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Original Research

Determination of Diagnostic Features of Serum Thyroid Hormones and Thyroglobulin Ratios in Normothyroid Differentiated Thyroid Carcinoma Cases

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ABSTRACT

Objectives: Ultrasonography and fine-needle aspiration biopsy (FNAB) are the gold standard methods in the prediction of benign and malignant thyroid nodules. However, despite being easily applicable, FNAB is an invasive procedure. Less invasive biomarkers should be utilized in the diagnosis of thyroid malignancies. In this study, we aimed to determine the parameters that can be used in the diagnosis of differentiated thyroid cancer (DTC) based on the serum thyroid and thyroglobulin (TG) levels which are routinely checked in patients followed up for thyroid nodules.

Methods: In the study, we evaluated patients who underwent thyroid surgery for nodular diseases between January 2015 and June 2022. Of the 1444 patients evaluated, 919 patients who met the inclusion criteria (normothyroid benign nodular disease or normothyroid DTC) were included in the study. Patients were divided into two groups as benign group (BG) and DTC group (DTCG). We compared patients' pre-operative serum thyroid and TG values and the diagnostic properties of their ratios.

Results: Of the 919 patients included, 517 (56.3%) were in BG and 402 (43.7%) were in DTCG. In DTCG, 318 patients were female and 84 patients were male. The mean age in the DTCG was 47.8 years. Comparison of DTCG and BG revealed a significant difference between T3/T4 ratio (p=0.002), T3/TSH ratio (p≤0.001), T4/TSH ratio (p≤0.001), TG/TSH ratio (p≤0.001), and TSH/TG ratio (p≤0.001). However, evaluation of the specified values by ROC analysis showed that the T3/T4 ratio did not make a significant difference between the two groups (p=0.1), whereas the other values displayed a significant difference (p≤0.001 for T3/TSH, p=0.001 for T4/TSH, p≤0.001 for TG/TSH, and p<0.001 for TSH/TG).

Conclusion: T3/TSH (cutoff =2.183), T4/TSH (cutoff=0.6), and TG/TSH (cutoff=29.67) values were found to be significant tumor markers for the prediction of malignancy in thyroid nodules, and low values were found to be associated with malignancy. TSH/TG (cutoff=0.031) value was also significant in predicting malignancy while high values were found to be associated with malignancy. Thyroid hormone and TG ratios may alter the preferred treatment method for thyroid nodules.

Keywords: Differentiated thyroid cancer, T3, T4, thyroglobulin, TSH

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Thyroid diseases are commonly seen today and differentiated thyroid cancers (DTC) are also on the increase. Among the patient population, the incidence of palpable thyroid nodules is 5% in female patients and approximately 1% in male patients. The prevalence of thyroid nodules increases with advancing age. Thanks to the developing technology and ease of access to health centers, incidental thyroid nodules represent a high rate of 19% up to 68%.[1]

Approximately 7–15% of thyroid nodules cause thyroid cancer so some thyroid nodules should be further examined depending on the criteria determined due to the cancer risk.[1] Thyroid cancers are the most common endocrine malignancy today, representing 3.8% of all cancer patients. It is 3 times more common in women compared to men and ranked ninth globally in 2020 with an increasing incidence rate.[2,3] Thyroid cancer patients are classified as good in terms of prognosis in long-term follow-ups.[4] and recurrence rates are very low.[5] In addition, developments in diagnostic methods increase the recognition of thyroid cancers today.[6]

Today, ultrasonography and thyroid fine-needle aspiration biopsy (FNAB) are the gold standard in the differentiation of benign and malignant thyroid nodules.[7] However, although FNAB is an easily applicable procedure, it is invasive. In addition, an experienced interventional radiologist and cytopathologist should perform the procedure.[8]

Thyroid-stimulating hormone (TSH) should be measured first in all patients with thyroid nodules. The risk of malignancy increases in parallel with serum TSH levels in these patients. However, a low TSH usually suggests a benign nodule.[7,9,10] Some recent retrospective comparisons show that serum thyroid levels are significant in the prediction of thyroid cancers. It is predicted to be used for screening malignancy in thyroid cancer as it is a non-invasive procedure and relatively cost-friendly. In addition, it has been shown that an increased serum TSH and thyroglobulin (TG) ratio is a more efficient marker in the diagnosis of thyroid cancer compared to TSH alone.[11-13]

The aim of this study was to determine diagnostic ratios for the prediction of DTC by examining patients' serum levels that are routinely checked at the follow-up appointments of patients with thyroid nodules.

