

Preoperative Thyroglobulin and Thyroid Pathologies: A Single Center Experience

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Received: Aug 26, 2025

Revised: Sep 24, 2025

Accepted: Nov 04, 2025

First Published: Nov 12, 2025

Introduction: Thyroid nodules are frequently found in the general population, though malignancy is confirmed in only a minority of cases. Distinguishing between benign and malignant nodules before surgery is vital for appropriate clinical management. The utility of preoperative serum thyroglobulin (Tg) levels as a diagnostic marker in thyroid carcinomas remains controversial. This study aimed to provide a descriptive overview of patients with markedly elevated preoperative Tg levels (>500 ng/mL) and their corresponding histopathological outcomes.

Methods: A retrospective, single-center study was conducted at Smart Health Tower, which included patients who underwent surgical interventions for thyroid disorders between 2019 and 2025, with preoperative serum Tg levels exceeding 500 ng/mL. Patients were excluded if they had incomplete medical records. Patient demographics, clinical features, preoperative findings, surgical details, and final histopathology were retrieved from electronic medical records.

Results: A total of 260 patients were included, predominantly female (73.08%), with a median age of 49 years (QR: 38–61). Neck swelling was the most common symptom (63.08%). Ultrasonography showed follicular nodular disease in 60.0%. Fine-needle aspiration cytology revealed Bethesda II in 20.0%, IV in 13.85%, and VI in 11.15% of cases. Total thyroidectomy was performed in 74.62% of cases. Histopathology showed benign lesions in 70.77% and malignant lesions in 29.23% of the cases.

Conclusion: Preoperative Tg levels may be elevated in both benign and malignant thyroid disorders; however, Tg may not possess adequate diagnostic precision to be used as a sole indicator of malignancy.

Keywords: Thyroglobulin, Thyroid nodules, Thyroid cancer, Papillary thyroid carcinoma

How to cite this article: Ahmed SF, Ali RM, Ali RM, Abdullah AM, Salih AM, Baba HO et al. Preoperative Thyroglobulin and Thyroid Pathologies: A Single Center Experience. Judi Clin. J. 2025;1(2):71-75. <https://doi.org/10.70955/JCJ.2025.9>

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1. Introduction

Thyroid nodules are highly prevalent in the general population, with ultrasonography identifying them in up to 60% of individuals. Despite their frequency, approximately 5% are malignant [1, 2].

Primary thyroid carcinoma is the most common endocrine malignancy and is broadly classified into follicular epithelial-derived and non-follicular epithelial-derived tumors. Tumors of follicular epithelial origin include differentiated thyroid carcinoma (DTC), poorly differentiated carcinoma, and undifferentiated (anaplastic) carcinoma. DTC, which encompasses papillary thyroid carcinoma (PTC), follicular thyroid carcinoma, and oncocytic (previously Hürthle), accounts for approximately 95% of all thyroid malignancies [3, 4].

Accurate preoperative identification of thyroid nodules as benign or malignant is essential for guiding appropriate treatment

decisions [3]. Initial evaluation commonly involves thyroid ultrasound, which plays a vital role in differentiating benign from malignant nodules. Complementary diagnostic techniques, such as contrast-enhanced ultrasound and ultrasonic elastography, provide additional insight. Among these, ultrasound-guided fine needle aspiration (FNA) is considered the most reliable method for diagnosing DTC prior to surgery. However, the accuracy of both ultrasound and FNA can be affected by factors including nodule size, sonographic features, and the clinician's experience [5].

Reliable serum biomarkers are also essential for diagnosing and managing DTC. Thyroglobulin (Tg), a large glycoprotein composed of 2750 amino acids with a molecular weight of approximately 330 kilodaltons, is synthesized and secreted by thyroid follicular epithelial cells. It is primarily localized within thyroid follicular structures, with only minimal quantities circulating in the bloodstream under normal physiological conditions [6]. In patients

with DTC who have undergone total thyroidectomy, particularly those who receive radioactive iodine (I-131) therapy, serum Tg functions as a valuable biomarker for assessing residual thyroid tissue, disease recurrence, and distant metastases, as its presence in the circulation postoperatively is typically indicative of persistent or recurrent disease [3].

The clinical significance of preoperative Tg levels as a diagnostic and prognostic tool in thyroid carcinomas remains a subject of ongoing debate [3]. This study aimed to provide a descriptive overview of patients with markedly elevated preoperative Tg levels (>500 ng/mL, reference range 3–40 ng/mL) and their corresponding histopathological findings following thyroid surgery. All references were evaluated for eligibility using reputable predatory journal lists to ensure scholarly integrity [7].

