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**RESEARCH**

# Combined preoperative thyroglobulin and ACR-TIRADS assessment: implications for fine-needle aspiration biopsy strategy and thyroid cancer diagnosis

## Preoperatif tiroglobulin ve ACR-TIRADS değerlendirmelerinin birlikte kullanılması: ince iğne aspirasyon biyopsisi stratejisi ve tiroid kanseri tanısı üzerindeki etkileri

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**Abstract**

**Purpose:** The aim of this study is to evaluate the relationship of Thyroglobulin (Tg) with the American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS) and Bethesda and its correlation with malignancy.

**Materials and Methods:** The study included 603 cases. Ultrasonography (US), fine needle aspiration biopsy (FNAB), Tg and anti-Tg results were evaluated retrospectively. Nodules were scored according to the ACR-TIRADS. FNAB results were evaluated according to the Bethesda. The relationship between Tg levels, ACR-TIRADS, and FNAB results was evaluated to determine the risk of thyroid malignancy.

**Results:** The mean age of cases was 50.98±13.73 (min-max: 18-79). 85.1% of the patients were female. Tg was statistically significantly higher in malignant patients (Bethesda 6). In the ROC analysis, the optimum cut-off value for Tg in predicting malignancy was found to be 245 ng/dL. Mean Tg levels were statistically significantly higher in the TIRADS 4, 5 groups than in the TIRADS 2 and 3 groups.

**Conclusion:** Results showed that Tg is elevated in thyroid nodular disease, especially in malignant nodules. The Tg levels increased in parallel with the ACR-TIRADS malignancy-risk score. If these results are supported by other studies, the evaluation of Tg together with ACR-TIRADS may make an additional contribution to the FNAB decision and the prediction of thyroid malignancies.

**Keywords:** Thyroglobulin, ACR-TIRADS, FNAB, thyroid cancer

**Öz**

**Amaç:** Bu çalışmada, Tiroglobulin'in (Tg) Amerikan Radyoloji Koleji Tiroid Görüntüleme Raporlama ve Veri Sistemi (ACR-TIRADS) ve Bethesda ile ilişkisi ve malignite ile korelasyonu değerlendirilmesi amaçlanmıştır.

**Gereç ve Yöntem:** Çalışmaya 603 olgu dahil edilmiştir. Ultrasonografi (US), ince iğne aspirasyon biyopsisi (İİAB), Tg ve anti-Tg sonuçları retrospektif olarak değerlendirilmiştir. Nodüller ACR-TIRADS'a göre skorlanmış ve İİAB sonuçları Bethesda'ya göre değerlendirilmiştir. Tiroid malignitesi riskini belirlemek için Tg seviyeleri, ACR-TIRADS ve İİAB sonuçları arasındaki ilişki değerlendirilmiştir.

**Bulgular:** Olguların ortalama yaşı 50,98±13,73 (min-max: 18-79) idi. Hastaların %85,1'i kadındı. Tg, malign hastalarda (Bethesda 6) istatistiksel olarak anlamlı derecede yüksekti. ROC analizinde, maligniteyi öngörmede Tg için optimum kesme değeri 245 ng/dL olarak bulundu. Ortalama Tg düzeyleri TIRADS 4, 5 gruplarında TIRADS 2 ve 3 gruplarına göre istatistiksel olarak anlamlı derecede yüksekti.

**Sonuç:** Bulgular, Tg'nin tiroid nodüler hastalığında, özellikle malign nodüllerde yükseldiğini göstermiştir. Tg düzeyleri ACR-TIRADS malignite risk skoruyla paralel olarak artmıştır. Bu sonuçların diğer çalışmalarla desteklenmesi durumunda, Tg'nin ACR-TIRADS ile birlikte değerlendirilmesi İİAB kararına ve tiroid malignitelerinin öngörülmesine ek katkı sağlayabilir.

