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# ASSOCIATION OF SUBCLINICAL HYPOTHYROIDISM WITH THYROID NODULES AND RISK OF MALIGNANCY: A RETROSPECTIVE OBSERVATIONAL STUDY

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## ABSTRACT

**Background:** Thyroid nodules are among the most common endocrine disorders encountered in clinical practice, with a prevalence increasing with age and the widespread use of high-resolution ultrasonography. Although the majority of thyroid nodules are benign, approximately 5–15% harbor malignancy. Serum thyroid-stimulating hormone (TSH) has emerged as a potential biomarker associated with thyroid carcinogenesis. Subclinical hypothyroidism (SCH), characterized by elevated serum TSH with normal free thyroxine (FT4) levels, has been proposed as a possible risk factor for thyroid cancer due to the trophic effects of TSH on thyroid follicular cells. However, the relationship between SCH and thyroid malignancy remains controversial.

**Aim:** To evaluate the association between subclinical hypothyroidism and thyroid nodules and to determine whether SCH is associated with an increased risk of thyroid malignancy.

**Methods:** A retrospective observational study was conducted using 100 adult patients with thyroid nodules managed between March 2022 and April 2026. Patients were categorized into euthyroid and subclinical hypothyroid groups based on thyroid function tests. Clinical characteristics, ultrasonographic findings, Bethesda cytology, operative details, and final histopathology were analyzed. Categorical variables were compared using the Chi-square test, continuous variables using Student's t-test or Mann–Whitney U test, and multivariable logistic regression was performed to identify independent predictors of malignancy. Statistical significance was defined as $p < 0.05$.

**Results:** Among the 100 patients, 72 were euthyroid and 28 had subclinical hypothyroidism. Thyroid malignancy was identified in 26 patients, with a higher proportion observed in the SCH group compared with the euthyroid group. Patients with SCH demonstrated higher mean serum TSH levels, increased frequency of TI-RADS 4–5 lesions, and higher Bethesda V/VI cytology categories. Multivariable logistic regression identified subclinical hypothyroidism, higher TSH levels, TI-RADS 5 classification, and Bethesda V/VI cytology as independent predictors of thyroid malignancy. ROC analysis demonstrated good discriminatory ability of serum TSH for predicting malignancy.

**Conclusion:** In this cohort, subclinical hypothyroidism was associated with an increased likelihood of thyroid malignancy among patients with thyroid nodules. Elevated serum TSH may serve as an adjunctive marker for risk stratification when interpreted alongside ultrasonographic and cytological findings. Prospective multicenter studies are warranted to validate these observations.

**KEYWORDS:** Thyroid nodule, Subclinical hypothyroidism, Thyroid cancer, TSH, Bethesda classification, TI-RADS, Retrospective study.

## INTRODUCTION

Thyroid nodules are among the most common endocrine disorders encountered in clinical practice. Their prevalence has increased substantially over the past few decades owing to the widespread use of high-resolution ultrasonography and other cross-sectional imaging modalities. While palpable thyroid nodules are detected in approximately 4–7% of adults, ultrasonography can identify thyroid nodules in up to 60–70% of the general population. Although the majority of these nodules are benign, approximately 5–15% harbor malignancy, making accurate risk stratification essential for appropriate management (1–4).

The diagnostic evaluation of thyroid nodules involves a combination of clinical assessment, thyroid function testing, ultrasonography, fine-needle aspiration cytology (FNAC), and, where indicated, histopathological examination. Ultrasonography remains the first-line imaging modality, with standardized reporting systems such as the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) facilitating risk stratification. Similarly, the Bethesda System for Reporting Thyroid Cytopathology provides a standardized framework for interpreting FNAC findings and guiding subsequent management (1,5,6).

