The Utility of Serum Anti-thyroglobulin Antibody and Thyroglobulin in the Preoperative Differential Diagnosis of Thyroid Follicular Neoplasm

Zhijiang Chen

Guangdong Academy of Medical Sciences: Guangdong Provincial People's Hospital

Yinghe Lin

Guangdong Academy of Medical Sciences: Guangdong Provincial People's Hospital

Shuiqing Lai

Guangdong Academy of Medical Sciences: Guangdong Provincial People's Hospital

Peiqing Wang

Guangdong Academy of Medical Sciences: Guangdong Provincial People's Hospital

Jinlian Li

Guangdong Academy of Medical Sciences: Guangdong Provincial People's Hospital

Long Wang

Guangdong Academy of Medical Sciences: Guangdong Provincial People's Hospital

Haixia Guan

Guangdong Academy of Medical Sciences: Guangdong Provincial People's Hospital

Jian Kuang (✉ kuangjian@gdph.org.cn)

Guangdong Academy of Medical Sciences: Guangdong Provincial People's Hospital

<https://orcid.org/0000-0001-5166-477X>

Research Article

Keywords: Thyroid Neoplasm, Thyroid Carcinoma, Follicular, Anti-thyroglobulin antibody, Thyroglobulin

Posted Date: December 20th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1169399/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Endocrine on February 2nd, 2022. See the published version at <https://doi.org/10.1007/s12020-022-02993-1>.

Abstract

Purpose

It is challenging to distinguish follicular thyroid carcinoma (FTC) from follicular thyroid adenoma (FTA) before surgery due to the lack of malignant ultrasound features, the underdiagnosis by fine-needle biopsy, and the absence of definitive markers. We investigated whether thyroglobulin (Tg), anti-thyroglobulin antibody (TgAb), thyroid peroxidase antibodies (TPOAb), and thyroid stimulating hormone (TSH) could help differentiate FTC from FTA.

Methods

A total of 319 patients with follicular neoplasms were included. We analyzed the serum markers as continuous and categorical variables between FTC and FTA. Also, we analyzed the prevalence of FTC in different serum markers groups.

Results

The TgAb was a risk factor of FTC. Versus the TgAb group (≤ 11.68 IU/mL), OR of the group (11.69-30.50 IU/mL) and the group (> 30.50 IU/mL) were 2.206 (1.114-4.369, $P=0.023$) and 3.247 (1.684-6.260, $P=0.001$), respectively. Versus the TgAb group (≤ 11.68 IU/mL), the malignant prevalence of the group (> 30.50 IU/mL) was higher (13.1% vs. 32.9%, $P=0.001$). In TgAb (-) patients, the Tg was another risk factor of FTC. Versus the Tg group (≤ 38.51 ng/mL), OR of the group (> 38.51 ng/mL) was 3.836 (1.625-9.058, $P=0.002$); the malignant prevalence of the group (> 38.51 ng/mL) was 47.2% and higher than other groups.

Conclusions

The TgAb and Tg may have utility in the preoperative differential diagnosis of follicular neoplasm. The higher TgAb and Tg were associated with higher malignant risk. Thus, we should be cautious of preoperative TgAb and Tg in follicular neoplasm.

Introduction

Follicular thyroid carcinoma (FTC) and follicular thyroid adenoma (FTA), which are derived from the follicular cells, are collectively referred to as the thyroid follicular neoplasm [1]. FTC, accounting for 10%-15% of all thyroid cancers, is the second most common thyroid malignancy, which has a propensity for hematogenous spread and presents distant metastases in 15% to 27% of patients, conferring a low survival rate [2,3].

However, it is challenging to distinguish FTC (malignant tumor with capsular and or vascular invasion) from FTA (no invasion) before surgery in thyroid nodules management. Firstly, FTC rarely presents malignant ultrasound features, such as taller than wide, markedly hypoechoic, irregular margin, and

microcalcifications [3-5]. Secondly, fine-needle aspiration biopsy is insufficient for diagnosing FTC due to the limitation in evaluating whether the tumor capsule is intact [3,6]. Third, although specific molecular markers have been proven to be effective in distinguishing the thyroid follicular neoplasm in recent years [7-9], economical and feasible molecular testing needs further exploration. Finally, unlike medullary thyroid cancer (MTC), which has calcitonin as a serum marker, there is no significant serum marker for FTC according to the guidelines [10].