**Anahtar kelimeler**: Tiroglobulin, ACR-TIRADS, İİAB, tiroid kanseri

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## INTRODUCTION

Thyroid nodules are a common condition in the adult age group in all societies. Due to advancements in diagnostic imaging techniques, the detection rate of these nodules has risen substantially in recent years, with literature reporting a prevalence ranging from 19% to 68% in healthy individuals [1-3]. The primary clinical objective in evaluating thyroid nodules is the accurate differentiation between benign and malignant lesions. Studies have focused more on this issue in recent years. Imaging methods (especially ultrasound), thyroid fine-needle aspiration biopsy (FNAB), laboratory findings, and radionuclide scintigraphic examination methods are used together in the evaluation of thyroid nodules and in the differentiation of benign and malignant. In the approach to ultrasonographically detected nodules, there are occasional indecisions in making the FNAB decision in terms of benign-malignant distinction [1]. In order to eliminate these instabilities and provide guidance in FNAB planning and evaluation in terms of malignancy risk, the American Thyroid Association (ATA) and the Thyroid Imaging Reporting and Data System (TI-RADS) guidelines have been developed and widely used in recent years. These guidelines were developed based on ultrasonographic (USG) evaluation of thyroid nodules by taking into account the number, size, echogenicity, nodule boundary, nodule shape, internal structure and calcification status [4-6].

Thyroglobulin (Tg) is a glycoprotein synthesized exclusively by thyroid follicular cells, playing a central role in the production and storage of thyroxine and triiodothyronine. Additionally, Tg is used as a tumor marker in the postoperative follow-up of well-differentiated thyroid cancers in clinical practice [2,7]. Elevated Tg levels have been documented in various conditions characterized by thyroid enlargement, including nodular thyroid disease, Graves' disease, subacute thyroiditis, and thyrotoxicosis factitia[8,9]. Moreover, some studies have shown that preoperative Tg elevation is associated with well-differentiated thyroid cancers, but the role of Tg as a preoperative tumor marker has not been clarified [9-11].

The relationship between thyroglobulin and ultrasonography-based thyroid nodule morphology is still an understudied topic. Consequently, the potential clinical utility of Tg in the diagnosis and long-term management of thyroid disorders has yet to be fully established. In this study, we compared Tg and ultrasonographically determined thyroid nodule characteristics classified according to the American College of Radiology (ACR)-TIRADS. Our primary objective was to evaluate whether Tg levels provide incremental diagnostic value when integrated with ultrasonographic findings, particularly in differentiating benign from malignant lesions and refining the clinical indications for fine-needle aspiration biopsy (FNAB).

## MATERIALS AND METHODS

This study was conducted as a retrospective screening and evaluation of the results of the cases followed up for thyroid nodular disease in the internal medicine and endocrinology clinics of Malatya Turgut Özal University Faculty of Medicine between March 2022 and November 2023. The ethics committee approval of the study was obtained from the local ethics committee of Malatya Turgut Özal University with approval no 2022-16 (06.02.2022). The study was performed in compliance with the Declaration of Helsinki.

### Sample

The study included cases over 18 years of age with normal thyroid function tests and available reports of Tg, anti-Tg, FNAB, and thyroid ultrasound. Individuals under 18 years of age, those with acute and subacute thyroiditis, Graves' disease, thyroid-stimulating hormone (TSH) abnormalities, and those using radioactive iodine and steroids were excluded from the study. Nodules, classified as TR 1 according to ACR-TIRADS and being purely cystic, were not included in the study. Based on a statistical power of 99%, a Type I error rate of 0.01, an effect size of 0.4, and a two-tailed hypothesis test, the minimum required sample size was calculated as 606. Based on the existing criteria, results from 603 cases were obtained and included in the study.

### Procedure

Researchers questioned the cases through face-to-face interviews about thyroid disease, history of thyroid surgery, and drug use. Neck examinations were performed by doctors in terms of thyroid evaluation of the cases. Thyroid USG, thyroid FNAB, Tg and anti-Tg results were found by a system scan of the cases. The results of Tg, anti-Tg and thyroid USG just before the FNAB were included in the study. Pathology reports of those who

underwent thyroid surgery were evaluated. Preoperative Tg and anti-Tg results of patients who underwent surgery were evaluated, postoperative results were not included. Written informed consent forms were obtained from the patients.

A comparison was made between the detected Tg results and US thyroid nodule size, number, ACR-TIRADS classification, demographic characteristics, and FNAB results.