Methods

This study is a retrospective, cross-sectional, and single-center study.

In our study, we evaluated patients who underwent thyroid surgery for nodular diseases between January 2015 and June 2022. The number of patients evaluated initially was 1444. Nine hundred and nineteen patients who met the inclusion criteria (patients with euthyroid, benign nodule, or DTC, aged between 17 and 82) were included in the study. Patients who were not followed up by our clinic in the pre-operative and post-operative period, and non-euthyroid patients in the pre-operative period (n=525) were excluded from the study (Fig. 1). Patients were divided into two groups as the benign group (BG) and the DTC group (DTCG).

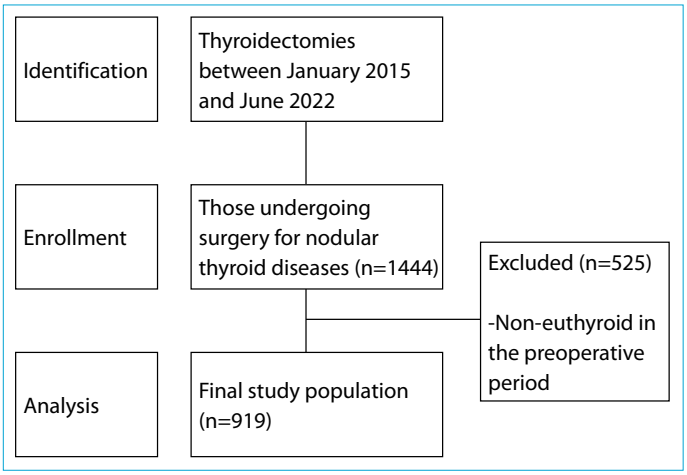

Figure 1. The sample collection scheme.

We compared serum thyroid and TG values (T3, T4, TSH, and TG) and their ratios (T3/T4, T3/TSH, T4/TSH, TG/TSH, and TSH/TG) of the benign and DTCGs in the pre-operative period. In our study, we accepted pg/mL for T3, ng/dL for T4, μIU/mL for TSH, and ng/mL for TG as the baseline. Based on these parameters, diagnostic properties were determined by comparing BG with DTCG and intragroup comparison of DTCG.

Study approval was obtained from the Ethics Committee of Gazi University Faculty of Medicine with the decision numbered 642 dated August 08, 2022. This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 26.0, SPSS Inc, Chicago, IL, USA) program. Descriptive statistics of numerical and categorical data were analyzed and numerical parameters were expressed as median (min-max) or mean±SD, while categorical variables were expressed as frequency and percentage. Kolmogorov–Smirnov test, histogram analyses, and skewness/kurtosis data were used to evaluate the conformity of numerical variables to normal distribution. Levene's test was used to analyze the intergroup homogeneity characteristics of numerical parameters. An independent t-test was performed to compare two independent groups for parameters with normal

distribution. Mann–Whitney U-test was used to compare two independent groups for parameters without normal distribution. Kruskal–Wallis test was used to compare multiple independent groups for parameters without normal distribution. Spearman's correlation analysis test was used to assess the correlation between numerical parameters. Simple linear regression analyses were performed to analyze the efficiency of appropriate parameters with each other. Binary logistic regression analysis was performed to determine the predictive factors. The accuracy of binary relationships and model analyses was confirmed by the Hosmer–Lemeshow test. The chi-square test and Fisher's exact test were performed to analyze the relationship between binary categorical groups. Significant parameters that could affect mortality were subjected to ROC analysis and diagnostic data were presented. The relationship between categorical groups and numerical parameters was summarized with boxplot graphs. The type-I error rate was 5% for the entire study, while $p<0.05$ was considered significant.

Results

The study included a total of 919 patients, 207 male (22.5%) and 712 female (77.5), who met the inclusion criteria. The benign (n=517) patient group constituted 56.3% of the entire patient population. When the patients were divided into two groups as the benign and DTCGs, the mean age of the BG (49.85±11.71) was significantly higher compared to the mean age of the DTCG (47.88±12.79) (p=0.048). Evaluation of nodule sizes in both groups showed that the BG had significantly higher nodule sizes compared to DTCG ($p\leq0.001$) (Table 1).