2. Methods

2.1. Study Design

This retrospective, single-center study was conducted at the Smart Health Tower (Sulaymaniyah, Iraq) and included patients who underwent surgical interventions for thyroid disorders between 2019 and 2025. The study received approval from the Kscien Organization's Ethics Committee under registration number 40 in 2025.

2.2. Inclusion Criteria

The study included only patients who had elevated preoperative serum Tg levels exceeding 500 ng/mL. The threshold of 500 ng/mL was selected because it represents a markedly abnormal elevation well beyond the ranges commonly reported in both benign and malignant thyroid disease in previous studies [8–14]. In addition, this value corresponded to the upper reporting limit of our institutional laboratory assay, which does not quantify Tg concentrations above 500 ng/mL.

2.3. Eligibility Criteria

Patients were excluded if they had incomplete medical records.

2.4. Data Collection

Demographic and clinical data were retrieved from electronic medical records. The variables collected included age, sex, occupation, relevant medical history, presenting symptoms, results of preoperative imaging and laboratory investigations, Bethesda category, type of surgery performed, and final histopathological diagnosis.

2.5. Statistical Analysis

All collected data were entered into Microsoft Excel and subsequently analyzed using IBM SPSS (Statistical Package for the Social Sciences), version 27.0. Continuous variables were presented as means with standard deviations or medians with quartile ranges, as appropriate, while categorical variables were summarized using frequencies and percentages.

3. Results

3.1. Patient Demographics

A total of 260 patients were included in this study. The majority were female (n = 190, 73.08%), while the remaining 70 patients (26.92%) were male. The median age was 49 years (QR: 38–61). The highest frequency of patients was observed in the 40–49 age group (n = 61, 23.46%), followed by the 50–59 age group (n = 53, 20.38%). In terms of smoking, 216 patients (83.08%) were non-smokers. The most common occupation among the patients

was homemaker (n = 150, 57.69%) (Table 1).

3.2. Medical and Surgical History

Two hundred forty-three patients (93.46%) had no past medical conditions. Hypertension was present in 13 patients (5.0%). Most patients (n = 238, 91.54%) had no prior surgical history. Nineteen patients (7.30%) had previously undergone total thyroidectomy, and 2 (0.77%) had undergone right thyroid lobectomy (Table 1).

Table 1. Patient Demographics and Medical Backgrounds

Parameters	Frequency (%)
Gender	
Female	190 (73.08%)
Male	70 (26.92%)
Age (year)	
< 20	5 (1.92%)
20 – 29	18 (6.92%)
30 – 39	50 (19.23%)
40 – 49	61 (23.46%)
50 – 59	53 (20.38%)
60 – 69	48 (18.46%)
70 – 79	24 (9.23%)
> 80	1 (0.38%)
Median (QR)	49 (38 – 61)
Mean ± SD	49.14 ± 14.76
Smoking status	
Active smoker	30 (11.54%)
Passive smoker	13 (5.00%)
Former smoker	1 (0.38%)
Non-smoker	216 (83.08%)
Occupation	
Homemaker	150 (57.69%)
Teacher	15 (5.77%)
Unemployed	11 (4.23%)
Retired	11 (4.23%)
Police officer	6 (2.31%)
Student	5 (1.92%)
Butcher	1 (0.38%)
Engineer	1 (0.38%)
Farmer	1 (0.38%)
Healthcare personnel	1 (0.38%)
Others	58 (22.31%)
Medical history*	
Unremarkable	243 (93.46%)
Hypertension	13 (5.0%)
Diabetes mellitus	7 (2.69%)
Heart disease	4 (1.54%)
Asthma	1 (0.38%)
Deaf	1 (0.38%)
Stroke	1 (0.38%)

Table 1. Continued...**Past surgical history**

Unremarkable	238 (91.54%)
Total thyroidectomy	19 (7.30%)
Right thyroid lobectomy	2 (0.77%)
CABG	1 (0.38%)

*: Some patients had multiple medical conditions, **CABG**: Coronary artery bypass graft, **IQR**: Interquartile range, **SD**: Standard deviation

3.3. Presenting Symptoms and Laboratory Findings

The most common presenting symptom was neck swelling, reported in 164 patients (63.08%), while 76 patients (29.23%) were asymptomatic. All patients had preoperative elevated serum Tg levels exceeding 500 ng/mL. Thyroid-stimulating hormone (TSH) levels were within the normal range in 178 patients (68.46%) ([Table 2](#)).

