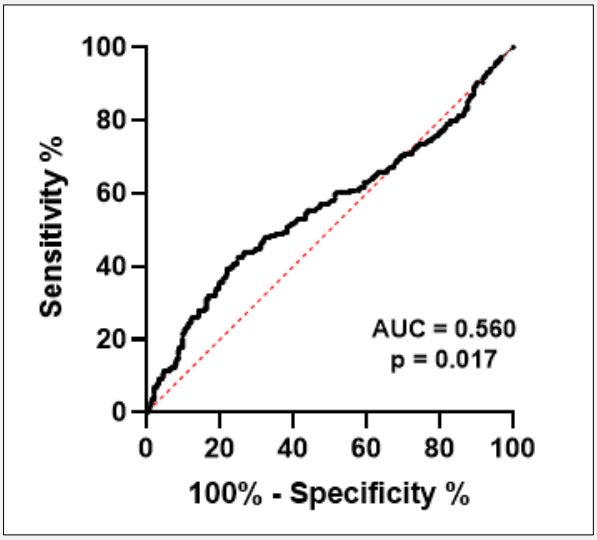

Figure 4. ROC curve analysis of diagnostic efficacy of Tg in PTC with LNM.

creased gradually, and PTC was the most common type of thyroid cancer. However, there were no good indicators in laboratory tests that could be used for PTC screening. In our study, among the indexes of thyroid function, TT3, TT4, FT3, FT4, TSH, and TPO-Ab had no significant difference between benign thyroid tumor and PTC groups, but the level of serum Tg in benign tumor group was significantly higher than that in PTC group. A few previous studies have reported that the level of serum Tg in PTC patients was higher than that in benign thyroid tumor patients [17-19]. Petric et al. reported that the median preoperative Tg concentrations in patients with and without carcinoma were 86 and 41 ng/mL, respectively [18]. In contrast, there were some

studies which reported that serum Tg in PTC patients was lower than that in benign thyroid tumor patients. Earlier in 1979, Gerfo et al. reported that patients with nontoxic nodular goiter disease had serum Tg levels of 107 ng/mL and those patients with thyroid cancer had serum Tg levels of 94 ng/mL [20]. Hocevar et al. reported that serum Tg of papillary cancer and nodular goiter patients were 26 and 178.5 ng/mL, respectively [21]. Lee et al. reported that serum Tg of benign and PTC patients were 15.4 and 8.8 ng/mL, respectively [22], which was most consistent with our results.

In this study, most PTC patients were in T1 - T2 stage, and the tumor diameters were generally smaller (≤ 2 cm), while those of the benign group were usually larger (> 2 cm). Serum Tg of PTC patients was lower than that of the benign group, which indicated that there was a significant correlation between serum Tg and tumor sizes in the benign or PTC patients. On the other hand, our results showed that the prevalence of TgAb positivity in PTC patients was significantly higher than that in the benign thyroid tumor patients. Then, the level of serum TgAb in patients with PTC was significantly higher than that in patients with benign thyroid diseases, which was consistent with the results of Hsieh [23]. The used kit of Tg in our study included the mouse monoclonal anti-Tg conjugated-alkaline phosphatase. When the TgAb was present in the serum, it maybe interfered with the determination of Tg. Immunometric assays of Tg were prone to interference from TgAb, which commonly caused falsely low serum Tg measurements [24, 25]. When the level of serum TgAb was very high, the measured Tg would be lower than the real value, which would affect the accuracy of serum Tg. On the contrary, when the level of TgAb was very low, the reference significance of Tg would be greater. So, high level of serum TgAb affected the detection of serum Tg, which led to the decrease of serum Tg in patients with PTC, compared with the benign tumor group.

Although serum Tg was affected by many factors, such as age and gender of patients, tumor sizes, and serum TgAb level, the logistic regression analysis revealed that only the gender, tumor sizes, and serum TgAb were the independent predictors of PTC group, and serum Tg was not an independent predictor of PTC patients. Therefore, the preoperative serum Tg level cannot be used to distinguish benign and malignant thyroid diseases. According to the most recent literature, the preoperative measurement of Tg alone fails to discriminate thyroid cancers from benign lesions [26].