The relationship between gender and proportional values was analyzed. Analysis of T3/T4 (p=0.03), T3/TSH (p=0.02), and TG/TSH (p=0.01) values revealed higher values in the male group, while TSH/TG (p=0.01) values were higher in the female group, with statistical significance (Table 2).

Binary LR analysis was performed separately for age, gender, and some proportional parameters, and their predictive properties were examined individually for the prediction of malignancy. Our study revealed that T3/TSH (B=–0.203,

Table 1. Descriptive data, demographic, and laboratory characteristics

Parameters[a]	**Benign Group**[ǂ] **(n=517, 56.3%)**	**Differentiated thyroid cancer group**[Φ] **(n=402, 43.7%)**	**p**
Age (Mean±SD), year	49.85±11.71	47.88±12.79	**0.048**
Sex, *n (%)*			
Female	394 (55.3)	318 (44.7)	0.30
Male	123(59.4)	84 (40.6)	
Nodule Size (cm)	2.40 (0.20–9.0)	1.60 (0.20–7.50)	**<0.001**
Extra-thyroidal spread, *n (%)*			
Positive (+)	-	45 (11.2)	
Negative (-)	-	357 (88.8)	
Lymphatic Invasion, *n (%)*			
Positive (+)	-	23 (5.7)	
Negative (-)	-	379 (94.3)	
Vascular Invasion, *n (%)*			
Positive (+)	-	33 (8.2)	
Negative (-)	-	369 (91.8)	
T3 (pg/mL)	3.40 (2.43–4.50)	3.30 (2.18–4.50)	0.002
T4 (ng/dL)	0.91 (0.58–1.38)	0.93 (0.58–1.38)	0.16
TSH (IU/mL)	1.28 (0.39–5.07)	1.65 (0.38–5.24)	<0.001
TG (ng/mL)	85.0 (0.20–2963.0)	27.15 (0.04–18937.0)	<0.001
T3/T4	3.80 (1.84–6.33)	3.59 (1.73–6.94)	0.002
T3/TSH	2.65 (0.48–9.23)	2.02 (0.41–8.97)	<0.001
T4/TSH	0.71 (0.11–3.19)	0.53 (0.14–2.97)	<0.001
TG/TSH	62.75 (0.09–3265.0)	14.36 (0.04–13100.0)	<0.001
TSH/TG	0.01 (0.0003–10.60)	1.25 (0.000076–22.48)	<0.001

SD: Standard deviation; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid-stimulating hormone; TG: Thyroglobulin.

Table 2. Gender relationship of laboratory and proportional parameters

Lab.	Female (n=712)	Male (n=207)	p
T3/T4	3.66 (1.73–6.94)	3.77 (1.90–6.55)	**0.03**
T3/TSH	2.30 (0.41–9.23)	2.59 (0.64–8.78)	**0.02**
T4/TSH	0.63 (0.11–3.19)	0.71 (0.14–2.71)	0.15
TG/TSH	28.18 (0.04–11617.0)	58.03 (0.04–13100.0)	**0.01**
TSH/TG	0.03 (0.0008–21.35)	0.01 (0.0007–22.48)	**0.01**

Lab.: Laboratory; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid-stimulating hormone; TG: Thyroglobulin.

Table 3. Logistic regression analysis and effect levels of some factors that can be used in the prediction of malignancy at the first admission

Malignancy (Differentiated thyroid carcinoma)[ǂ]						
Factors	**B**	**−2LL**	**R^2 Nagelkerke**	**p**	**Exp(B)**	**95% CI**
Gender	0.167	1258.48	0.002	0.29	1.182	0.863–1.618
T3/TSH	−0.203	1232.48	0.039	**<0.001**	0.816	0.754–0.884
T4/TSH	−0.564	1241.54	0.026	**<0.001**	0.569	0.435–0.744
TSH/TG	0.248	527.40	0.061	**0.002**	1.282	1.095–1.500

Reference category: Benign nodular group; LL: Log Likelihood; CI: Confidence ınterval; [ǂ]Age, TG/TSH and T3/T4 parameters were excluded from the logistic regression analysis as they did not meet the Hosmer–Lemeshow and/or Box-Tidwell model compatibility assumptions. T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid-stimulating hormone; TG: Thyroglobulin.