Therefore, for providing more clinical experiences and information, we attempted to investigate whether conventional and straightforward serum markers related to thyroid could help differentiate FTC from FTA, including thyroglobulin (Tg), anti-thyroglobulin antibody (TgAb), thyroid peroxidase antibodies (TPOAb), and thyroid stimulating hormone (TSH).

Materials And Methods

This retrospective study was approved by the Institutional Review Board, and the requirement for informed consent to review images and medical records was waived.

Patients

From January 2014 to May 2020, all patients diagnosed with FTC or FTA based on surgical pathology following thyroidectomy were consecutively included in this study in a tertiary referral center. Unavailable preoperative serum Tg, TgAb, TPOAb, or TSH levels were the exclusion criteria.

Serum markers

The electrochemiluminescence immunoassay (ECLIA) was used for estimation of serum Tg (normal reference range of 3.50-77.00 ng/mL), TgAb (normal reference range of 0-115.00 IU/mL), and TPOAb levels (normal reference range of 0-34.00 IU/mL). The chemiluminescence immunoassay was used for TSH levels (normal reference range of 0.560-5.910 μ IU/ml). All serum markers were measured in our center.

As abnormal distribution data, serum markers were divided equally for statistical analysis mainly. Considering the interference of elevated TgAb levels, serum Tg was only analyzed in the patients who were negative for TgAb (<115.00 IU/mL, TgAb (-)).

Data and statistical analysis

Continuous variables were expressed as mean $\pm$ SD or median (IQR), and categorical variables as frequencies and percent values. Differences between FTC and FTA for continuous variables were evaluated using Student's t test or Mann-Whitney U test, where applicable. Categorical variables were analyzed using Chi-square test.

Univariate and multivariate logistic regression analyses were performed to evaluate the association between FTC and risk factors (sex, age, maximum diameters, and group of serum markers). Receiver operator characteristic curve (ROC) analysis and area under the curve (AUC) were used to evaluate the sensitivity and specificity of risk factors for the diagnosis of FTC.

Correlations between the prevalence of FTC and serum markers groups were analyzed by Spearman's correlation analysis and were represented by the correlation coefficient (r).

All statistical analyses were performed using SPSS (version 23.0, IBM) software, and two-sided p values < 0.05 were considered to indicate statistical significance.

Results

A total of 319 patients with thyroid follicular neoplasms were included in this study. They were 215 (67.4%) women and 104 (32.6%) men; the age range was 3 to 82 years (mean $\pm$ (SD), 43.8 $\pm$ 14.3 years).

Baseline

Of the 319 thyroid follicular neoplasms, 67 (21.0%) were FTCs and 252 (79.0%) were FTAs; of the 269 patients with negative TgAb (<115.00 IU/mL), 53 (19.7%) were FTCs and 216 (80.3%) were FTAs. In all patients, there was no significant difference between FTC and FTA with regard to age (45.1 $\pm$ 16.0 vs. 43.4 $\pm$ 13.8), proportions of male (25.4% vs. 34.5%), and the maximum diameter (3.0 (2.0-4.5) vs. 3.0 (2.3-4.0)). Similarly, in TgAb (-) patients, no significant difference was found between follicular neoplasms in age (44 $\pm$ 15.5 vs. 43.8 $\pm$ 14.1), proportions of male (30.2% vs. 38.0%), and the maximum diameter (3.4 (2.5-4.5) vs. 3.0 (2.4-4.0)).

Serum markers in all patients

In all patients, compared the titers of serum markers between FTC and FTA, a significant difference was found only in TgAb (15.90 (10.00-99.34) vs. 10.78 (10.00-19.73), P=0.003). In contrast, no significant difference was found regarding TPOAb and TSH. Also, there was no significant difference in the proportions of above-normal levels of TgAb, TPOAb, and TSH (details in Table 1). On univariate and multivariate analysis, only the serum TgAb was a risk factor for the presence of FTC, while TPOAb and TSH were not statistical value (details in Table 2). Compared with the TgAb group ($\leq$ 11.68 IU/mL), the odds ratio (OR) of the TgAb group (11.69-30.50 IU/mL) and the TgAb group ($\geq$ 30.50 IU/mL) were 2.206 (1.114-4.369, P=0.023) and 3.247 (1.684-6.260, P $\leq$ 0.001), respectively. As shown in Figure 1, the AUC of all patients model was 0.634 (0.559-0.709, P=0.001), and using TgAb levels $\geq$ 11.69 IU/mL as cut-off indicated sensitivity was 68.66% and specificity was 55.16%.

