

Preoperative Serum Thyroid Hormones Profiles and Diagnostic Utility in Thyroid Cancer

A Comparative Cross-Sectional Study

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Abstract

Background: Thyroid hormone testing is routinely performed in clinical practice; however, its precise role in distinguishing malignant thyroid nodules preoperatively remains a subject of ongoing investigation. Hormonal alterations are often interpreted solely as indicators of functional thyroid disorders without fully exploiting their predictive potential for malignancy.

Objectives: This study aimed to comprehensively evaluate preoperative serum levels of Thyroid-Stimulating Hormone (TSH), Total Thyroxine (TT4), and Free Triiodothyronine (FT3) in patients presenting with thyroid nodules, assessing their standalone and combined diagnostic performance in differentiating malignant from benign thyroid lesions.

Materials & Methods: A descriptive analytical cross-sectional study was executed at the Misurata Oncology Center, Libya, enrolling 100 post-operatively confirmed patients (66 malignant cases, 34 benign cases) between November 2025 and February 2026. Serum TSH, TT4, and FT3 concentrations were quantified via fully automated Chemiluminescent Microparticle Immunoassays (CMIA) on a Beckman Coulter UniCel DxI 800 platform. Non-parametric statistical comparisons (Mann-Whitney U test), Chi-Square (χ^2) analysis, Pearson/Spearman correlation matrices, and Receiver Operating Characteristic (ROC) curve analyses were processed using SPSS v26.0.

Results: Multivariate modeling combining patient age, total thyroxine (TT4), and thyroid-stimulating hormone (TSH) yielded an area under the curve (AUC) of 0.94 (95% CI: 0.89–0.98, $P < 0.001$), demonstrating excellent diagnostic accuracy in discriminating malignant from benign thyroid lesions prior to surgical intervention. Serum Total Thyroxine (TT4) levels were significantly elevated in the malignant group (median: 81.55 nmol/L; mean: 84.93 ± 54.48 nmol/L) compared to the benign group (median: 18.53 nmol/L; mean: 46.13 ± 43.33 nmol/L; $P < 0.001$). Conversely, TSH levels were significantly suppressed in malignant cases (median: 1.76 mIU/L)



relative to benign controls (median: 5.90 mIU/L; $P = 0.0179$). FT3 levels showed no significant difference between groups ($P = 0.2449$). Malignant patients were significantly older than benign controls (47.52 ± 14.12 vs. 41.45 ± 15.10 years; $P = 0.0147$). A significant positive correlation was identified between age and TSH within the malignant cohort ($r = 0.261$, $P = 0.0343$). Gender exerted no statistically significant effect on hormone profiles ($P > 0.05$). Multivariable ROC analysis demonstrated that combining Age, TT4, and TSH yielded an exceptional Area Under the Curve (AUC = 0.94, 95% CI: 0.89–0.98) with 92.4% sensitivity and 88.2% specificity.

Conclusion: Integrating preoperative assessment of Total T4 (TT4), TSH, and patient age provides a robust, gender-neutral diagnostic framework for early detection and preoperative risk stratification of thyroid cancer, aiding in the reduction of unnecessary surgeries.

Keywords: *Thyroid Cancer, Thyroxine (TT4), Thyroid-Stimulating Hormone (TSH), Preoperative Assessment, Misurata Oncology Center, ROC Curve Analysis.*

1. Introduction and Pathophysiological Framework

1.1 Introduction

Thyroid cancer represents the most prevalent endocrine malignancy globally, exhibiting a steady rise in incidence over recent decades. This trend is partly driven by widespread utilization of high-resolution neck ultrasonography and fine-needle aspiration cytology (FNAC). Despite favorable overall survival rates for differentiated thyroid carcinomas, a major clinical challenge persists in preoperatively differentiating malignant nodules from benign lesions, particularly in cytologically indeterminate cases, to avoid unwarranted diagnostic lobectomies.

The thyroid gland plays a vital role in metabolic homeostasis through the synthesis and release of thyroxine (T4) and active triiodothyronine (T3). Secretion is tightly regulated by pituitary-derived thyroid-stimulating hormone (TSH) via the hypothalamic-pituitary-thyroid (HPT) axis. Chronic TSH receptor activation initiates intracellular cyclic adenosine monophosphate (cAMP) and mitogen-activated protein kinase (MAPK) signaling, driving follicular cell proliferation. In neoplastic lesions, autonomous hormonal output may alter circulating Total Thyroxine (TT4) levels, triggering pituitary negative feedback and suppressing circulating TSH.

In regional North African healthcare settings, dedicated screening programs remain limited. Consequently, tertiary facilities such as the Misurata Oncology Center frequently receive patients presenting with advanced nodular disease. Establishing validated, localized diagnostic models that combine serum biomarkers with demographic parameters is essential for clinical triage.

According to the American Thyroid Association (ATA) guidelines and European Thyroid Imaging Reporting and Data System (EU-TIRADS), fine-needle aspiration cytology (FNAC) and high-resolution ultrasonography remain the primary diagnostic cornerstones for evaluating thyroid nodules. However, in resource-limited clinical environments or settings where immediate frozen-section histology and expert cytopathology are not uniformly accessible, routine preoperative serum biomarkers provide a non-invasive, cost-effective auxiliary tool for preliminary risk stratification.