**Thyroid US and fine needle aspiration biopsy**

Detailed US evaluations of the patients were conducted before the FNAB procedure. Afterward, FNAB was conducted by an endocrinologist under USG guidance. Thyroid USG was performed by expert radiologists utilizing 5-12 MHz linear array transducers (GE LOGIQ 7). US features; a number of nodules, nodule size, echogenicity (anechoic:0 hyperechogenicity:1, isoechogenicity:1, hypoechogenicity:2, very hypoechogenicity:3, not determined: 1 ), nodule structure and composition (mixed: 1, spongiform:0, solid:2, cystic characteristics:0), shape (wider than tall:0 or taller than wider:3), margin (smooth:0, lobulated:2, irregular:2 or regular, extra-thyroidal extension:3), and the absence/presence of microcalcifications (3), macrocalcifications (1) and peripheral calcifications (2) were evaluated and scored according to 2017 ACR-TIRADS classification [12]. A nodule with less than 50% of its total surface area degenerated into cysts was referred to as a mixed solid-cystic nodule. Following the scoring, US nodule findings were classified according to ACR-TIRADS as below:

2 points: TR 2
3 points: TR 3
4-6 points: TR 4
7 points and above: TR 5

Those proven by pathology were classified as TR 6.

**Cytological evaluation**

All histopathological examinations were performed by a pathologist. 2017 Bethesda Thyroid Cytology results are classified according to the Cytopathology Reporting System:

I. Non-diagnostic or inadequate
II. Benign
III. Atypia of uncertain significance (AUS) or follicular lesion of uncertain significance (FLUS)
IV. Follicular neoplasm or a follicular suspected of neoplasm
V. Suspected of malignancy
VI. Malignant

Thyroid tissue samples were embedded in paraffin and stained with hematoxylin and eosin after being fixed in 10% neutral buffered formalin. Based on the 2017 World Health Organization classification, thyroid carcinoma was categorized.

**Thyroglobulin and anti-thyroglobulin testing**

Tg and anti-Tg tests were performed before the FNAB procedure and studied in the same laboratory. The electro-chemiluminescence immunoassay (Roche Diagnostics GmbH, Cobas e801, Mannheim, Germany) was used to measure serum Tg and anti-Tg. The unit for Tg was ng/dL, and for anti-Tg was IU/ml.

## Statistical analysis

Data were analyzed by using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and JAMOVI (version 2.6.44). The distribution of continuous variables was assessed using the Shapiro–Wilk test to determine the appropriateness of parametric or nonparametric statistical methods. Since most continuous variables did not meet the assumption of normality, nonparametric tests were preferred. The Mann–Whitney U test was used to compare continuous variables between two independent groups, while the Kruskal–Wallis test was applied for comparisons among three or more independent groups. These tests were selected due to their robustness in analyzing non-normally distributed data. Effect size analyses were performed to quantify the magnitude of group differences: rank-biserial correlation coefficients (rrb) were reported for Mann–Whitney U tests, and epsilon squared ($\varepsilon^2$) values were reported for Kruskal–Wallis tests. For rank-biserial correlation, effect sizes were interpreted as small ($0.10 \leq rrb < 0.30$), medium ($0.30 \leq rrb < 0.50$), and large ($rrb \geq 0.50$). For epsilon squared, effect sizes were classified as small ($0.01 \leq \varepsilon^2 < 0.06$), medium ($0.06 \leq \varepsilon^2 < 0.14$), and large ($\varepsilon^2 \geq 0.14$). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the relevant continuous variables and to determine optimal cut-off values. The Youden J index was used to identify the optimal cut-off point, calculated as sensitivity + specificity − 100. Spearman's rank correlation analysis was conducted to assess the

strength and direction of associations between continuous variables due to non-normal data distribution. Logistic regression analysis was performed to identify independent predictors of malignancy. The p-value < 0.05 was considered statistically significant.

## RESULTS

The mean age of 603 patients included in our study was 50.98±13.73 (min-max: 18-79). 85.1% of the patients were female. According to the FNAB results of the patients, 2.2% (n:13) were malignant and 12.4% (n:75) were non-diagnostic. The pathology results of all cases detected as malignant were compatible with papillary carcinoma.

According to the FNAB results (2017 Bethesda), the median Tg in the malignant group was 367 ng/dL and was found to be statistically significantly higher than in the benign group (p = 0.037) (Table 1, Figure 1). In cases with multiple nodules, a statistically significant increase in Tg levels was observed compared to cases with a single nodule (p=0.028).

Median Tg levels were statistically significantly higher in the TR 4, 5 groups than in the TR 2 and 3 groups (p<0.001). The demographic characteristics, comparisons of Tg level with FNAB results, and ACR-TIRADS score are given in Table 1 and Figure 2.