Table 4. ROC curve data of proportional parameters, AUC, and diagnostic findings

	AUC (95% CI)	Cutoff	p	Sensitivity (%)	Specificity (%)
Age	0.475	48.50	0.38	52.1	51.0
T3/T4	0.455	3.66	0.12	50.0	48.0
T3/TSH[¥]	0.611	2.183	**<0.001**	57.9	59.3
T4/TSH[¥]	0.599	0.600	**0.001**	56.8	58.8
TG/TSH[¥]	0.680	29.671	**<0.001**	63.2	63.7
TSH/TG	0.680	0.031	**<0.001**	64.2	62.7

AUC: Area under curve; ROC: Receiver operating characteristic; CI: Confidence Interval; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid-stimulating hormone; TG: Thyroglobulin; Reference Category: Benign nodular group. [¥]Smaller values are associated with a more positive (in favor of malignancy) number of cases.

R^2 nagelkerke=0.039, p<0.001) and T4/TSH (B=−0.564, R^2 nagelkerke=0.026, p<0.001) values were found to exert significant predictive features in the prediction of malignancy, with low values being associated with malignancy. On the other hand, it was found that TSH/TG (B=0.248, R^2 nagelkerke=0.061, p=0.002) values displayed significantly predictive properties in predicting malignancy, while high TSH/TG values were associated with malignancy. No significant predictive properties were observed for gender (Table 3).

Comparison of DTCG and the BG showed that the T3/T4 ratio (3.59 [1.73–6.94] was significant at 3.80 [1.84–6.33], p=0.002), T3/ TSH ratio (2.02 [0.41–8.97] at 2.65 [0.48–9.23], p≤0.001), T4/TSH ratio (0.53 [0.14–2.97] at 0.71 [0.11–3.19], p≤0.001), TG/TSH ratio (14.36 [0.04–13100.0] at 62.75 [0.09–3265.0], p≤0.001), and TSH/TG ratio (1.25 [0.000076–22.48] at 0.01 [0.0003–10.60], p≤0.001) (Table 1). However, evaluation of the specified values by ROC analysis showed that T3/T4 was not significant (p=0.1), while other values were found to be significant (p≤0.001 for T3/TSH, p=0.001 for T4/TSH, p=0.001 for TG/TSH, p<0.001 for TSH/TG). TG/TSH and T3/T4 parameters were excluded from the logistic regression analysis since they did not meet the Hosmer–Lemeshow and/or Box-Tidwell model compatibility assumptions. T3/TSH (p≤0.001), T4/TSH (p=0.001), and TSH/TG (p=0.002) values were all significant for other parameters in the logistic regression analysis (Fig. 2 and Table 4).

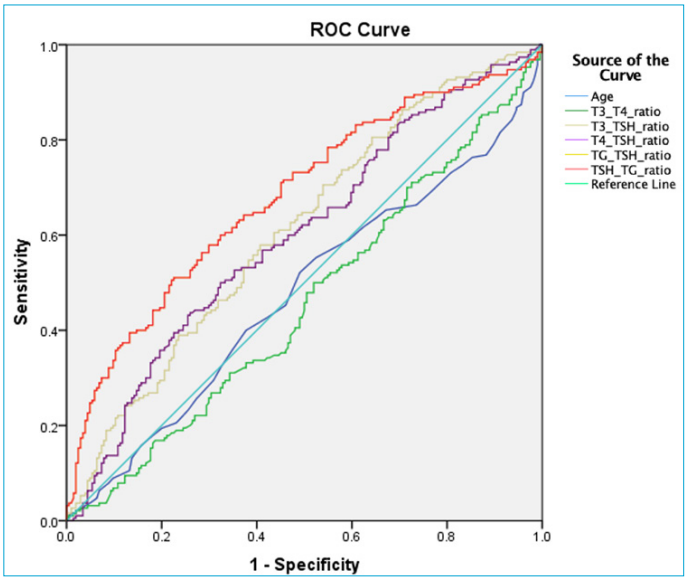

Figure 2. ROC analysis chart of parameters.

Discussion

Growth rates in thyroid cells increase due to TSH stimulation in differentiated thyroid carcinoma.[1] This function is acquired by expressing the TSH receptor on the cell membrane and increasing protein secretion.[12] Therefore, TSH values are higher in patients with malignant thyroid.[14] Lee et al.,[15] investigated the relationship between malignancy and pre-operative serum thyroid hormone and TG levels. The risk of thyroid malignancy increased in nodules with pre-operative TG>100 ng/mL (p=0.029). Pre-operative TG levels have a very high specificity in predicting thyroid cancer in case of suspected follicular neoplasm. Therefore, it was concluded that TG levels may be a useful marker in the cytologic diagnosis of indeterminate nodules to differentiate thyroid cancer from benign thyroid nodules.