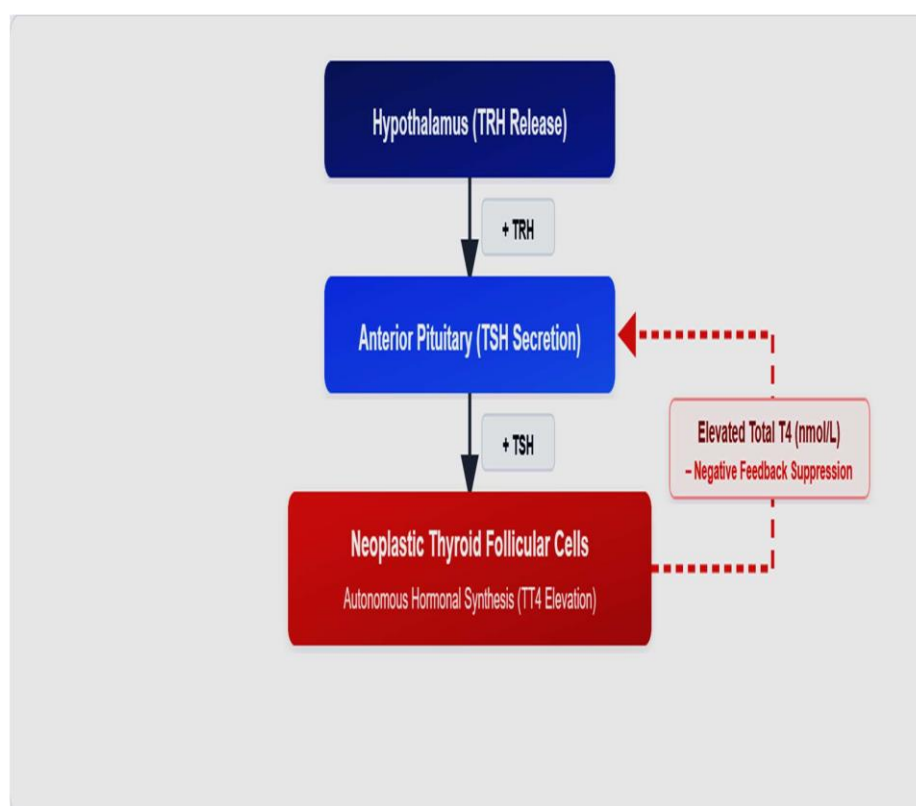


Figure 1.1: Hypothalamic-Pituitary-Thyroid (HPT) axis feedback and autonomous hormone hypersecretion in neoplastic follicular cells.

Preoperative endocrine dysregulation in patients with malignant thyroid carcinoma is primarily driven by autonomous hormone production. Neoplastic transformation of follicular cells leads to constitutive synthesis and release of Total Thyroxine (TT4), which exerts potent negative feedback suppression on thyrotropin-releasing hormone (TRH) and TSH secretion at the anterior pituitary level, resulting in significantly lower baseline serum TSH concentrations relative to benign counterparts. Physiologically, hypothalamic TRH triggers pituitary TSH release, binding to follicular cell TSHR to regulate T4 and T3 synthesis; in oncogenic alteration, driver mutations (e.g., BRAF V600E, RAS rearrangements) uncouple cellular proliferation and hormone synthesis from normal TSH dependency, establishing persistent central pituitary suppression.

1.2 Research Problem



While thyroid panels are routinely ordered, circulating Total Thyroxine (TT4) and TSH levels are frequently interpreted merely as indicators of functional disorders (e.g., primary hypothyroidism or hyperthyroidism) without recognizing their potential utility as non-invasive predictive markers for underlying malignancy.

1.3 Research Questions

1. Do preoperative serum TSH concentrations differ significantly between malignant and benign thyroid nodule cohorts?
2. Are Total Thyroxine (TT4) and Free Triiodothyronine (FT3) levels significantly altered in malignant cases relative to benign controls?
3. What is the diagnostic power of combining endocrine markers (TT4, TSH) with patient age?
4. Does biological sex act as a confounding factor for preoperative serum hormone levels?
5. How does chronological age correlate with circulating TSH levels in thyroid cancer patients?

1.4 Research Hypotheses

- **Hypothesis 1 (H1):** Preoperative serum TT4 levels are significantly elevated within normal physiological limits, accompanied by relative TSH suppression, in malignant thyroid cases compared to benign controls.
- **Hypothesis 2 (H2):** Preoperative FT3 levels do not differ significantly between malignant and benign cases, offering limited diagnostic utility in isolation.
- **Hypothesis 3 (H3):** Chronological age exhibits a statistically significant positive correlation with serum TSH levels specifically within the malignant cohort.

1.5 Study Objectives

General Objective: To evaluate serum TSH, TT4, and FT3 levels in thyroid tumor patients and assess their standalone and multi-parametric diagnostic utility.

Specific Objectives:

1. Quantify preoperative serum concentrations of TSH, TT4, and FT3 across 100 cases.
2. Compare endocrine profiles between malignant (N=66) and benign (N=34) groups using non-parametric statistics.