**Table 1. Comparison of thyroglobulin levels according to ACR-TIRADS, Bethesda, and demographic features.**

| **Variables** | | **Thyroglobulin level (ng/mL)** | **P** |
|---|---|---|---|
| Sex | **n(%)** | **Median (Q1-Q3)** | |
| Female | 513 (85.1) | 58.0 (22-166) | p=0.221* ES=0.053[a] |
| Male | 90 (14.9) | 63.4 (27.4-140) | |
| Number of Nodules[c] | | | |
| Single | 84 (15.5) | 41.1 (17.8-116) | P=0.028** ES=0.132[a] |
| Multiple | 427 (78.6) | 60.6 (25.5-175) | |
| FNAB Result (Bethesda) | | | |
| Non-diagnostic[d] | 75 (12.4) | 48.6 (20.8-96.8) | P=0.037** ES=0.0218[b] |
| Benign | 424 (70.3) | 59.1 (25.2-160) | |
| Atypia of undetermined significance | 87 (14.4) | 62.5 (16.8-161) | |
| Suspicion of follicular neoplasm | 1 (0.2) | 55.0 (55-55) | |
| Suspicious malignant | 3 (0.5) | 50.1 (38-72.1) | |
| Malignant | 13 (2.2) | 367 (91.5-500) | |
| ACR-TIRADS score | | | |
| TR 2 | 124 (20.6) | 31.6 (17.9-69.2) | P<0.001** ES=0.188[b] |
| TR 3 | 224 (37.1) | 44.3 (19.8-80.9) | |
| TR 4 | 217 (35.9) | 127 (44.2-270.6) | |
| TR 5 | 38 (6.3) | 245 (96-500) | |

n: number, %: percent, Q1: 25th percentile, Q3: 75th percentile, p<0.05 statistically significant, *Mann-Whitney U test, **Kruskal Wallis test; ES=Effect size (criterion showing the strength of the relationship), FNAB=Fine needle aspiration biopsy
a: Rank biserial effect sizes were calculated for the Mann-Whitney U test.
b: Epsilon squared effect sizes were calculated for the Kruskal Wallis test.
c: The nodule number of 32 patients was unknown and was excluded from the analysis.
d: Non-diagnostic group was excluded from all analytical tests.

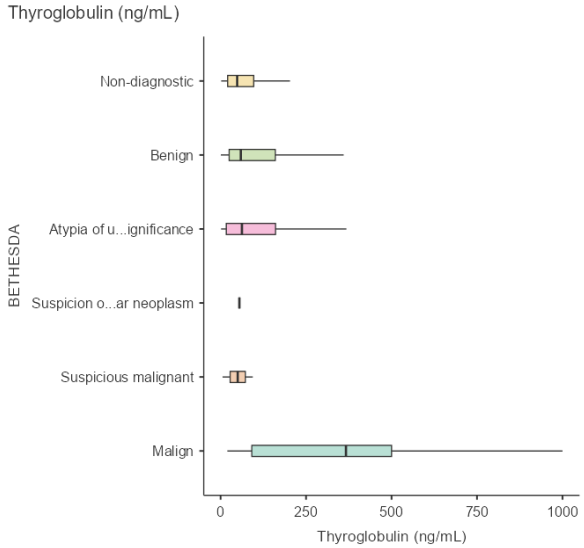



**Figure 1. Thyroglobulin levels according to BETHESDA class (box-plot plot)**

In the figure, the right-most end of the horizontal lines represents the largest value, and the left-most end represents the smallest value. The lower left border of the boxes represents quartile 1, the inside line represents median value, and the upper right border represents quartile 3; Note: All patients were included in the analysis.

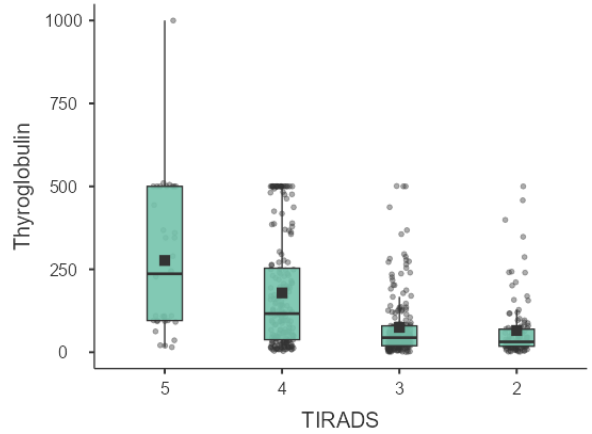



**Figure 2. Thyroglobulin levels according to ACR-TIRADS score (box-plot plot)**

In the figure, the lower edge of the green boxes corresponds to the 25th percentile, and the upper edge corresponds to the 75th percentile. The black line inside the green boxes indicates the median (50th percentile) value. The small black squares inside the green boxes represent the arithmetic mean; The non-diagnostic group was excluded from the ACR-TIRADS score.