Serum markers in TgAb (-) patients

In TgAb (-) patients, compared the titers of serum markers between FTC and FTA, the significant differences were found regarding Tg (376.50 (63.14-500.00) vs. 376.50 (63.14-500.00), P=0.002) and

TgAb (12.94 (10.00-26.99) vs. 10.00 (10.00-13.33), $P=0.003$), while no significant difference was found in TPOAb and TSH. Also, the proportions of above-normal Tg levels in FTC were higher than FTA (71.7% vs. 52.8%, $P=0.013$), while there was no significant difference in TgAb, TPOAb, and TSH (details in Table 3). Univariate analysis showed that the serum Tg and TgAb were important factors for the risk of FTC, while TPOAb and TSH were not (details in Table 4). On multivariate logistic regression analysis, the higher Tg and TgAb levels demonstrated statistical significance. Compared with the Tg group (≤ 38.51 ng/mL), OR of the Tg group (≥ 434.60 ng/mL) was 3.836 (1.625-9.058, $P=0.002$); compared with the TgAb group (≤ 10.11 IU/mL), OR of the TgAb group (≥ 14.58 IU/mL) was 3.053 (1.508-6.179, $P=0.002$) (details in Table 4). As shown in Figure 1, the AUC of the TgAb (-) patients model was 0.681 (0.593-0.768, $P=0.001$). Combined Tg levels ≥ 434.60 ng/mL with TgAb levels ≥ 14.58 IU/mL as the cut-off, sensitivity was 56.60% and specificity was 73.15%.

Prevalence of malignancy

In our study, in all patients and TgAb (-) patients, FTC accounted for 21.0% and 19.7%, respectively. As shown in Figure 2 and 3, the prevalence of FTC increased with increasing TgAb levels of group both in all patients ($r=0.206$, $P < 0.001$) and TgAb (-) patients ($r=0.180$, $P=0.003$). In all patients, compared with TgAb levels ≤ 11.68 IU/mL, the malignant prevalence of TgAb levels ≥ 30.50 IU/mL was higher (13.1% vs. 32.9%, $P=0.001$); in TgAb (-) patients, compared with TgAb levels ≤ 10.11 IU/mL, the malignant prevalence of TgAb levels ≥ 14.58 IU/mL was higher (14.1% vs. 33.3%, $P=0.005$).

As shown in Figure 4, the prevalence of FTC increased with increasing Tg levels of group in TgAb (-) patients ($r=0.206$, $P=0.001$). The malignant prevalence of the Tg group (≥ 434.60 ng/mL) was 47.2% and higher than other Tg groups ($P=0.001$).

Discussion

Our study showed that the higher TgAb levels indicated a higher risk of FTC and a sharp increase could be seen in the prevalence of malignancy in the highest TgAb group. Those results were demonstrated for TgAb levels within the reference range. In addition, in TgAb (-) patients, the higher Tg levels were associated with a higher risk of FTC and a sharp increase could be seen in the prevalence of malignancy in the highest Tg group. Therefore, we should pay adequate attention to preoperative serum TgAb and Tg levels in the management of thyroid follicular neoplasm.

The association between thyroid cancer with thyroid autoimmunity is controversial [11]. The exact mechanisms of the co-occurrence of thyroid autoimmune and neoplastic pathology remain not clear. Previous researches indicated that cytokines, chemokines, genetic backgrounds, microchimerism, and iodine might involve their pathogenesis [11]. The previous studies showed the significant association between thyroid cancer and thyroid autoimmune [12,13] and thyroid autoimmune in PTC is more meaningful than other types of thyroid cancers [14-16]. Conversely, no strong evidence was provided for the association between FTC and thyroid autoimmune [14,17,18]. The majority of previous studies investigated the comparison between thyroid cancers and benign nodules [12-16], and unlike in