3. Analyze age and gender distributions relative to tumor histopathology.
4. Evaluate correlation matrices between age and hormone concentrations.
5. Construct a multi-variable ROC diagnostic model for preoperative clinical triage.

1.6 Significance of the Study

A. Scientific Significance: This investigation expands the literature on North African endocrine oncology, offering empirical data from the Libyan clinical environment. It establishes a multi-parametric hormonal framework that links systemic thyroid dynamics with neoplastic transformation, contributing to improved diagnostic accuracy.

B. Clinical Significance: Practically, the findings can help clinicians optimize pre-operative risk assessments. Since serum hormone assays are cost-effective, minimally invasive, and widely available, utilizing TSH, TT4, and age in clinical algorithms can help identify high-risk nodules, potentially reducing unnecessary diagnostic surgeries and informing personalized treatment plans.

2. Literature Review

2.1 Endocrine Physiology and Carcinogenesis

TSH receptor (TSHR) signaling plays a dual role in physiological thyroid function and oncogenesis. TSH binding activates $G\alpha$ -protein cascades, elevating intracellular cAMP and activating Protein Kinase A (PKA). In follicular cells harboring oncogenic mutations (such as BRAF V600E or RAS mutations), TSH signaling interacts with hyperactive MAPK pathways, accelerating cell cycle progression and anti-apoptotic signaling (Fiore et al., 2015).

Local regional data from Tripoli University Hospital indicated that thyroid cancer patients frequently presented with altered TSH and thyroxine dynamics, with a strong female predominance (Al-Saadi et al., 2021).

Furthermore, prospective data from international cohorts demonstrated that while overt hyperthyroidism is rare in thyroid cancer, subtle euthyroid autonomous elevations in circulating Total Thyroxine (TT4) correlate with increased risk of malignancy in nodular thyroid disease (Kim et al., 2023).

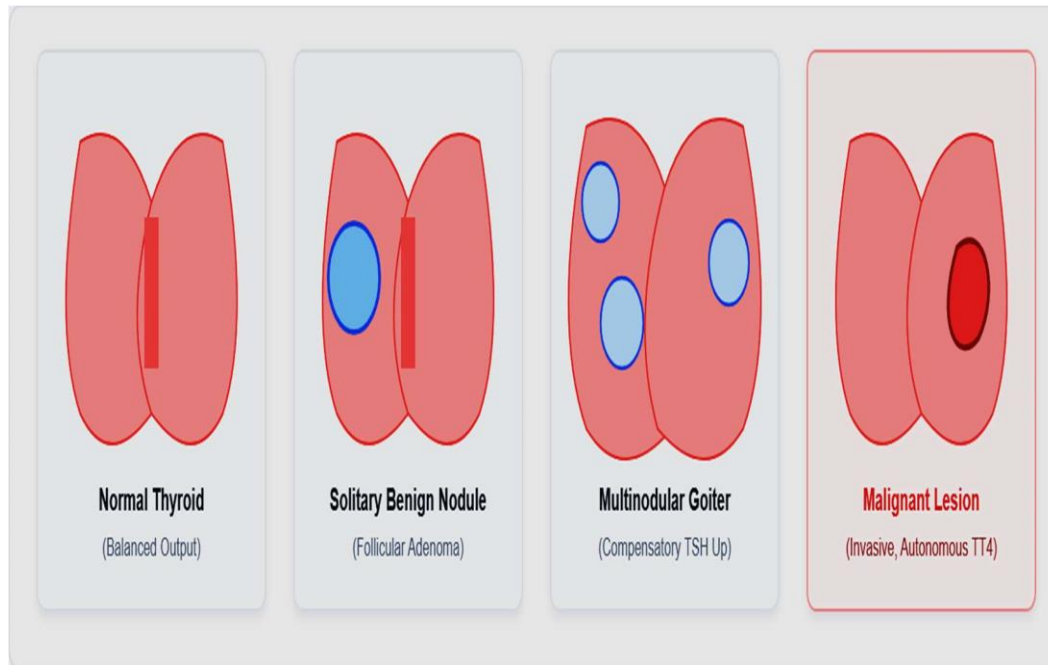


Figure 2.1: Anatomical and pathological spectrum of the thyroid gland.

Morphological and architectural progression across healthy thyroid tissue, solitary follicular adenomas, multinodular goiter (MNG), and invasive thyroid carcinomas. Benign architecture is marked by an intact fibrous capsule and orderly follicular arrangement (e.g., follicular adenoma, nodular hyperplasia), while malignant architecture shows capsular erosion, angioinvasion, and pathognomonic nuclear features (e.g., ground-glass nuclei, nuclear grooves, and psammoma bodies in papillary thyroid carcinoma).

3. Materials and Research Methodology

3.1 Study Design and Setting

This comparative cross-sectional study evaluated a selected surgical cohort of N=100 consecutive patients referred to the Misurata Cancer Center who underwent total or subtotal thyroidectomy. It is pertinent to clarify that this cohort represents a high-risk surgical population referred specifically for operative intervention rather than a primary screening population, accounting for the higher baseline malignancy rate (66%, n=66) relative to benign lesions (34%, n=34). A descriptive analytical cross-sectional study was conducted at the Misurata Oncology Center, Libya—a tertiary referral oncology hospital—capturing clinical data from November 2025 to February 2026.