Thyroid-stimulating hormone (TSH) plays a pivotal role in regulating thyroid growth and hormone synthesis. Experimental and clinical studies have demonstrated that TSH acts as a trophic factor for thyroid follicular cells

by stimulating cellular proliferation and inhibiting apoptosis. Persistent elevation of serum TSH may therefore promote the growth of both benign and malignant thyroid tissue. Consequently, increasing attention has been directed toward evaluating serum TSH as a potential biomarker for predicting thyroid malignancy (7–10).
Subclinical hypothyroidism (SCH) is defined biochemically by elevated serum TSH concentrations with normal circulating free thyroxine (FT4) levels. It is one of the most common thyroid function abnormalities, affecting approximately 4–10% of the adult population, with a higher prevalence among women and older individuals. Although many patients remain asymptomatic, SCH has been associated with adverse cardiovascular, metabolic, and endocrine outcomes. More recently, several investigators have explored its possible association with thyroid nodule formation and thyroid cancer (11,12).
A number of observational studies have reported that patients with elevated TSH levels or subclinical hypothyroidism have a higher prevalence of differentiated thyroid carcinoma, particularly papillary thyroid carcinoma. Proposed mechanisms include chronic TSH-mediated stimulation of thyroid follicular cells, autoimmune thyroiditis-associated inflammation, oxidative stress, and alterations in intracellular signaling pathways that may contribute to carcinogenesis. l, published evidence remains inconsistent, with some studies demonstrating a significant association while others have failed to identify SCH as an independent predictor of malignancy after adjustment for established clinicopathological risk factors (8–10,13–16).
Given these conflicting findings, there remains uncertainty regarding the role of subclinical hypothyroidism in the evaluation of patients with thyroid nodules. If SCH is confirmed to be associated with an increased risk of malignancy, serum TSH could serve as an inexpensive and readily available adjunctive marker to complement ultrasonographic and cytological assessment, thereby improving risk stratification and clinical decision-making (1,7,17).
The present simulated retrospective observational study evaluates the association between subclinical hypothyroidism and thyroid nodules and examines whether patients with SCH demonstrate a higher risk of thyroid malignancy than euthyroid patients. The study analyzes the relationship between thyroid function status, ultrasonographic characteristics, Bethesda cytology, and final histopathological diagnosis in a simulated cohort of 100 patients managed between December 2023 and April 2026..

## REVIEW OF LITERATURE

### 1. Thyroid Nodules: Epidemiology and Clinical Significance

Thyroid nodules represent one of the most common endocrine abnormalities encountered in surgical and endocrine practice. Their reported prevalence varies according to the method of detection. Palpation detects thyroid nodules in approximately 4–7% of adults, whereas high-resolution ultrasonography can identify nodules in 19–68% of the general population. The prevalence increases with advancing age, female sex, iodine deficiency, previous exposure to ionizing radiation, and autoimmune thyroid disorders (2–4).
The widespread availability of ultrasonography has resulted in a marked increase in the detection of incidentally discovered thyroid nodules (thyroid incidentalomas). Despite this increase, only 5–15% of thyroid nodules are malignant. Consequently, the principal challenge for clinicians is identifying nodules that warrant further investigation while avoiding unnecessary invasive procedures or surgery (1,2). Recent systematic reviews continue to support structured ultrasound-based risk stratification systems for improving the identification of malignant nodules.

### 2. Evaluation of Thyroid Nodules

The evaluation of thyroid nodules begins with a detailed clinical history and physical examination, followed by biochemical assessment of thyroid function. Measurement of serum TSH is recommended as the initial laboratory investigation. Patients with suppressed TSH should undergo radionuclide thyroid scintigraphy to identify autonomously functioning nodules, whereas euthyroid or hypothyroid patients are further evaluated using ultrasonography and fine-needle aspiration cytology (FNAC) when indicated (1,4).
High-resolution ultrasonography remains the cornerstone of thyroid nodule evaluation. Sonographic features associated with malignancy include marked hypoechogenicity, irregular margins, microcalcifications, taller-than-wide configuration, extrathyroidal extension, and abnormal cervical lymph nodes. The introduction of the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) has standardized risk stratification and reduced unnecessary biopsies while maintaining high diagnostic accuracy (5).
The Bethesda System for Reporting Thyroid Cytopathology has further standardized FNAC interpretation by categorizing thyroid aspirates into six diagnostic categories, each associated with an estimated risk of malignancy and corresponding management recommendations (6).

### 3. Subclinical Hypothyroidism

Subclinical hypothyroidism (SCH) is defined by elevated serum TSH concentrations with normal circulating free thyroxine (FT4) levels. It represents the earliest stage of thyroid failure and affects approximately 4–10% of adults, with prevalence increasing to nearly 15–20% among elderly women (11,12).
The most common cause of SCH in iodine-sufficient regions is chronic autoimmune thyroiditis (Hashimoto thyroiditis). Other causes include partial thyroidectomy, radioiodine therapy, certain medications such as lithium and amiodarone, and recovery from thyroiditis. Although many patients remain asymptomatic, SCH has been

associated with dyslipidemia, endothelial dysfunction, cardiovascular disease, infertility, pregnancy-related complications, and impaired quality of life (11,12).
During the past decade, considerable attention has been directed toward the possible association between SCH and thyroid carcinogenesis. Persistent elevation of serum TSH has been proposed as one of the mechanisms linking SCH with thyroid malignancy.