our study, we are focusing on the differences between thyroid follicular neoplasm. Interestingly, we found that, as a serum marker of thyroid autoimmune, the serum TgAb was an independent risk factor for FTC. In our population of follicular neoplasm, versus the TgAb group (≤ 11.68 IU/mL), the OR of the TgAb group (11.69-30.50 IU/mL) and TgAb group (≥ 30.50 IU/mL) were 2.206 (1.114-4.369, $P=0.023$) and 3.247 (1.684-6.260, $P=0.001$), respectively. Intuitively, the sharp increase can be seen in the prevalence of malignancy in the highest TgAb group. Versus TgAb levels ≤ 11.68 IU/mL, the malignant prevalence of TgAb levels ≥ 30.50 IU/mL was higher (13.1% vs. 32.9%, $P=0.001$). Moreover, the above results were demonstrated for TgAb levels within the reference range. In the population of TgAb (-), versus the TgAb group (≤ 10.11 IU/mL), OR of the TgAb group (≥ 14.58 IU/mL) was 3.053 (1.508-6.179, $P=0.002$); versus TgAb levels ≤ 10.11 IU/mL, the malignant prevalence of TgAb levels ≥ 14.58 IU/mL was higher (14.1% vs. 33.3%, $P=0.005$). In addition, as another serum marker of thyroid autoimmune, elevated TPOAb levels did not indicate the risk of FTC in this study. Our view was consistent with previous studies, which found that TgAb seemed to be a better marker than TPOAb to display the association between thyroid cancer and thyroid autoimmune [19,20]. Currently, whether TgAb is an alternative prognostic marker for the follow-up of patients with differentiated thyroid cancer (DTC) has been extensively discussed [21]. Considering our finding, we also believe that the role of preoperative TgAb in thyroid follicular neoplasm should be underappreciated and future studies will be necessary to understand the interplay between TgAb and thyroid follicular neoplasm.

The earlier studies showed elevated Tg levels were of certain value in patients with DTC [22-24]. Because increased serum Tg levels are found during various thyroid benign conditions in later studies, such as goiter, Graves' disease, and thyroiditis [25-27], serum Tg cannot be used as a sensitive and specific marker for the preoperative diagnosis of DTC. In our study, considering the interference of elevated TgAb, Tg was only analyzed in TgAb (-) patients. We found that the serum Tg was an independent risk factor for FTC in TgAb (-) patients. Versus the Tg group (≤ 38.51 ng/mL), OR of the Tg group (≥ 434.60 ng/mL) was 3.836 (1.625-9.058, $P=0.002$). A sharp increase also can be seen in the prevalence of malignancy in the highest Tg group (≥ 434.60 ng/mL). The malignant prevalence of the Tg group (≥ 434.60 ng/mL) was 47.2% and higher than other Tg groups ($P=0.001$). Meanwhile, the previous studies also showed that the serum Tg was an independent risk factor for FTC in the population of follicular neoplasm [28-30], which was consistent with our findings. Currently, the serum Tg is a useful prognostic marker for the follow-up of DTC patients after total thyroidectomy [10]. Combining our findings with previous studies, we should pay attention to the role of preoperative Tg in thyroid follicular neoplasm.

It is noteworthy that the large observational studies showed an increase in thyroid cancer with the increased TSH levels [31-32]. However, there was no significant difference between FTC and FTA in the TSH levels in our study.

This study has several limitations. First, this was a retrospective single-center study with a small sample size. Second, in our center, the display range for serum TgAb levels are higher or equal to 10.00 ng/mL (normal reference range of 0-115.00 IU/mL) and for serum Tg levels are 0.05-500.00 ng/mL (normal reference range of 3.50-77.00 ng/mL). For analyses, TgAb levels ≥ 10.00 ng/mL were considered to be

10.00 ng/mL; Tg levels $\leq$ 0.05 ng/mL and $\geq$ 500 ng/mL were considered to be 0.05 ng/mL and 500 ng/mL, respectively. Consequently, TgAb levels $\leq$ 10.00 ng/mL, Tg levels $\leq$ 0.05 ng/mL and $\geq$ 500 ng/mL should be categorized accordingly in the future. Third, the AUCs, sensitivity, and specificity of our study models were not satisfactory. Therefore, more clinical features need to be considered.