In the correlation analyses between Tg, ACR-TIRADS score, and nodule characteristics, a weak positive correlation was found between Tg level and nodule sizes (0.344, 0.337), and a very weak negative correlation with age (-0.107). Again, a moderate positive correlation was found between the Tg level and ACR-TIRADS score (0.410) (Table 2).

**Table 2. Spearman correlation matrix**

| Variable | | Thyroglobulin (ng/mL) | BETHESDA | TIRADS | Size (long) | Size (short) | Age | Nodule Number |
|---|---|---|---|---|---|---|---|---|
| TIRADS | r | 0.391*** | 0.337*** | — | | | | |
| | n | 543 | 543 | — | | | | |
| Size (long) | r | 0.344*** | -0.019 | 0.033 | — | | | |
| | n | 540 | 540 | 540 | — | | | |
| Size (short) | r | 0.337*** | -0.015 | 0.018 | 0.900*** | — | | |
| | n | 512 | 512 | 512 | 512 | — | | |
| Age | r | -0.107* | -0.035 | -0.029 | -0.023 | -0.024 | — | |
| | n | 543 | 543 | 543 | 540 | 512 | — | |
| Nodule Number | r | 0.085 | -0.050 | -0.069 | 0.034 | 0.033 | 0.125** | — |
| | n | 511 | 511 | 511 | 511 | 486 | 511 | — |

* p < .05, ** p < .01, *** p < .001. All patients were included in the analysis.

The diagnostic role of the thyroglobulin value in predicting malignancy was investigated using ROC analysis (AUC=0.678, p=0.019), and the optimum cut-off value for Tg was found to be 245 ng/dL (sensitivity=53.3%, specificity=84.6%) (Figure 3 and Table 3).

**Table 3. The optimum cut-off value for Thyroglobulin (ng/mL)**

| Cutpoint | Sensitivity (%) | Specificity (%) | Youden's index |
|---|---|---|---|
| 200.1 | 53.33% | 79.73% | 0.331 |
| 201 | 53.33% | 79.92% | 0.333 |
| 202.2 | 53.33% | 80.11% | 0.334 |
| 203 | 53.33% | 80.3% | 0.336 |
| 207 | 53.33% | 80.49% | 0.338 |
| 208.4 | 53.33% | 80.68% | 0.340 |
| 210 | 53.33% | 80.87% | 0.342 |
| 211 | 53.33% | 81.06% | 0.344 |
| 215 | 53.33% | 81.25% | 0.346 |
| 217 | 53.33% | 81.44% | 0.348 |
| 219 | 53.33% | 81.63% | 0.350 |
| 224 | 53.33% | 81.82% | 0.352 |
| 226 | 53.33% | 82.01% | 0.353 |
| 228 | 53.33% | 82.2% | 0.355 |
| 229 | 53.33% | 82.39% | 0.357 |
| 231 | 53.33% | 82.58% | 0.359 |
| 232 | 53.33% | 82.77% | 0.361 |
| 235 | 53.33% | 82.95% | 0.363 |
| 236.1 | 53.33% | 83.14% | 0.365 |
| 237 | 53.33% | 83.33% | 0.367 |
| 240 | 53.33% | 83.71% | 0.370 |
| 241 | 53.33% | 84.28% | 0.376 |
| 243 | 53.33% | 84.47% | 0.378 |
| **245** | 53.33% | 84.66% | **0.380** |
| 272 | 46.67% | 86.55% | 0.332 |
| 274 | 46.67% | 86.74% | 0.334 |
| 277.3 | 46.67% | 86.93% | 0.336 |
| 278 | 46.67% | 87.12% | 0.338 |
| 282 | 46.67% | 87.31% | 0.340 |
| 287 | 46.67% | 87.5% | 0.342 |
| 288 | 46.67% | 87.69% | 0.344 |
| 289.9 | 46.67% | 87.88% | 0.345 |