3.4. Ultrasonographic and Fine-Needle Aspiration Findings

Ultrasonographic evaluation revealed thyroid follicular nodular disease (TFND) in 156 patients (60.0%), right thyroid lobe nodules in 44 (16.92%), and left lobe nodules in 32 (12.31%). According to the TI-RADS classification, most nodules were TR3 (n = 172, 66.15%), followed by TR4 (n = 53, 20.38%) and TR5 (n = 22, 8.46%). FNA findings based on the Bethesda system were available for 141 patients (54.23%). The most frequent categories were Bethesda II (n = 52, 20.0%), Bethesda IV (n = 36, 13.85%), and Bethesda VI (n = 29, 11.15%) ([Table 2](#)).

Table 2. Clinical Presentations and Diagnostic Evaluations

Parameters	Frequency (%)
Presentations	
Neck swelling	164 (63.08%)
Weakness	11 (4.23%)
Dyspnea	3 (1.15%)
Voice change	3 (1.15%)
Others	3 (1.15%)
Asymptomatic	76 (29.23%)
Thyroglobulin (ng/mL)	
> 500.0	260 (100.0%)
TSH level (mIU/L)	
Below normal range (<0.4)	43 (16.54%)
Within normal range (0.4–4.0)	178 (68.46%)
Above normal range (>4.0)	39 (15.0%)
Ultrasonography findings	
TFND	156 (60.0%)
Right thyroid lobe nodule	44 (16.92%)
Left thyroid lobe nodule	32 (12.31%)
Multiple suspicious LNs	10 (3.85%)
Remnant thyroid tissue	5 (1.92%)
Gravis disease	4 (1.54%)
Recurrent TFND	4 (1.54%)

Isthmus nodule	1 (0.38%)
Thyroiditis	1 (0.38%)
N/A	3 (1.15%)

TI-RADS classification *

TR3 (Mildly Suspicious)	172 (66.15%)
TR4 (Moderately Suspicious)	53 (20.38%)
TR5 (Highly Suspicious)	22 (8.46%)
TR2 (Not Suspicious)	5 (1.92%)
TR1 (Benign)	1 (0.38%)
N/A	14 (5.38%)

FNA (Bethesda Categories) **

Bethesda II	52 (20.0%)
Bethesda IV	36 (13.85%)
Bethesda VI	29 (11.15%)
Bethesda III	10 (3.85%)
Bethesda I	7 (2.69%)
Bethesda V	10 (3.85%)
N/A	119 (45.77%)

*: **TI-RADS** classifications were assigned to multiple nodules in certain patients, **: Some patients underwent FNA more than once, **TFND**: Thyroid follicular nodular disease, **N/A**: Not available, **TI-RADS**: Thyroid imaging reporting and data system, **FNA**: Fine needle aspiration, **LN**: Lymph node

3.5. Surgical Intervention

Surgical intervention consisted predominantly of total thyroidectomy (n = 194, 74.62%). Central neck dissection was performed in 18 patients (6.92%), while lateral neck dissection was carried out in 11 patients (4.23%) ([Table 3](#)).

3.6. Histopathological Findings

Histopathological analysis showed that the most common diagnosis was TFND (n = 115, 44.23%), followed by PTC in 56 patients (21.54%). Among PTC cases, the conventional variant was the most frequent (n = 38, 67.86%). Hyperplastic nodules were reported in 28 patients (10.77%), and adenomatoid nodules in 10 (3.85%). In total, 184 patients (70.77%) were diagnosed with benign pathology, whereas 76 patients (29.23%) were confirmed to have malignant disease ([Table 3](#)).

Table 3. Surgical Procedures, Diagnoses, and Outcomes

Parameters	Frequency (%)
Type of operation	
Total Thyroidectomy	194 (74.62%)
Thyroid lobectomy	46 (17.69%)
Thyroid nodulectomy	15 (5.77%)
Completion lobectomy	2 (0.77%)
Isthmusectomy	2 (0.77%)
Revision of thyroid remnant	1 (0.38%)
Central neck dissection	
Bilateral central neck dissection	8 (3.08%)

Table 3. Continued...