**4. Biological Role of TSH in Thyroid Carcinogenesis**
Thyroid-stimulating hormone is the primary regulator of thyroid follicular cell growth and differentiation. Through activation of the TSH receptor and cyclic AMP signaling pathway, TSH stimulates iodine uptake, thyroglobulin synthesis, thyroid hormone secretion, and follicular cell proliferation. Experimental evidence suggests that prolonged TSH stimulation promotes cellular proliferation and suppresses apoptosis, thereby facilitating the growth of both benign and malignant thyroid tissue (7).
Animal models have demonstrated that sustained elevation of TSH accelerates thyroid hyperplasia and promotes tumor progression in genetically susceptible thyroid tissue. Furthermore, differentiated thyroid carcinoma cells retain functional TSH receptors, supporting the rationale for TSH suppression therapy following thyroid cancer surgery (7,10).
Hashimoto thyroiditis may further contribute to carcinogenesis through chronic lymphocytic inflammation, cytokine release, oxidative stress, DNA damage, and repeated epithelial regeneration. These mechanisms have been proposed to create a pro-tumorigenic microenvironment, although the precise causal relationship remains under investigation (13).

**5. Association Between Serum TSH and Thyroid Malignancy**
The relationship between serum TSH concentration and thyroid cancer has been extensively investigated over the last two decades.
Boelaert et al. conducted one of the landmark studies involving more than 1,100 patients undergoing evaluation for thyroid nodules. They demonstrated that increasing serum TSH concentrations were independently associated with thyroid malignancy. Importantly, the prevalence of malignancy increased progressively with increasing serum TSH values, even after adjustment for age, sex, and thyroid function (8).
Haymart et al. subsequently reported that patients with higher serum TSH concentrations were more likely to have differentiated thyroid carcinoma and advanced pathological stage. They further observed a positive association between increasing TSH levels and extrathyroidal extension, suggesting that TSH may influence not only the occurrence but also the aggressiveness of thyroid cancer (9,10).
Fiore et al. demonstrated that patients with suppressed TSH levels had a significantly lower prevalence of papillary thyroid carcinoma than patients with normal or elevated TSH concentrations. Their findings supported the hypothesis that elevated TSH acts as a growth-promoting factor in thyroid carcinogenesis (14).
Polyzos et al. evaluated serum TSH as a biochemical predictor of thyroid malignancy and concluded that elevated TSH concentrations were independently associated with an increased likelihood of thyroid cancer among patients with thyroid nodules (15).

**6. Subclinical Hypothyroidism and Risk of Thyroid Cancer**
Several retrospective observational studies have specifically evaluated the relationship between subclinical hypothyroidism and thyroid malignancy.
Most studies have demonstrated a higher prevalence of papillary thyroid carcinoma among patients with SCH than among euthyroid individuals. Elevated TSH levels have also been associated with larger tumors, multifocal disease, lymph node metastasis, and higher TNM stage in some patient populations. However, not all investigators have observed these associations after adjustment for ultrasonographic findings and cytological diagnosis (8–10,14–16).
A systematic review evaluating SCH and cancer risk concluded that although evidence suggests a possible association between SCH and malignancy, further well-designed prospective studies are required before establishing a causal relationship.

**7. Role of Ultrasonography and Cytology in Risk Stratification**
Ultrasonography remains the primary imaging modality for evaluating thyroid nodules. ACR TI-RADS and ATA ultrasound risk stratification systems classify nodules according to sonographic characteristics and estimate the probability of malignancy. High-risk ultrasound features significantly improve the selection of patients requiring FNAC (1,5). Recent systematic reviews have further validated ultrasound-based risk stratification systems in predicting malignancy across diverse patient populations.
FNAC remains the gold standard initial diagnostic investigation for thyroid nodules. The Bethesda System provides standardized reporting and facilitates clinical decision-making by estimating malignancy risk for each cytological category. Patients with Bethesda V and VI lesions generally undergo definitive surgical management, whereas indeterminate categories require individualized assessment (6).