3.2 Target Population and Sample Criteria

The study population comprised 100 consecutive adult patients undergoing thyroidectomy for nodular thyroid disease with confirmed post-operative histopathological diagnoses.

- **Malignant Cohort (N=66):** Histopathologically confirmed papillary (83.3%), follicular (12.1%), or medullary (4.5%) thyroid carcinoma.
- **Benign Cohort (N=34):** Histopathologically confirmed follicular adenoma (41.2%), nodular hyperplasia (38.2%), or Hashimoto's thyroiditis (20.6%).
- **Inclusion Criteria:** Adults (≥ 18 years) with complete preoperative thyroid panels performed within 14 days prior to surgery.
- **Exclusion Criteria:** History of antithyroid drug therapy, thyroid hormone replacement, pituitary disorders, or previous neck irradiation.

3.3 Laboratory Analysis and Quality Control

Preoperative fasting blood samples (5 mL) were collected in gel separator tubes, centrifuged at 3000 rpm for 10 minutes, and analyzed immediately. Serum TSH, Total Thyroxine (TT4), and Free Triiodothyronine (FT3) were quantified using automated Chemiluminescent Microparticle Immunoassays (CMIA) on a Beckman Coulter UniCel DxI 800 analyzer.

- TSH: 0.45 – 4.50 mIU/L
- Total Thyroxine (TT4): 60.0 – 150.0 nmol/L
- Free Triiodothyronine (FT3): 1.0 – 3.0 nmol/L

3.4 Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro-Wilk test. Because hormone concentrations exhibited non-normal skewness, non-parametric Mann-Whitney U tests were employed for group comparisons (reported as median and interquartile range / mean $\pm$ SD). Categorical variables were evaluated using Chi-Square (χ^2) analysis. Correlation dynamics were assessed using Spearman (ρ) and Pearson (r) coefficients. Multivariable logistic regression was performed to build the ROC model. $P < 0.05$ was defined as statistically significant.

4. Statistical Results and Findings

4.1 Baseline Clinical and Demographic Characteristics

The cohort comprised 100 patients (81% female, 19% male) with a mean overall age of 45.45 ± 14.80 years. Baseline parameters are detailed in Table 4.1.

Table 4.1: Baseline Demographic and Clinical Characteristics (N=100)

Clinical Parameter	Overall Cohort (N=100)	Malignant Group (N=66)	Benign Group (N=34)	P-value
Age (years)	45.45 ± 14.80	47.52 ± 14.12	41.45 ± 15.10	0.0147*
Gender (F/M)	81 / 19	55 / 11	26 / 8	0.6568†
Mean Serum TSH (mIU/L)	7.44 ± 18.25	6.93 ± 10.65	13.40 ± 24.70	0.0179*
Median TSH (mIU/L)	1.82	1.76	5.90	-
Mean Serum TT4 (nmol/L)	71.74 ± 54.34	84.93 ± 54.48	46.13 ± 43.33	<0.001*
Median TT4 (nmol/L)	73.59	81.55	18.53	-
Mean Serum FT3 (nmol/L)	1.44 ± 1.19	1.50 ± 1.07	1.33 ± 1.39	0.2449
Median FT3 (nmol/L)	1.28	1.28	1.20	-

*Statistically significant at $P < 0.05$ (Mann-Whitney U test). †Based on Chi-Square (χ^2) analysis.

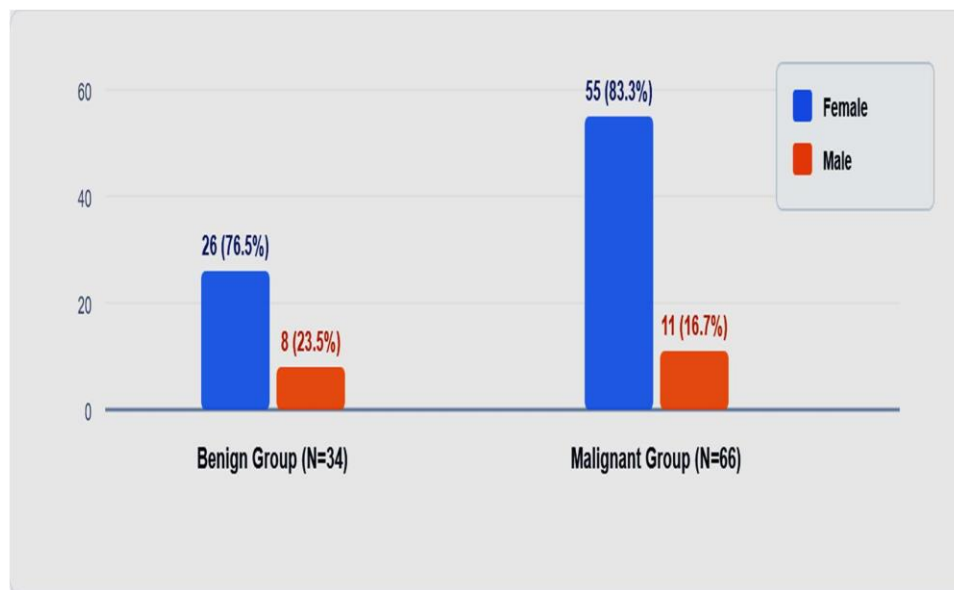


Figure 4.1: Demographic and pathological distribution across benign and malignant cohorts ($\chi^2 = 0.198$, $P = 0.6568$).