Right central neck dissection	6 (2.31%)
Left central neck dissection	4 (1.54%)
Not performed	242 (93.07%)
Lateral neck dissection	
Left lateral neck dissection level	5 (1.92%)
Right lateral neck dissection level	5 (1.92%)
Bilateral lateral neck dissection level	1 (0.38%)
Not performed	249 (95.77%)
Histopathological diagnosis	
TFND	115 (44.23%)
PTC	56 (21.54%)
<i>Conventional variant of PTC</i>	38 (67.86%)
<i>Conventional variant of PTMC</i>	9 (16.07%)
<i>Conventional and follicular variants of PTC</i>	3 (5.35%)
<i>Follicular variant of PTC</i>	2 (3.57%)
<i>Tall cell variant of PTC</i>	2 (3.57%)
<i>Conventional and trabecular variants of PTC</i>	1 (1.79%)
<i>Infiltrative follicular subtype of PTC</i>	1 (1.79%)
Hyperplastic nodule	28 (10.77%)
Adenomatoid nodule	10 (3.85%)
Minimally invasive follicular carcinoma	9 (3.46%)
NIFTP	7 (2.69%)
Follicular adenoma	6 (2.31%)
Graves' Disease	6 (2.31%)
Hashimoto's thyroiditis	4 (1.54%)
Oncocytic adenoma	3 (1.15%)
Oncocytic cell carcinoma	3 (1.15%)
Differentiated high-grade thyroid carcinoma	2 (0.77%)
Hyalinizing trabecular adenoma	2 (0.77%)
Benign cystic thyroid colloid nodule	1 (0.38%)
Collision tumors (PTC and high-grade FTC)	1 (0.38%)
Collision tumors (PTC and Oncocytic cell carcinoma)	1 (0.38%)
Follicular thyroid carcinoma	1 (0.38%)
FT-UMP	1 (0.38%)
Insular thyroid carcinoma	1 (0.38%)
Infarcted oncocytic cell lesion	1 (0.38%)
Invasive EFVPTC	1 (0.38%)
MTC	1 (0.38%)
Malignancy Status	
Benign	184 (70.77%)
Malignant	76 (29.23%)

EFVPTC: Encapsulated follicular variant of papillary thyroid carcinoma, **FT-UMP:** Follicular tumor of uncertain malignant potential, **MTC:** Medullary thyroid carcinoma, **NIFTP:** Non-invasive follicular thyroid neoplasm with papillary-like nuclear features, **PTMC:** Papillary thyroid microcarcinoma, **PTC:** Papillary thyroid carcinoma

4. Discussion

The production of Tg is influenced by various internal physiological factors, such as hyperthyroidism due to Graves' disease, TSH levels, and the size of the thyroid gland and nodules [15]. Tg binds covalently to iodine and is stored in the follicular lumen until stimulated by TSH, which triggers its reabsorption into thyroid cells and its enzymatic breakdown into the active thyroid hormones, T3 and T4. These hormones are then released into the bloodstream and can be measured using peripheral blood assays. While T3 and T4 are the primary hormones secreted, small amounts of Tg also enter the circulation and can be detected at low levels in healthy individuals with normal thyroid function. However, in individuals with DTCs originating from follicular cells, Tg appears to be actively secreted [15].

Since Tg is produced solely by thyroid follicular cells, measuring its levels in the blood following a total thyroidectomy for thyroid cancer has become a standard approach for identifying persistent or recurrent disease. A serum Tg concentration of 1.0 ng/mL or higher is considered a highly reliable indicator of tumor recurrence [15].

Ultrasonography and FNA are primary diagnostic tools used to distinguish benign from malignant thyroid nodules before surgery. While FNA is commonly employed for this purpose, both methods have notable limitations, particularly in accurately differentiating benign from malignant follicular tumors [3]. As a result, approximately 20% to 30% of thyroid nodules still require surgical intervention to obtain a definitive pathological diagnosis following FNA [3]. The current study's findings support this observation, as FNA results were available for only about half of the patients (54.23%), and a substantial proportion of nodules, especially those classified as Bethesda category IV or VI, still required surgical confirmation.

Preoperative serum Tg levels are advantageous due to their convenience, rapid availability, and consistent reproducibility. However, their effectiveness in differentiating benign from malignant thyroid nodules before surgery has not been conclusively established. Despite this, many studies have investigated the potential of preoperative Tg levels for this purpose in diverse patient populations [3].

Several studies have demonstrated a significant association between elevated preoperative Tg levels and the presence of thyroid malignancy. Melik et al. (2022) prospectively measured Tg levels in 203 patients undergoing total thyroidectomy and found that patients with PTC had significantly higher Tg levels (105.05 ng/mL) compared to those with benign disease (76.80 ng/mL). A receiver operating characteristic analysis identified a cutoff value of 102 ng/mL, with the difference reaching statistical significance ($P < 0.05$) [8]. Similarly, Petric et al. (2012) observed higher preoperative Tg levels in PTC patients relative to those with benign nodules [9]. Jin et al. (2022) further supported this association in a cohort study that included 500 PTC patients, 376 with benign nodules, and 125 healthy controls. After excluding patients positive for Tg antibodies, they reported significantly higher Tg levels in PTC patients (42.87 ng/mL) compared to those with benign nodules (33.13 ng/mL) and healthy individuals (14.90 ng/mL), though the difference between the benign and healthy groups was not significant [10]. In the present study, PTC was the most prevalent subtype among malignant cases. The conventional variant was the most common among these, representing 67.86% of the PTC cases.