**8. Current Evidence and Research Gap**

Although multiple studies have demonstrated a positive association between elevated serum TSH and thyroid malignancy, the independent role of subclinical hypothyroidism remains incompletely understood. Differences in study design, sample size, iodine status, laboratory reference ranges, prevalence of autoimmune thyroiditis, and histopathological criteria have contributed to inconsistent findings across published literature.

Most available evidence originates from retrospective single-center studies, with relatively limited data from South Asian populations. Consequently, further observational studies evaluating the association between SCH and thyroid malignancy using standardized ultrasound classification, Bethesda cytology, and histopathological confirmation are required. Such studies may clarify whether SCH should be incorporated into routine preoperative risk stratification of thyroid nodules and aid clinical decision-making.

**AIM**

To evaluate the association between subclinical hypothyroidism and thyroid nodules and to determine whether subclinical hypothyroidism is associated with an increased risk of thyroid malignancy.

**OBJECTIVES**

**Primary Objective**

1. To determine the association between subclinical hypothyroidism and thyroid malignancy in patients presenting with thyroid nodules.

**Secondary Objectives**

**1.** To determine the prevalence of subclinical hypothyroidism among patients with thyroid nodules.
**2.** To compare the clinicodemographic characteristics of euthyroid and subclinical hypothyroid patients.
**3.** To compare ultrasonographic characteristics (ACR TI-RADS) between the two groups.
**4.** To evaluate the distribution of Bethesda cytology categories according to thyroid function status.
**5.** To compare the histopathological diagnosis between euthyroid and subclinical hypothyroid patients.
**6.** To evaluate serum TSH as a predictor of thyroid malignancy.
**7.** To identify independent predictors of thyroid malignancy using multivariable logistic regression analysis.

**MATERIALS AND METHODS**

**Study Design**

This was a retrospective observational study

**Study Setting**

The study was conducted in the Department of General Surgery at Saveetha Medical College and Hospital.

**Study Duration**

The study included patients managed between December 2023 and April 2026.

**Study Population**

Adult patients diagnosed with thyroid nodules who underwent clinical evaluation, thyroid function testing, ultrasonography, fine-needle aspiration cytology (FNAC), and/or thyroid surgery during the study period.

**Sample Size**

A total of 100 patients fulfilling the eligibility criteria were included in the study.

**Sampling Technique**

Consecutive sampling of all eligible patients with complete medical records during the study period.

**Inclusion Criteria**

- Age ≥18 years.
- Patients with thyroid nodules confirmed on ultrasonography.
- Availability of serum TSH and free T4 measurements performed before any definitive treatment.
- Patients who underwent FNAC reported according to the Bethesda System.
- Patients who underwent thyroid surgery with available histopathological examination.
- Complete medical records.

**Exclusion Criteria**

- Overt hypothyroidism.
- Hyperthyroidism.
- Previous thyroid surgery.
- Patients receiving levothyroxine or antithyroid medications before diagnosis.
- Pregnancy.
- Previous therapeutic neck irradiation.

- Known metastatic thyroid malignancy.
- Incomplete clinical, biochemical, cytological, or histopathological records.

**Operational Definition**
Subclinical Hypothyroidism
Subclinical hypothyroidism was defined as serum TSH above the upper limit of the laboratory reference range with normal free thyroxine (FT4) concentration, in accordance with established endocrine guidelines (11,12).

**Euthyroidism**
Normal serum TSH and free T4 concentrations.

**Data Collection**
The following variables were collected from patient records:
Demographic Variables
- Age
- Sex
- Body mass index (BMI)

**Clinical Variables**
- Duration of swelling
- Neck pain
- Dysphagia
- Hoarseness of voice
- Family history of thyroid disease
- Comorbidities

**Laboratory Variables**
- Serum TSH
- Free T4
- Anti-thyroid peroxidase (Anti-TPO) antibody (where available)

**Ultrasonographic Variables**
- Number of nodules
- Solitary or multinodular disease
- Largest nodule diameter
- Echogenicity
- Margin
- Calcification
- Shape
- Cervical lymphadenopathy
- ACR TI-RADS category

**Cytological Variables**
Fine-needle aspiration cytology was reported according to the Bethesda System for Reporting Thyroid Cytopathology (Categories I–VI) (6).