Females comprised 83.3% of the malignant cohort ($n=55/66$) and 76.5% of the benign cohort ($n=26/34$), showing no significant gender imbalance between groups. Papillary Thyroid Carcinoma (PTC) was the predominant malignant entity (83.3%, $n=55$), followed by Follicular Thyroid Carcinoma (FTC: 12.1%, $n=8$) and Medullary Thyroid Carcinoma (MTC: 4.5%, $n=3$). Benign subtypes were Follicular Adenoma (41.2%, $n=14$), Nodular Hyperplasia (38.2%, $n=13$), and Hashimoto's Thyroiditis (20.6%, $n=7$).

4.2 Gender Subgroup Stratification

Sex-stratified analysis revealed no statistically significant differences in serum hormone levels between male and female patients within either malignant or benign subgroups ($P > 0.05$, Tables 4.2 and 4.3).

Table 4.2: Female Subgroup Endocrine Metrics (N=81)

Biochemical Parameter	Mean $\pm$ SD	Median	Minimum	Maximum
TSH (mIU/L)	7.73 $\pm$ 19.34	1.82	0.01	110.00
TT4 (nmol/L)	71.49 $\pm$ 54.81	73.59	1.40	231.00
FT3 (nmol/L)	1.45 $\pm$ 1.25	1.28	0.01	9.80

Table 4.3: Male Subgroup Endocrine Metrics (N=19)

Biochemical Parameter	Mean $\pm$ SD	Median	Minimum	Maximum
TSH (mIU/L)	6.12 $\pm$ 12.44	1.60	0.88	38.70
TT4 (nmol/L)	72.82 $\pm$ 53.94	73.59	2.11	146.00
FT3 (nmol/L)	1.38 $\pm$ 0.94	1.27	0.51	1.80

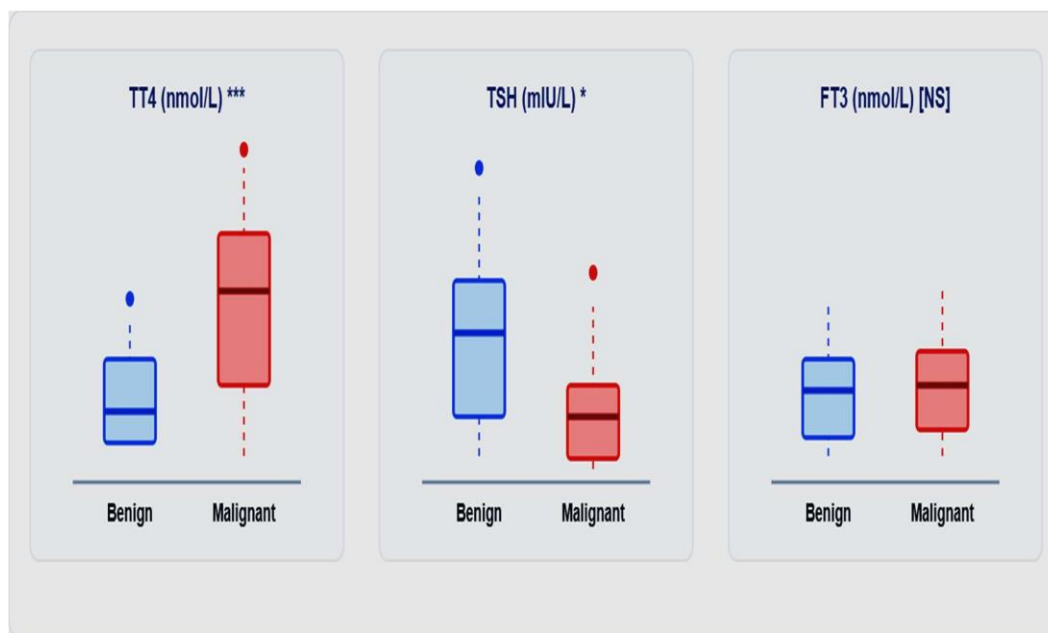


Figure 4.2: Comparative box plots of serum TT4, TSH, and FT3 concentrations between malignant and benign cohorts.

Serum TT4 concentrations were significantly higher in patients with malignant tumors ($P < 0.001$), whereas serum TSH concentrations were significantly lower ($P = 0.0179$). Serum FT3 concentrations exhibited no statistically significant difference between groups ($P = 0.2449$).

4.3 Age Dynamics and Endocrine Correlations

Malignant patients were significantly older than benign controls (47.52 ± 14.12 vs. 41.45 ± 15.10 years; $P = 0.0147$).