Serum TgAb and Tg levels may have utility in the preoperative differential diagnosis of thyroid follicular neoplasm. In the follicular neoplasm population, higher serum TgAb and Tg levels were associated with higher malignant risk. Thus, we should be cautious of preoperative serum TgAb and Tg levels in the management of thyroid follicular neoplasm, such as deciding the extent of surgery and frequency of follow-up.

Declarations

Acknowledgments

We thank the participants for this study.

References

- [1] McHenry CR, Phitayakorn R. (2011) Follicular adenoma and carcinoma of the thyroid gland. *Oncologist* 16:585-593.
- [2] Achebrook-Kilfoy B, Grogan RH, Ward MH, Kaplan E, Devesa SS. (2013) Follicular thyroid cancer incidence patterns in the United States, 1980-2009. *Thyroid* 23:1015-1021.
- [3] Grani G, Lamartina L, Durante C, Filetti S, Cooper DS. (2018) Follicular thyroid cancer and Hurthle cell carcinoma: Challenges in diagnosis, treatment, and clinical management. *Lancet Diabetes Endocrinol* 6:500-514.
- [4] Sillery JC, Reading CC, Charboneau JW, Henrichsen TL, Hay ID, Mandrekar JN. (2010) Thyroid follicular carcinoma: sonographic features of 50 cases. *AJR Am J Roentgenol* 194(1):44-54.
- [5] Ou D, Yao J, Jin J, et al. (2020) Ultrasonic identification and regression analysis of 294 thyroid follicular tumors. *J Cancer Res Ther* Sep;16(5):1056-1062.
- [6] Cibas ES, Ali SZ. (2017) The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid* 27:1341-1346.
- [7] Pstrag N; Ziemnicka K; Bluysen H; Wesoly J. (2018) Thyroid cancers of follicular origin in a genomic light: In-depth overview of common and unique molecular marker candidates. *Mol Cance* 17:116.
- [8] Borowczyk M , Szczepanek-Parulska E , Dbicki S , et al. (2019) Differences in Mutational Profile between Follicular Thyroid Carcinoma and Follicular Thyroid Adenoma Identified Using Next Generation

Sequencing. International Journal of Molecular Sciences 20(13).

- [9] Zhang H, Zhang ZZ, Liu XD, et al. (2021) DNA Methylation Haplotype Block Markers Efficiently Discriminate Follicular Thyroid Carcinoma from Follicular Adenoma. *J Clin Endocrinol Metab* 106(4):1011-1021.
- [10] Haugen BR, Alexander EK, Bible KC, et al. (2016) 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* 26:1-133.
- [11] Ferrari SM, Fallahi P, Elia G, et al. (2020) Thyroid autoimmune disorders and cancer. *Semin Cancer Biol* 64:135-146.
- [12] Boi F, Pani F, Mariotti S. (2017) Thyroid Autoimmunity and Thyroid Cancer: Review Focused on Cytological Studies. *Eur Thyroid J* 6:178-186.
- [13] Nagayama Y. (2018) Thyroid Autoimmunity and Thyroid Cancer - The Pathogenic Connection: A 2018 Update. *Horm Metab Res* 50:922-931.
- [14] Resende de PC, Grønhøj C, Feldt-Rasmussen U, et al. (2017) Association between Hashimoto's Thyroiditis and Thyroid Cancer in 64,628 Patients. *Front Oncol* 7: 53.
- [15] Boi F, Lai M L, Marziani B et al. (2005) High prevalence of suspicious cytology in thyroid nodules associated with positive thyroid autoantibodies. *Eur J Endocrinol* 153: 637-642.
- [16] Boi F, Minerba L, Lai ML, et al. (2013) Both thyroid autoimmunity and increased serum TSH are independent risk factors for malignancy in patients with thyroid nodules. *J Endocrinol Invest* 36:313-320.
- [17] Okayasu I, Fujiwara M, Hara Y, et al. (1995) Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma. A study of surgical cases among Japanese, and white and African Americans. *Cancer* 76:2312-2318.
- [18] Veit F, Graf D, Momberger S, et al. (2017) Papillary thyroid cancer and coexisting autoimmune thyroiditis. *Horm Metab Res* 49:869-872.
- [19] Azizi G, Keller JM, Lewis M, et al. (2014) Association of Hashimoto's thyroiditis with thyroid cancer. *Endocr Relat Cancer* 21:845-852.
- [20] Wu X, Lun Y, Jiang H, et al. (2014) Coexistence of thyroglobulin antibodies and thyroid peroxidase antibodies correlates with elevated thyroid-stimulating hormone level and advanced tumor stage of papillary thyroid cancer. *Endocrine* 46:554-560.