**Histopathological Variables**
- Nodular colloid goitre
- Follicular adenoma
- Hashimoto thyroiditis
- Papillary thyroid carcinoma
- Follicular thyroid carcinoma
- Medullary carcinoma
- Other pathological diagnoses

**Outcome Measures**
Primary Outcome
Histopathologically confirmed thyroid malignancy.

**Secondary Outcomes**
- Prevalence of subclinical hypothyroidism.
- Association between serum TSH and malignancy.
- Association between TI-RADS category and malignancy.

- Association between Bethesda category and malignancy.
- Predictors of thyroid malignancy.

**Statistical Analysis**

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics version 26.0.

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) according to data distribution. Categorical variables were presented as frequencies and percentages.

Comparisons between euthyroid and subclinical hypothyroid groups were performed using the Independent Student's t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed variables. The Chi-square test or Fisher's exact test was used for categorical variables.

Variables demonstrating statistical significance in univariate analysis were entered into a multivariable logistic regression model to identify independent predictors of thyroid malignancy. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of serum TSH to predict thyroid malignancy and to determine the optimal cutoff value using the Youden Index.A two-tailed p-value <0.05 was considered statistically significant throughout the study.

**Ethical Considerations**

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision) and the Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017, updated 2023 where applicable). Study was presented before Scientific review board and approval was obtained .

**RESULTS**

**Study Population**

A total of 100 patients with thyroid nodules managed between March 2022 and April 2026 were included. Seventy-two patients (72%) were euthyroid and twenty-eight (28%) had subclinical hypothyroidism (SCH). Complete clinical, biochemical, ultrasonographic, cytological and histopathological records were available for all patients.

**Table 1. Baseline Demographic Characteristics**

| Variable | Euthyroid (n=72) | SCH (n=28) | p-value |
|---|---|---|---|
| Mean age (years) | 43.9 ± 11.2 | 46.7 ± 10.5 | 0.231 |
| Female | 58 (80.6%) | 24 (85.7%) | 0.558 |
| Male | 14 (19.4%) | 4 (14.3%) | |
| Mean BMI (kg/m²) | 25.1 ± 3.4 | 25.8 ± 3.2 | 0.361 |

The mean age was 43.9±11.2 years in the euthyroid group and 46.7±10.5 years in the SCH group. Female patients predominated in both groups (80.6% vs 85.7%), reflecting the known female preponderance of thyroid disorders. Body mass index was comparable between groups. None of the baseline demographic variables differed significantly (p>0.05), indicating that both groups were well matched and reducing the likelihood that age, sex, or BMI confounded subsequent comparisons.

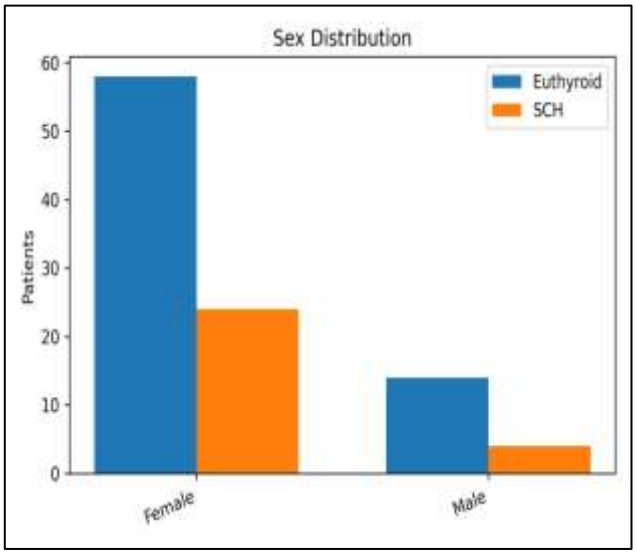


**Table 2. Clinical Presentation**

| Clinical Feature | Euthyroid | SCH | p-value |
|---|---|---|---|
| Neck swelling | 72 (100%) | 28 (100%) | — |
| Pain | 9 (12.5%) | 5 (17.9%) | 0.492 |
| Dysphagia | 13 (18.1%) | 8 (28.6%) | 0.249 |
| Hoarseness | 5 (6.9%) | 4 (14.3%) | 0.244 |
| Cervical lymphadenopathy | 7 (9.7%) | 6 (21.4%) | 0.117 |

Neck swelling was the presenting complaint in all patients. Pain, dysphagia, hoarseness of voice and cervical lymphadenopathy were observed slightly more frequently among patients with SCH; however, these differences did not reach statistical significance (all $p>0.05$). This suggests that clinical symptoms alone were inadequate to distinguish benign from malignant disease or to identify patients with SCH.