Recently, some research demonstrated a significantly higher level of preoperative serum Tg in PTC patients and found preoperative serum Tg was a predictive factor for metastasis of PTC patients [27-30]. Our results confirmed that serum Tg were associated with lymph node metastasis in PTC patients and Tg may be an important marker for the localization of LNM in the neck. We have also measured post-surgery thyroglobulin (Tg) concentrations in order to investigate the predictive value of Tg for the presence of lymph node metastases after surgery. The results will be presented in the near future.

CONCLUSION

Serum Tg in the PTC group was significantly lower than in the benign thyroid tumor group; however, serum Tg was not useful as an independent predictor of PTC patients. For the PTC patients, high preoperative serum Tg predicts the cervical lymph node metastasis.

Data Availability Statement:
Our data can be shared publicly through the mailbox of the corresponding author. However, to prevent the disclosure of the original confidential data, our organization allows us to upload the original data only after the article is accepted.

Declaration of Interest:
The authors have no conflicts of interest to declare.

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(1):7-30. (PMID: 31912902)

2. Jung CK, Little MP, Lubin JH, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. J Clin Endocrinol Metab 2014;99(2):E276-85. (PMID: 24248188)

3. Kim J, Gosnell JE, Roman SA. Geographic influences in the global rise of thyroid cancer. Nat Rev Endocrinol 2020;16(1):17-29. (PMID: 31616074)

4. Ritter A, Mizrachi A, Bachar G, et al. Detecting Recurrence Following Lobectomy for Thyroid Cancer: Role of Thyroglobulin and Thyroglobulin Antibodies. J Clin Endocrinol Metab 2020; 105(6):dgaa152. (PMID: 32219303)

5. Evans C, Tennant S, Perros P. Thyroglobulin in differentiated thyroid cancer. Clin Chim Acta 2015;444:310-7. (PMID: 25444737)

6. Kars A, Aktan B, Kilic K, et al. Preoperative serum thyroglobulin level as a useful predictive marker to differentiate thyroid cancer. ORL J Otorhinolaryngol Relat Spec 2018;80(5-6):290-5. (PMID: 30253396)

7. Kim HJ, Mok J-O, Kim CH, et al. Preoperative serum thyroglobulin and changes in serum thyroglobulin during TSH suppression independently predict follicular thyroid carcinoma in thyroid nodules with a cytological diagnosis of follicular lesion. Endocr Res 2017;42(2):154-62. (PMID: 27936964)

8. Lin H-C, Liou M-J, Hsu H-L, et al. Combined analysis of circulating epithelial cells and serum thyroglobulin for distinguishing disease status of the patients with papillary thyroid carcinoma. Oncotarget 2016;7(13):17242-53. (PMID: 26684026)

9. Patell R, Mikhael A, Tabet M, Bena J, Berber E, Nasr C. Assessing the utility of preoperative serum thyroglobulin in differentiated thyroid cancer: a retrospective cohort study. Endocrine 2018; 61(3):506-10. (PMID: 29948933)

10. Bahçecioğlu AB, Ozkan E, Araz M, Elhan AH, Erdoğan MF. Can Serum Thyroglobulin Levels Help to Identify the Involved Neck Compartment of Differentiated Thyroid Carcinoma? Horm Metab Res 2022;54(10):658-63. (PMID: 36055278)

11. Min Y, Huang Y, Wei M, et al. Preoperatively Predicting the Central Lymph Node Metastasis for Papillary Thyroid Cancer Patients With Hashimoto's Thyroiditis. Front Endocrinol (Lausanne) 2021;12:713475. (PMID: 34367075)

12. Kim H, Kim YN, Kim HI, et al. Preoperative serum thyroglobulin predicts initial distant metastasis in patients with differentiated thyroid cancer. Sci Rep 2017;7(1):16955. (PMID: 29209067)