AUC (Area under curve):0.678

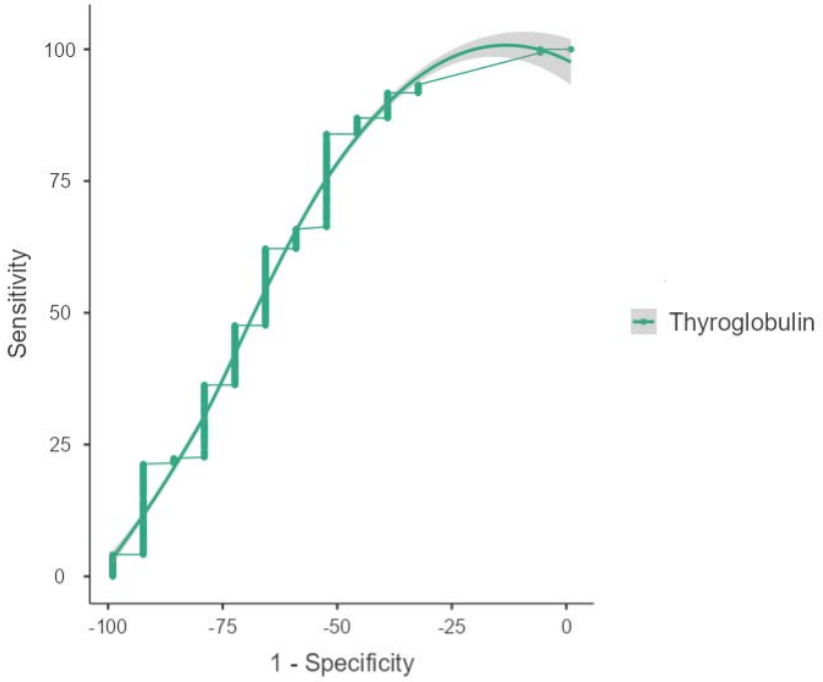



**Figure 3. ROC curve for predicting thyroid malignancy according to BETHESDA classification based on thyroglobulin (ng/mL).**

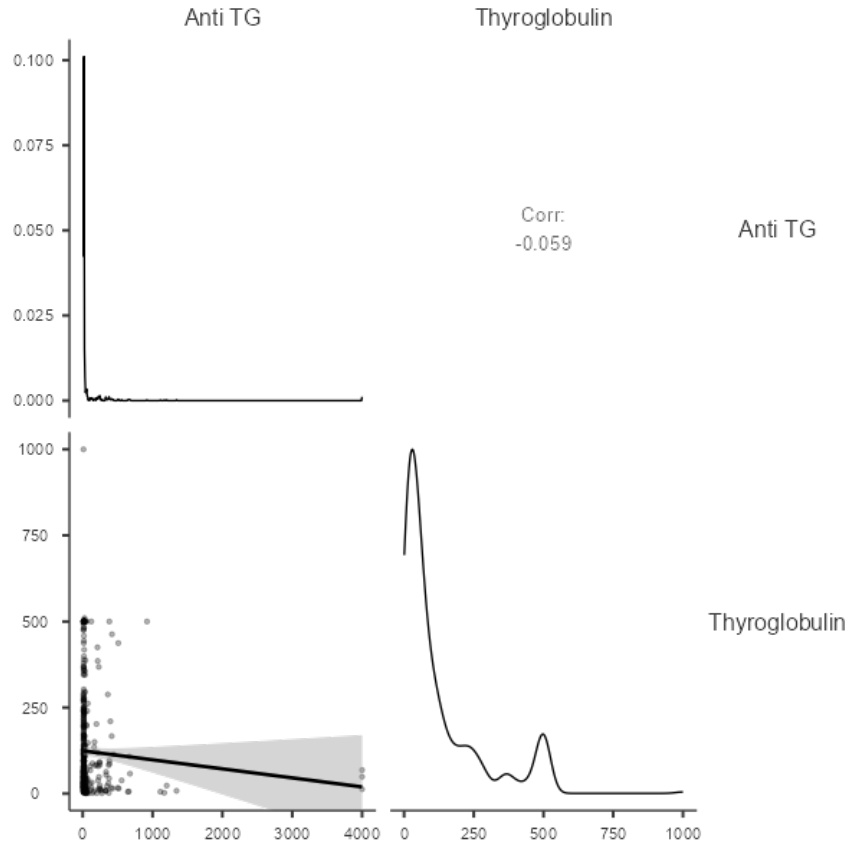
The non-diagnostic group was not included in the ROC analysis. According to the BETHESDA classification, benign and atypia of undetermined significance groups were accepted as benign, and suspicion of follicular neoplasm, suspicious malignant, and malignant groups were accepted as malignant.