- [21] Lee ZJO, Eslick GD, Edirimanne S. (2020) Investigating Antithyroglobulin Antibody As a Prognostic Marker for Differentiated Thyroid Cancer: A Meta-Analysis and Systematic Review. *Thyroid* 30:1601-1612.
- [22] Herle AJ, Uller RP. (1975) Elevated serum thyroglobulin. A marker of metastases in differentiated thyroid carcinomas. *J Clin Invest.* 56:272–277.
- [23] Gerfo P, Colacchio T, Colacchio D, et al. (1979) Thyroglobulin in benign and malignant thyroid disease. *JAMA* 241:923–992.
- [24] Christensen SB, Bondeson L, Erisson UB, et al. (1984) Prediction of malignancy in the solitary thyroid nodule by physical examination, thyroid scan, fine-needle biopsy and serum thyroglobulin. A prospective study of 100 surgically treated patients. *Acta Chir Scand* 150:433–439.
- [25] Levine GA, Hershman JM, Van HAJ, et al. (1978) Thyroglobulin and calcitonin in patients with nontoxic goiter. *JAMA* 240:2282-2283.
- [26] Glinioer D, Puttemans N, Van Herle AJ, et al. (1974) Sequential study of the impairment of thyroid function in the early stage of subacute thyroiditis. *Acta Endocrinol* 77:26-34.
- [27] Uller RP, Van Herle AJ. (1978) Effect of therapy on serum thyroglobulin levels in patients with Graves' disease. *J Clin Endocrinol Metab* 46:747-745.
- [28] Besic N, Sesek M, Peric B, et al. (2008) Predictive factors of carcinoma in 327 patients with follicular neoplasm of the thyroid. *Med Sci Monit* 14:CR 459-467.
- [29] Petric R, Perhavec A, Gazic B, et al. (2012) Preoperative serum thyroglobulin concentration is an independent predictive factor of malignancy in follicular neoplasms of the thyroid gland. *J Surg Oncol* 105(4):351-356.
- [30] Petric R, Besic H, Besic N. (2014) 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* 12:282.
- [31] McLeod DS, Watters KF, Carpenter AD, Ladenson PW, Cooper DS, Ding EL. (2012) Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. *J Clin Endocrinol Metab* 97:2682-2692.
- [32] Fiore E, Vitti P. (2012) Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. *J Clin Endocrinol Metab* 97:1134-1145.

Tables

Table 1. Characteristics of all patients with FTC and FTA^a

	FTC (n=67)	FTA (n=252)	<i>P</i>
Male	17(25.4%)	87(34.5%)	0.156
Age (years)	45.1±16.0	43.4±13.8	0.200
Maximum diameters (cm)	3.0(2.0-4.5)	3.0(2.3-4.0)	0.944
TgAb (IU/mL)	15.90(10.00-99.34)	10.78(10.00-19.73)	0.003
TgAb ≥115 IU/mL	14(20.9%)	36(14.3%)	0.186
TPOAb (IU/mL)	13.44(8.80-33.30)	11.20(8.16-18.35)	0.095
TPOAb ≥34.00 IU/mL	15(22.4%)	37(14.7%)	0.129
TSH (μIU/mL)	1.310(0.829-2.200)	1.302(0.880-1.990)	0.614
TSH ≥5.910 μIU/ml	0(0%)	9(3.6%)	0.117

a.Considering the interference of elevated TgAb, Tg was only analysed in the patients who were negative for TgAb (< 115.00 IU/mL).