13. Signore A, Lauri C, Di Paolo A, et al. Predictive Role of Serum Thyroglobulin after Surgery and before Radioactive Iodine Therapy in Patients with Thyroid Carcinoma. Cancers (Basel) 2023; 15(11):2976. (PMID: 37296937)

14. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154(6): 787-803. (PMID: 16728537)

15. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26(1): 1-133. (PMID: 26462967)

16. Melik MA, Baskonus I, Yilmaz L. Assessment of preoperative thyroglobulin levels in papillary thyroid cancer. J Can Res Ther 2022;18(4):1042-4. (PMID: 36149159)

17. Jin J, Wu G, Ruan C, et al. Preoperative platelet distribution width-to-platelet ratio combined with serum thyroglobulin may be objective and popularizable indicators in predicting papillary thyroid carcinoma. J Clin Lab Anal 2022;36(6):e24443. (PMID: 35441746)

18. Petric R, Besic H, Besic N. Preoperative serum thyroglobulin concentration as a predictive factor of malignancy in small follicular and Hürthle cell neoplasms of the thyroid gland. World J Surg Oncol 2014;12:282. (PMID: 25213012)

19. Petric R, Perhavec A, Gazic B, Besic N. Preoperative serum thyroglobulin concentration is an independent predictive factor of malignancy in follicular neoplasms of the thyroid gland. J Surg Oncol 2012;105(4):351-6. (PMID: 21751218)

20. Gerfo PL, Colacchio T, Colacchio D, Feind C. Thyroglobulin in Benign and Malignant Thyroid Disease. JAMA 1979;241(9):923-5. (PMID: 762873)

21. Hocevar M, Auersperg M. Role of serum thyroglobulin in the pre-operative evaluation of follicular thyroid tumours. Eur J Surg Oncol 1998;24(6):553-7. (PMID: 9870733)

22. Lee EK, Chung K-W, Min HS, et al. Preoperative serum thyroglobulin as a useful predictive marker to differentiate follicular thyroid cancer from benign nodules in indeterminate nodules. J Korean Med Sci 2012;27(9):1014-8. (PMID: 22969246)

23. Hsieh C-J, Wang P-W. Sequential changes of serum antithyroglobulin antibody levels are a good predictor of disease activity in thyroglobulin-negative patients with papillary thyroid carcinoma. Thyroid 2014;24(3):488-93. (PMID: 23971786)

24. Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 1998; 83(4):1121-7. (PMID: 9543128)

25. Spencer C, Petrovic I, Fatemi S. Current thyroglobulin autoantibody (TgAb) assays often fail to detect interfering TgAb that can result in the reporting of falsely low/undetectable serum Tg IMA values for patients with differentiated thyroid cancer. J Clin Endocrinol Metab 2011;96(5):1283-91. (PMID: 21325460)

26. Trimboli P, Treglia G, Giovanella L. Preoperative measurement of serum thyroglobulin to predict malignancy in thyroid nodules: A systematic review. Horm Metab Res 2015;47(4):247-52. (PMID: 25384015)

27. Chang Q, Zhang J, Wang Y, et al. Nomogram model based on preoperative serum thyroglobulin and clinical characteristics of papillary thyroid carcinoma to predict cervical lymph node metastasis. Front Endocrinol (Lausanne). 2022;13:937049. (PMID: 35909521)

28. Jeon MJ, Kim WG, Jang EK, et al. Thyroglobulin level in fine-needle aspirates for preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid carcinoma: two different cutoff values according to serum thyroglobulin level. Thyroid 2015;25(4):410-6. (PMID: 25607926)

29. Chen B, Yan Z, Bao Y, et al. Detection of thyroglobulin for diagnosis of metastatic lateral cervical lymph nodes in papillary thyroid carcinoma: accuracy and application in clinical practice. Transl Cancer Res 2024;13(2):1043-51. (PMID: 38482434)

30. Giovanella L, Bongiovanni M, Trimboli P. Diagnostic value of thyroglobulin assay in cervical lymph node fine-needle aspirations for metastatic differentiated thyroid cancer. Curr Opin Oncol 2013;25(1):6-13. (PMID: 23090642)