A logistic regression model was constructed to estimate the risk of malignancy in thyroid nodules. The overall model was statistically significant according to the omnibus test ($p = 0.002$). Independent variables included in the model were age, gender, longitudinal nodule size, and serum thyroglobulin level. These variables were selected based on their established clinical relevance in thyroid malignancy risk assessment and their statistical association with malignancy in univariate analyses. Among the variables included in the model, serum thyroglobulin level was identified as an independent predictor for malignancy. Each one-unit increase in thyroglobulin level was associated with a 1.005-fold increase in the odds of the nodule being malignant (Table 4). In the correlation analysis performed to evaluate whether anti-Tg affected the Tg results, no significant correlation was found between Tg and anti-Tg (Figure 4).

**Table 4. Logistic regression analysis for malignancy prediction**

| Variable | B | P. | OR | 95% CI. for OR | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Age | -.019 | .404 | .981 | .937 | 1.026 |
| Gender | .929 | .184 | 2.531 | .643 | 9.964 |
| Long size | -.061 | .081 | .941 | .878 | 1.008 |
| Thyroglobulin | .005 | **.008** | **1.005** | 1.001 | 1.008 |
| Constant | -1.982 | .132 | .138 | | |

Note: B: beta, OR: Odds Ratio, $p<0.05$ statistically significant




Note. * p < .05, ** p < .01, *** p < .001

**Figure 4. Correlation graphics of thyroglobulin levels with anti-thyroglobulin levels.**

## DISCUSSION

Thyroid nodular disease and malignancies are frequently studied subjects due to their high prevalence worldwide. Although many approaches have been developed for FNAB and surgical planning for thyroid nodules, full consensus has not been achieved. Discussions and updates are still ongoing. Although the Tg molecule is specific to the thyroid gland, its predictive importance in thyroid pathologies has not been clarified. Again, there are not enough studies in the literature on the relationship of Tg with nodule characteristics and the role of this relationship in predicting malignancy. Actually, our study may be the most organized study on this subject, evaluating Tg and US nodule characteristics and ACR-TIRADS. In our study, we have obtained results that can guide in this respect.

There are studies investigating the role of Tg alone in differentiated thyroid cancers; however, the use of elevated Tg levels as a tumor marker for predicting malignancy has yielded conflicting results [13-15]. Among the studies on this subject, Melik et al. prospectively evaluated 203 cases who underwent total thyroidectomy, and found that preoperative Tg was significantly higher in malignant patients. They reported that a Tg level above 102 ng/dL served as a predictive cutoff value [16]. Similarly, Kars et al. evaluated 133 patients who underwent total thyroidectomy and demonstrated that the preoperative Tg levels were significantly higher in patients with differentiated thyroid malignancy [17]. In

a large-scale study involving 2,130 cases, Wang H et al. reported that preoperative Tg elevation was significant, particularly in thyroid cancers with lymph node metastasis. They suggested that when evaluated together with USG and age factors, preoperative Tg could make an additional contribution to more accurate staging [18]. In contrast, Youn et al., in their retrospective analysis of 374 cases, reported that Tg levels increased in correlation with nodule size and thyroid volume; however, they found no significant difference between benign and malignant cases[14]. Likewise, Kihara et al. reported no significant difference in preoperative Tg levels between benign and malignant cases in their study of 445 patients who underwent surgery for thyroid nodular disease[19]. In our study, preoperative Tg levels were significantly higher in patients with malignant disease, in accordance with studies suggesting that preoperatively elevated Tg levels may predict thyroid malignancy. We have found the Tg predictive cut-off value for malignancy as 245 ng/dL. In addition, the fact that there was no significant correlation between Tg results and anti-Tg results in our study supports the reliability of the results. However, it is possible that different patient populations may yield different threshold values. Therefore, the proposed cutoff value of 245 ng/dL should be considered a hypothesis generated by this study and requires validation in future studies before it can be recommended for clinical use.