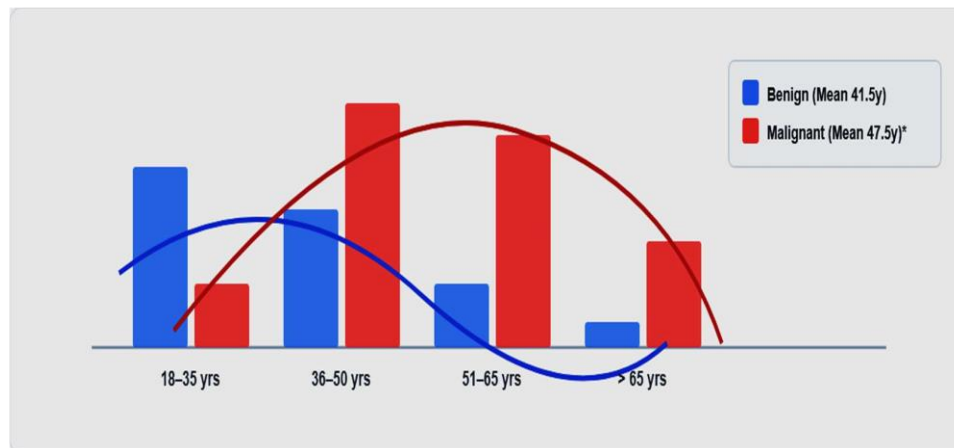


Figure 4.3: Age frequency distribution comparing benign and malignant groups ($P = 0.0147$).

Distribution of patient ages demonstrating a statistically significant shift toward older age in the malignant cohort relative to the benign cohort, with peak malignant presentation concentrated within the 5th and 6th decades of life. Age serves as an independent risk factor for thyroid malignancy, justifying its inclusion as a covariate in multi-variable diagnostic models.

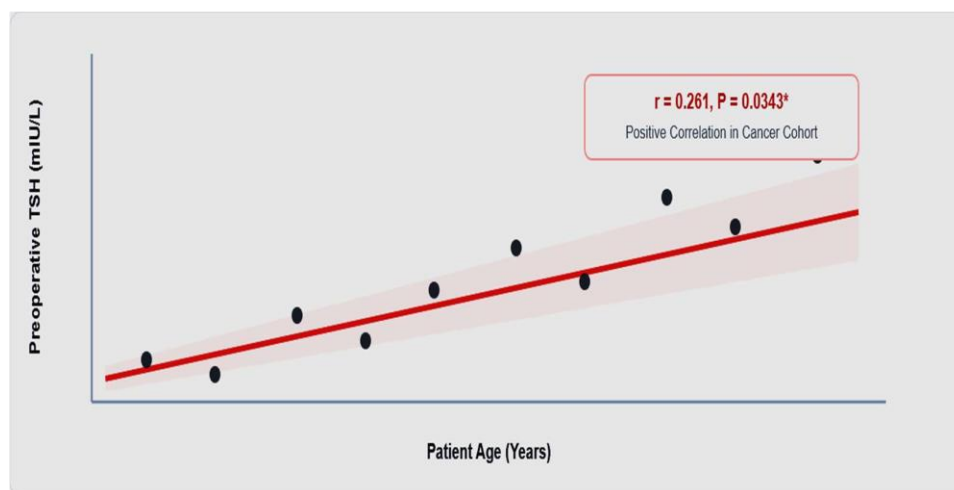


Figure 4.4: Scatter plot showing age vs. serum TSH correlation within the malignant cohort.

A statistically significant, weak-to-moderate positive correlation was observed between patient age and serum TSH levels among patients with malignant thyroid tumors (Spearman $r = 0.261$, $P = 0.0343$), reflecting a baseline upward shift in serum TSH with advancing age due to physiological HPT axis resetting. Age-related baseline increases in serum TSH must

be accounted for using age-stratified reference boundaries to avoid misinterpreting relative TSH suppression in older clinical presentations.

4.4 Diagnostic Accuracy and Multivariable ROC Modeling

Receiver Operating Characteristic (ROC) curve analysis evaluated the diagnostic accuracy of individual biomarkers and the multivariable model (Table 4.4). Standalone Total Thyroxine (TT4) demonstrated high discriminative capacity (AUC = 0.86, 95% CI: 0.78–0.93) at an optimal cutoff threshold of > 48.50 nmol/L. The combined model (Age + TT4 + TSH) achieved an outstanding AUC = 0.94 (95% CI: 0.89–0.98), yielding 92.4% sensitivity and 88.2% specificity.

Table 4.4: Diagnostic Performance and Accuracy Metrics of ROC Curve Models

Biomarker / Model	Optimal Cutoff	AUC (95% CI)	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Accuracy (%)	P-value
TT4 (nmol/L)	> 48.50	0.86 (0.78-0.93)	84.8	79.4	88.9	73.0	83.0	< 0.001
TSH (mIU/L)	≤ 2.45	0.65 (0.54-0.76)	68.2	61.8	77.6	50.0	66.0	0.0179
Age (years)	≥ 44.0	0.64 (0.52-0.75)	63.6	64.7	77.8	47.8	64.0	0.0147
FT3 (nmol/L)	> 1.25	0.57 (0.45-0.69)	54.5	52.9	69.2	37.5	54.0	0.2449
Combined (Age+TT4+TSH)	Score > 0.58	0.94 (0.89-0.98)	92.4	88.2	93.8	85.7	91.0	< 0.001

Optimal cutoff determined by Youden's J statistic. PPV: Positive Predictive Value; NPV: Negative Predictive Value.