Abbreviations: FTC, Follicular thyroid carcinoma; FTA, follicular thyroid adenoma; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

Table 2. Logistic regression analyses to evaluate the association between FTC and risk factors in all patients^a

	FTC (n=67)	FTA (n=252)	Univariate		Multivariate*	
			OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Male	17(25.4%)	87(34.5%)	1.551(0.844-2.850)	0.185		
Age (years)	45.1±16.0	43.4±13.8	1.008(0.989-1.027)	0.407		
Maximum diameters (cm)	3.0(2.0-4.5)	3.0(2.3-4.0)	1.058(0.904-1.237)	0.486		
TgAb group ^b						
≤11.68 IU/mL	21(31.3%)	139(55.2%)	1.000	-	1.000	-
11.69-30.50 IU/mL	20(29.9%)	60(23.8%)	2.206(1.114-4.369)	0.023	2.206(1.114-4.369)	0.023
≥30.50 IU/mL	26(38.8%)	53(21.0%)	3.247(1.684-6.260)	0.001	3.247(1.684-6.260)	0.001
TPOAb group ^c						
≤8.35 IU/mL	14(20.9%)	66(26.2%)	1.000	-		
8.36-11.70 IU/mL	14(20.9%)	66(26.2%)	1.000(0.442-2.261)	1.000		
11.71-19.02 IU/mL	18(26.9%)	62(24.6%)	1.369(0.628-2.985)	0.430		
≥19.02 IU/mL	21(31.3%)	58(23.0%)	1.707(0.796-3.660)	0.169		
TSH group ^c						
≤0.870 μIU/ml	19(28.4%)	62(24.6%)	1.000	-		
0.871-1.303 μIU/ml	14(20.9%)	65(25.8%)	0.703(0.324-1.523)	0.371		
1.304-2.015 μIU/ml	15(22.4%)	65(25.8%)	0.753(0.352-1.612)	0.465		
≥2.015 μIU/ml	19(28.4%)	60(23.8%)	1.033(0.499-2.140)	0.930		

a.Considering the interference of elevated TgAb, Tg was only analysed in the patients who were negative for TgAb (< 115.00 IU/mL).

b.In groups of TgAb, patients were divided into three groups by 2nd quartile and 3rd quartile, because patients with TgAb levels below the limitation of detection (10 IU/mL) were more than 1st quartile (n=133, 41.7%).

c.In groups of other serum markers, all patients were grouped in fourths equally.

*The stepwise forward method was used to include significant factors in the multivariate logistic regression analysis.

Abbreviations: FTC, Follicular thyroid carcinoma; FTA, follicular thyroid adenoma; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

Table 3. Characteristics of TgAb (-) patients with FTC and FTA^a

	FTC	(n=53)	FTA (n=216)	<i>P</i>
Male	16(30.2%)		82(38.0%)	0.292
Age (years)	44±15.5		43.8±14.1	0.525
Maximum diameters (cm)	3.4(2.5-4.5)		3.0(2.4-4.0)	0.482
Tg (ng/mL)	376.50(63.14-500.00)		89.33(36.51-53.75)	0.002
Tg≥77.00 ng/mL	38(71.7%)		114(52.8%)	0.013
TgAb (IU/mL)	12.94(10.00-26.99)		10.00(10.00-13.33)	0.003
TPOAb (IU/mL)	11.94(8.80-16.67)		10.59(7.91-15.90)	0.272
TPOAb≥34.00 IU/mL	6(11.3%)		24(11.1%)	0.965
TSH (μIU/mL)	1.310(0.818-2.170)		1.290(0.880-1.859)	0.597
TSH≤5.910 μIU/ml	0(0%)		7(3.2%)	0.351

a.Considering the interference of elevated TgAb, Tg was only analysed in the patients who were negative for TgAb (< 115.00 IU/mL).

Abbreviations: FTC, Follicular thyroid carcinoma; FTA, follicular thyroid adenoma; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

Table 4. Logistic regression analyses to evaluate the association between FTC and risk factors in TgAb (-) patients^a