Evaluation of thyroid nodules in terms of malignancy with FNAB according to their US appearance features is used as the basic management method [20,21]. Studies exist to identify nodules that carry a risk of malignancy based on ultrasonography findings. However, the widespread use of US has markedly increased thyroid nodule detection, resulting in excessive FNAB procedures and the overdiagnosis of low-risk thyroid cancers. These developments have raised concerns regarding overutilization and overtreatment [22,23]. In recent years, the ATA, European Society for Medical Oncology (ESMO), European Thyroid Association (ETA), and TI-RADS guidelines have been published in various forms due to the conflicting results in these studies, the lack of a clear consensus, and issues with over-processing and over-diagnosis [22,24]. Foroughi et al. stated in their study that evaluations to be made in the light of TI-RADS may reduce the frequency of unnecessary FNAB applications [25]. Studies conducted in accordance with these guidelines have consistently identified several US features associated with malignancy, including nodule size, solid composition, marked hypoechogenicity, irregular margins, microcalcifications, heterogeneous echotexture, a taller-than-wide shape, and the presence of cervical lymphadenopathy [20-24,26,27]. In light of the evaluations of these findings and the scoring guidelines, suggestions were made to perform FNAB and to continue further evaluations [20-24,26,27].

According to the 2017 American College of Radiology (ACR) TI-RADS classification, the estimated malignancy risk is <2% for TR1 and TR2 nodules, 2–5% for TR3, 5–20% for TR4, and >20% for TR5[12]. Subsequently, numerous studies have investigated the concordance between malignancy risk stratification by ACR TI-RADS and the Bethesda cytopathology system, yielding heterogeneous results. Consequently, this issue remains an area of ongoing investigation [28-31]. In light of the studies mentioned above, problems and uncertainties remain in estimating malignancy risk when decisions about FNAB are based solely on radiological evaluations. Particularly, contradictory findings in comparative studies between TIRADS and Bethesda, and the wide gap in the assessment of malignancy risk in TIRADS 5, such as >20%, appear to be notable handicaps. After ACR-TIRADS, updates such as K-TIRADS, C-TIRADS, and EU-TIRADS have been introduced to reduce these handicaps. In the present study, elevated serum Tg levels were found to be associated with higher ACR TI-RADS categories. The significantly higher Tg levels observed in TR 4-5 compared to TR 2 and 3 may highlight the importance of Tg in predicting preoperative thyroid malignancy and making FNAB decisions. At this point, evaluating Tg elevation together with the ACR-TIRADS may provide additional contributions in predicting malignancy and making FNAB decisions.

Although the thyroid gland has been extensively studied, no study has been found in the literature regarding the characteristic features of thyroid nodules and the Tg relationship. Gao et al. in their study on pregnant women in China, compared Tg levels between those with and without thyroid nodular disease and found that Tg was significantly higher in cases with nodules. They also stated that Tg elevation may be a functional biomarker for thyroid nodules and goiter [32]. Gurkan et al. when they evaluated the preoperative Tg values of 298 surgical cases and specimen pathology reports, found that Tg was significantly higher in cases with nodular goiter compared to goiter due to lymphocytic thyroiditis

and other pathologies [33]. While these studies indicate that Tg levels are elevated in nodular thyroid disease, they do not provide insight into the association between Tg levels and specific structural or ultrasonographic features of thyroid nodules. Our study is the first to evaluate Tg together with the ACR-TIRADS classification and yielded compatible results. Again, according to the results of our study, Tg levels increased with multiple nodules and nodule size. In the latest ATA guideline published in 2025, preoperative measurement of Tg was also discussed, and routine preoperative measurement was not recommended because of its limited diagnostic accuracy. However, this guideline again does not include a perspective on Tg and thyroid nodule characteristics [34]. As discussed above, the predictive value of Tg elevation for thyroid malignancy remains complex. Evaluating Tg levels not in isolation but in combination with ACR TI-RADS classification may offer a novel perspective for malignancy risk stratification. Our study is valuable because of the information it provides on this subject, but it is obvious that more organized and randomized prospective studies are needed.

The limitations of our study include its single-center and retrospective nature, and the low number of malignancy cases. Additionally, while the 2.2% malignancy rate in our study reflects the real-world prevalence, the small number of malignant cases limits the statistical power to draw robust conclusions. However, the total number of cases is quite high, and it is the first study with meaningful results on the subject.

As a conclusion, our study showed that Tg is elevated in thyroid nodular disease, especially in malignant nodules. It has made a valuable contribution to the literature, especially since the Tg level increased in parallel with the increase in the ACR-TIRADS malignancy-risk score. It is thought that, if these results are supported by other studies, the evaluation of Tg together with ACR-TIRADS may make an additional contribution to the FNAB decision and the prediction of thyroid malignancies. Developments in this direction may reduce the amount of invasive FNAB with potential complications and may also produce cost-effective results in terms of cost burden. Further studies are needed on the relationship between Tg and nodule characters and TIRADS to better understand the role of the Tg molecule in thyroid diseases, especially in predicting malignancies.

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