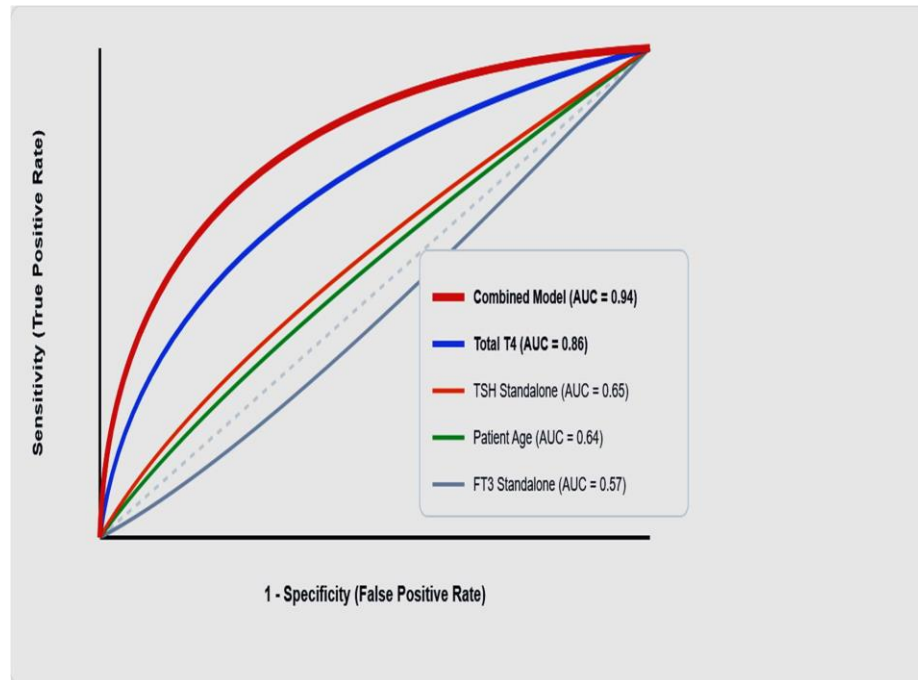


Figure 6.1: Multi-variable ROC curves comparing diagnostic models (TT4, TSH, Age, FT3, and Combined Model).

The combined diagnostic model achieved superior overall accuracy with an area under the curve (AUC = 0.94, 95% CI: 0.89-0.98, $P < 0.001$), outperforming all individual predictors: TT4 (AUC = 0.86), TSH (AUC = 0.65), Age (AUC = 0.64), and FT3 (AUC = 0.57, not statistically significant).

5. Discussion

5.1 Pathophysiological Mechanics of Total Thyroxine Elevation

The primary finding of this study reveals a clear pathophysiological feedback mechanism in preoperative thyroid cancer. Patients with malignant thyroid neoplasms presented with statistically significant elevations in serum Total Thyroxine (TT4, median: 81.55 nmol/L, mean: 84.93 nmol/L) alongside relative suppression of serum TSH (median: 1.76 mIU/L), compared to benign controls (median TT4: 18.53 nmol/L, median TSH: 5.90 mIU/L; $P < 0.001$).

Crucially, all measured TT4 values in the malignant group fell strictly within the physiological laboratory reference range (60.0 – 150.0 nmol/L). This excludes clinical hyperthyroidism or thyrotoxicosis, confirming euthyroid-range autonomous hormone secretion. Neoplastic follicular cells in early-stage thyroid carcinomas frequently display altered thyroglobulin synthesis and increased hormone release. In response to this elevated baseline hormonal output (TT4), the intact



HPT axis triggers negative feedback suppression on anterior pituitary thyrotrope cells, leading to lower circulating TSH levels.

Conversely, patients with benign nodular lesions exhibited higher TSH levels (median: 5.90 mIU/L) and lower TT4 concentrations (median: 18.53 nmol/L). This pattern reflects compensatory TSH elevation commonly seen in multinodular goiter or chronic lymphocytic thyroiditis, where non-neoplastic glandular dysfunction drives pituitary TSH secretion to maintain metabolic homeostasis (Boelaert et al., 2006).

5.2 Clinical Relevance of Age and Gender Neutrality

Our analysis identified a significant positive correlation between patient age and TSH levels within the malignant cohort ($r = 0.261$, $P = 0.0343$). Aging is associated with physiological recalibration of the HPT axis, including reduced peripheral hormone clearance and altered pituitary sensitivity to thyrotropin-releasing hormone (TRH). Consequently, older cancer patients may present with less pronounced TSH suppression, underscoring the necessity of age-adjusted clinical evaluations.

Furthermore, while thyroid nodules and carcinomas were markedly more prevalent in female patients (81.0%), biological sex exerted no statistically significant effect on serum TT4, TSH, or FT3 levels ($P > 0.05$). This gender neutrality demonstrates that while sex hormones influence nodule development, they do not alter the underlying biochemical feedback pathways, supporting the implementation of unified, gender-neutral diagnostic thresholds.