Karvounis et al.,[13] proposed that TG/TSH and/or TSH/TG ratios could be a marker of malignancy, with the hypothesis that malignant cells may respond differently to TSH than benign cells since TSH is a factor that directly affects the secretion of TG. In their study, they found that both TG/TSH and TSH/TG ratios differed significantly between malignant and BGs in univariate analysis. They examined 134 patients with malignancy and reported significant differences in the TG/TSH and TSH/TG values (p=0.02); however, the diagnostic ROC curve did not confirm these results. (TSH/TG=0.428, TG/TSH=0.572). They determined the cutoff value for the TG/TSH ratio as 15.6 ng/mIU.[13] In our large series of 402 patients with DTC, we observed significant differences in the TG/TSH ratio (14.36 [0.04–13100.0] vs. 62.75 [0.09–3265.0], p≤0.001) and TSH/TG ratio (1.25 [0.000076–22.48] vs. 0.01 [0.0003–10.60], p≤0.001), and we demonstrated these results in the diagnostic ROC analysis (p≤0.001 for TG/TSH, p<0.001 for TSH/TG). In our study, the cutoff value for TG/TSH was determined as 29.67. In their study with 244 malignant patients, Tam et al.[16] reported that the TSH/TG ratio could be used as a novel marker to differentiate benign and malignant thyroid nodules in the pre-operative period and that it could help to determine the malignancy risk in nodules with indeterminate cytology and help the management of these patients. Wang et al.[12] found that increased serum TSH/TG (cutoff=0.024) in the pre-operative period was associated with thyroid malignancies at a higher rate compared to TSH alone. They also found that this ratio constitutes a risk factor for thyroid malignancies. In our study, we also found that the TSH/TG (cutoff=0.031) value exhibited a significant predictive feature in the prediction of malignancy and high values were associated with malignancy. Yazici et al.[11] found that TSH/TG ratio was significant in univariate analysis; however, they failed to find any other parameters other than FNAB to be significant in multivariate analysis.

Ratios that can be used in the diagnosis of DTCs were determined by logistic regression and ROC analysis based on the serum levels routinely assessed in patients followed up with thyroid nodules. It has been shown that cutoff values obtained in this study can guide surgical and medical treatment modalities in the pre-operative period.

In our study, T3/TSH (cutoff=2.183), T4/TSH (cutoff=0.6), and TG/TSH (cutoff=29.67) values were used as tumor markers for DTCs and they were found to have significant predictive properties in the prediction of malignancy where low values are associated with malignancy. On the other hand, TSH/TG (cutoff=0.031) value was found to have a significant predictive feature in predicting malignancy with high values suggesting malignancy.

Conclusion

It is apparent that serum biomarkers, which are routinely checked in thyroid malignancies, are of great importance considering that they are non-invasive and cost-friendly. Our study has shown that TG/TSH and TSH/TG ratios that can be obtained from routine follow-up examinations can be utilized as preliminary data regarding treatment modalities both at the time of diagnosis and before surgery, to reduce the need for interventional procedure and evaluation by the specialist radiologist and histopathologist in the pre-operative period. Large-scale and long-term prospective randomized studies are needed to confirm the obtained values as tumor markers.

Disclosures

Acknowledgments: There are no acknowledgments. This study was presented as a graduation thesis in medicine in 2022 and was

previously presented as an oral presentation at the 11th Turkish National Endocrine Surgery Congress that took place in Antalya, Turkey between March 16 and 19, 2023.

Informed consent: Consent was obtained from the patients included in the study.

Ethics Committee Approval: The study was approved by the Ethics Committee of Gazi University Faculty of Medicine (No: 642, dated 08.08.2022).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – Y.F.A., C.B., M.A.; Design – Y.F.A., C.B.; Supervision – M.A., C.B.; Materials – U.E., Y.F.A., C.B.; Data collection &/or processing – U.E., E.G., Y.F.A., C.B.; Analysis and/ or interpretation – E.G., Y.F.A., C.B.; Literature search – Y.F.A., C.B.; Writing – Y.F.A., C.B.; Critical review – E.G., M.A.

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