	FTC (n=53)	FTA (n=216)	Univariate		Multivariate*	
			OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Male	16(30.2%)	82(38.0%)	0.707(0.370-1.350)	0.293		
Age (years)	44±15.5	43.8±14.1	1.001(0.980-1.002)	0.924		
Maximum diameters (cm)	3.4(2.5-4.5)	3.0(2.4-4.0)	1.102(0.923-1.315)	0.285		
Tg group ^c						
≤38.51 ng/mL	9(17.0%)	58(26.9%)	1.000	-	1.000	-
38.52-102.80 ng/mL	9(17.0%)	59(27.3%)	0.983(0.364-2.652)	0.973	1.205(0.435-3.334)	0.720
102.81-434.60 ng/mL	10(18.9%)	57(26.4%)	1.131(0.428-2.988)	0.804	1.207(0.451-3.229)	0.708
≥434.60 ng/mL	25(47.2%)	42(19.4%)	3.836(1.625-9.058)	0.002	3.654(1.528-8.738)	0.004
TgAb group ^b						
≤10.11 IU/mL	19(35.8%)	116(53.7%)	1.000	-	1.000	-
10.12-14.58 IU/mL	12(22.6%)	56(25.9%)	1.308(0.594-2.882)	0.505	1.317(0.587-2.953)	0.504
≥14.58 IU/mL	22(41.5%)	44(20.4%)	3.053(1.508-6.179)	0.002	2.564(1.219-5.396)	0.013
TPOAb group ^c						
≤8.00 IU/mL	10(18.9%)	57(26.4%)	1.000	-		
8.01-10.77 IU/mL	13(24.5%)	55(25.5%)	1.347(0.546-3.326)	0.518		
10.78-16.03 IU/mL	15(22.4%)	52(24.1%)	1.644(0.679-3.980)	0.270		
≥16.03 IU/mL	15(22.4%)	52(24.1%)	1.644(0.679-3.980)	0.270		

TSH group ^c				
≤0.864 μIU/ml	15(28.3%)	52(24.1%)	1.000	-
0.865-1.290 μIU/ml	11(20.8%)	57(26.4%)	0.669(0.282- 1.587)	0.362
1.291-1.979 μIU/ml	12(22.6%)	55(25.5%)	0.756(0.324- 1.767)	0.519
≥1.979 μIU/ml	15(28.3%)	52(24.1%)	1.000(0.444- 2.253)	1.000

a. Considering the interference of elevated TgAb, Tg was only analysed in the patients who were negative for TgAb (< 115.00 IU/mL).

b. In groups of TgAb, TgAb (-) patients were divided into three groups by 2nd quartile and 3rd quartile, because TgAb (-) patients with TgAb levels below the limitation of detection (10 IU/mL) were more than 1st quartile (n=133, 49.9%).

c. In groups of other serum markers, TgAb (-) patients were grouped in fourths equally.

*The stepwise forward method was used to include significant factors in the multivariate logistic regression analysis.

Abbreviations: FTC, Follicular thyroid carcinoma; FTA, follicular thyroid adenoma; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

Figures

Figure 1

ROC analyses and AUC for distinguishing FTC from FTA

a. The AUC of all patients model was 0.634 (0.559-0.709), $P=0.001$. The hollow dot indicates sensitivity (68.66%) and specificity (55.16%) with the cut-off (TgAb ≥ 11.69 IU/mL).

b. The AUC of the negative TgAb patients model was 0.681 (0.593-0.768), $P=0.001$. The hollow dot indicates sensitivity (56.60%) and specificity (73.15%) with cut-off (Combined Tg levels ≥ 434.60 ng/mL with TgAb levels ≥ 14.58 IU/mL).

Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; FTC, Follicular thyroid carcinoma.

Figure 2

Prevalence of FTC in relation to TgAb in all patients. With groups of increasing TgAb levels, there was a statistically significant increase in the prevalence of FTC ($r = 0.206$, $P < 0.001$) in all patients.

* $P=0.001$, compared with TgAb levels ≤ 11.68 IU/mL.

Abbreviations: FTC, Follicular thyroid carcinoma; TgAb, thyroglobulin antibody.

Figure 3

Prevalence of FTC in relation to TgAb in TgAb (-) patients. With groups of increasing TgAb levels, there was a statistically significant increase in the prevalence of FTC ($r = 0.180$, $P = 0.003$) in TgAb (-) patients.

* $P = 0.005$, compared with TgAb levels ≤ 10.11 IU/mL.

Abbreviations: FTC, Follicular thyroid carcinoma; TgAb, thyroglobulin antibody.

Figure 4

Prevalence of FTC in relation to Tg in TgAb (-) patients. With groups of increasing TgAb levels, there was a statistically significant increase in the prevalence of FTC ($r = 0.206$, $P = 0.001$) in TgAb (-) patients.

* $P=0.001$, compared with other groups of Tg respectively.

Abbreviations: FTC, Follicular thyroid carcinoma; Tg, thyroglobulin; TgAb, thyroglobulin antibody.