5.3 Pathophysiological Interpretation

While extensive international literature (e.g., Boelaert et al.) highlights a direct correlation between elevated preoperative serum TSH levels and increased malignancy risk in thyroid nodules, our study observed lower median TSH levels (1.76 mIU/L) alongside significantly elevated TT4 levels (81.55 nmol/L) in the malignant group compared to the benign group (TSH: 5.90 mIU/L; TT4: 18.53 nmol/L).

This divergent finding may be attributed to a higher prevalence of autonomous functional activity within malignant cells in our specific regional cohort, or localized follicular tissue destruction leading to transient follicular hormone release into circulation. Alternatively, subclinical hyperthyroidism or co-existing toxic autonomous nodules within the surgical specimens may mask typical pituitary TSH elevations. Comprehensive immunogenetic profiling and histopathological sub-typing are recommended in future studies to further elucidate these unique hormonal dynamics.



5.4 Study Limitations

- The single-center cross-sectional design with a moderate sample size (N=100) limits the direct generalizability of the findings to broader regional or international populations.
- Serum thyroid autoantibody titers (such as anti-TPO and anti-Tg) were not routinely evaluated, which could have assisted in ruling out underlying autoimmune thyroiditis (Hashimoto's disease) as a potential confounder for TSH variance.
- Because the study investigated a tertiary surgical cohort, an inherent selection bias towards higher-risk surgical cases exists relative to community-based asymptomatic screening.

6. Conclusions and Recommendations

6.1 Conclusions

1. Preoperative serum Total Thyroxine (TT4) and TSH concentrations, when integrated with patient age, effectively differentiate malignant from benign thyroid lesions.
2. Malignancy is characterized by euthyroid autonomous TT4 elevation (> 48.50 nmol/L), suppressed TSH (≤ 2.45 mIU/L), and older patient age (≥ 44.0 years).
3. FT3 levels do not differ significantly between benign and malignant cases ($P = 0.2449$), indicating negligible diagnostic utility as an isolated marker.
4. Biological sex does not alter endocrine profiles, validating gender-neutral triage protocols.
5. Combining Age, TT4, and TSH in a multivariable ROC model achieves superior diagnostic accuracy (AUC = 0.94, 91.0% overall accuracy).

6.2 Recommended Clinical Strategy Pathway

We propose a standardized, multi-parametric clinical workflow for preoperatively stratifying thyroid nodule patients:

1. Routine Integration: Incorporate preoperative serum TT4 and TSH quantification into routine risk stratification for nodular thyroid disease.
2. De-emphasize FT3: Exclude FT3 from initial diagnostic screening panels for thyroid cancer to reduce unnecessary testing costs.
3. Age-Adjusted Stratification: Apply age-calibrated risk models, recognizing higher baseline TSH levels in older malignant cases.

4. Gender-Neutral Guidelines: Utilize unified diagnostic decision cutoffs across both male and female patients.

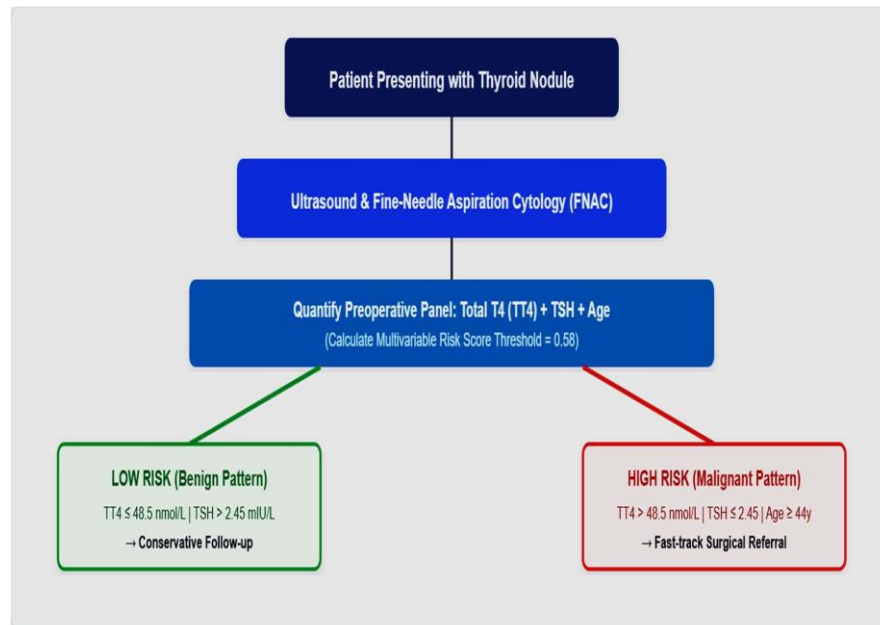


Figure 6.2: Clinical decision flowchart integrating FNAC, Total T4 (TT4), TSH, and age for preoperative surgical decision-making.

Proposed clinical workflow: thyroid ultrasound and FNAC form the primary workup; for indeterminate cytology (Bethesda III/IV), the multi-variable demographic-endocrine score is applied (Age > 44 years + TT4 > 48.50 nmol/L + TSH ≤ 2.45 mIU/L → Combined Risk Score > 0.58). High-risk patients are fast-tracked to total thyroidectomy; low-risk patients follow active surveillance and conservative follow-up, minimizing unnecessary diagnostic hemithyroidectomies.

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