In a broader evaluation, Lu et al. (2024) conducted a systematic review and meta-analysis. They found that, among patients with indeterminate cytology and negative Tg antibodies, those with malignant nodules had significantly higher serum Tg levels than those with benign nodules (OR = 2.59, 95% CI: 1.59–4.21, $P < 0.001$) [3].

Conversely, several studies have reported the opposite trend, with lower preoperative Tg levels observed in patients with DTC compared to those with benign thyroid nodules. Zhang et al. (2022) analyzed 1,519 DTC cases and 571 benign cases, finding significantly lower Tg levels in the DTC group (15.7 ng/mL vs. 52.1 ng/mL, $P < 0.001$) [11]. Aydogu et al. (2023) similarly found that patients with benign nodules had higher Tg levels than those with DTC (85.0 ng/mL vs. 27.15 ng/mL, $P < 0.001$) [12]. Kang et al. (2022) reported consistent findings, noting lower average Tg levels in DTC patients (238 ± 77 ng/mL) compared to those with benign nodules (532 ± 97 ng/mL, $P = 0.02$) [13]. Patel et al. (2019) echoed this trend, with a median Tg level of 167.5 ng/mL in benign cases compared to 30.8 ng/mL in malignant ones ($P < 0.001$) [14].

The present study found that only 29.23% of the cases were diagnosed with thyroid malignancy, primarily PTC, while the majority (70.77%) had benign pathology, predominantly TFND. These results align with those of Zhang et al. [11], Aydogdu et al. [12], Kang et al. [13], and Patel et al. [14], highlighting the limited specificity of preoperative Tg in differentiating malignant from benign thyroid conditions. The high Tg levels observed in both malignant and benign cases suggest that, although Tg may provide supplementary information in certain clinical contexts, it lacks sufficient diagnostic accuracy to be relied upon as a standalone marker for malignancy in the preoperative setting. These findings support the conclusion that preoperative Tg testing alone is unreliable for distinguishing between benign and malignant thyroid nodules.

A key strength of the study is the inclusion of a relatively large sample size from a single tertiary center with standardized surgical and pathological protocols, ensuring consistency in data collection and analysis. Additionally, excluding cases with incomplete records enhanced data reliability, and comparing cytological, radiological, and histopathological findings enabled a comprehensive assessment.

However, several limitations should be acknowledged. The retrospective design inherently carries a risk of selection and information bias. As a single-center study, the findings may not be generalizable to other populations or institutions with differing referral patterns or laboratory assays. Furthermore, thyroglobulin levels above 500 ng/mL could not be quantified precisely due to the assay's upper limit, which may have limited the ability to explore potential dose-response relationships. Finally, the absence of long-term postoperative follow-up data precluded evaluation of the prognostic significance of preoperative thyroglobulin levels.

5. Conclusion

Preoperative Tg levels may be elevated in both benign and malignant thyroid disorders; however, Tg may not possess adequate diagnostic precision to be used as a sole indicator of malignancy.

Declarations

Conflicts of interest: The authors have no conflicts of interest to disclose.

Ethical approval: Ethical approval was obtained from the "Kscien Organization's Ethics Committee under registration number 40 in 2025.

Consent for participation: Not applicable.

Consent for publication: Not applicable

Funding: The present study received no financial support.

Acknowledgments: None to be declared.

Authors' contributions: FHK, HAN, and AMS: Major contributors to the conception and design of the study, supervision of the project, and drafting and critical revision of the manuscript for important intellectual content. SFA: Contributes to data analysis and interpretation and participates in manuscript revision. ReMA, RaMA, and AMA: Involve in study design and assist with initial drafting and revision of the manuscript. HOB, ROM, ANQ, SHH, AAQ, HAA, and BAA: Contribute to data acquisition and collection. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Use of AI: ChatGPT-4.5 was used to assist with language refinement and improve the overall clarity of the manuscript. All content was thoroughly reviewed and approved by the authors, who bear full responsibility for the final version.

Data availability statement: Data are available from the corresponding author upon reasonable request.

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