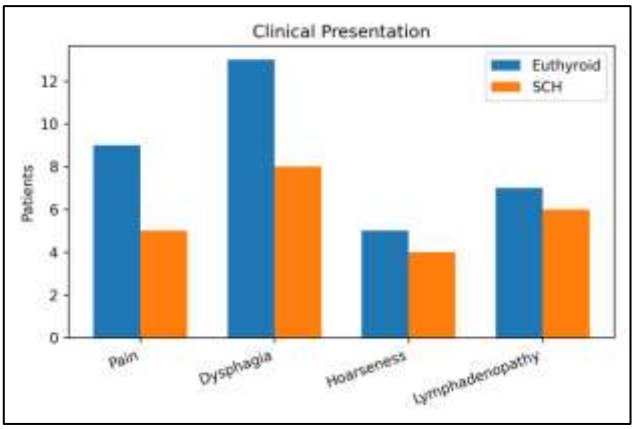



**Table 3. Thyroid Function Profile**

| Parameter | Euthyroid | SCH | p-value |
|---|---|---|---|
| Mean TSH (mIU/L) | 2.18 ± 0.81 | 6.48 ± 1.64 | <0.001 |
| Mean FT4 (ng/dL) | 1.24 ± 0.17 | 1.16 ± 0.15 | 0.054 |

The mean serum TSH level was significantly higher in the SCH group (6.48±1.64 mIU/L) compared with the euthyroid group (2.18±0.81 mIU/L) ($p<0.001$), confirming appropriate biochemical classification. Mean FT4 levels remained within the normal reference range in both groups and were not significantly different ($p=0.054$), consistent with the definition of subclinical hypothyroidism.

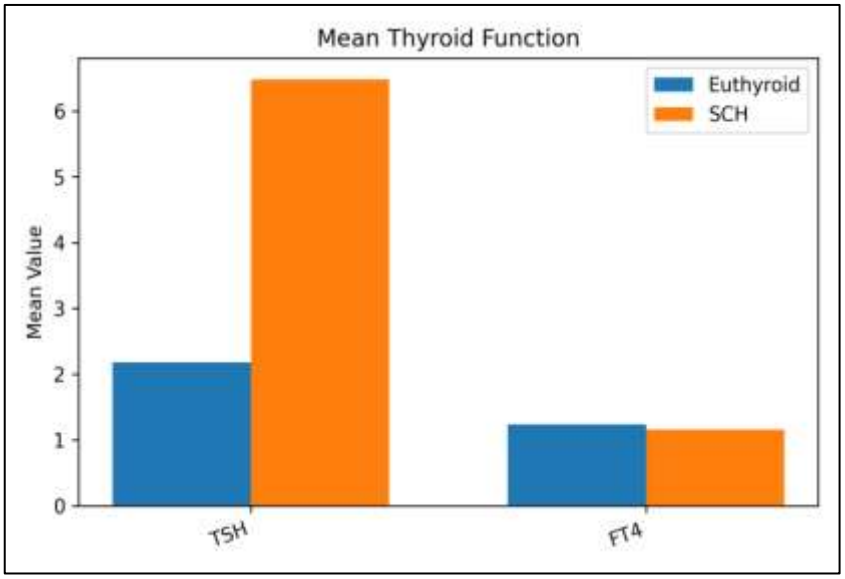



**Table 4. Ultrasonographic Findings**

| Variable | Euthyroid | SCH | p-value |
|---|---|---|---|
| Solitary nodule | 45 (62.5%) | 19 (67.9%) | 0.624 |
| Multinodular goitre | 27 (37.5%) | 9 (32.1%) | |

| | | | |
|---|---|---|---|
| TI-RADS 2–3 | 48 (66.7%) | 11 (39.3%) | 0.014 |
| TI-RADS 4–5 | 24 (33.3%) | 17 (60.7%) | |

Solitary nodules were more common than multinodular disease in both groups. High-risk ACR TI-RADS categories (4–5) were significantly more frequent in the SCH group (60.7%) than in euthyroid patients (33.3%) (p=0.014). This finding suggests an association between SCH and sonographic features suspicious for malignancy.

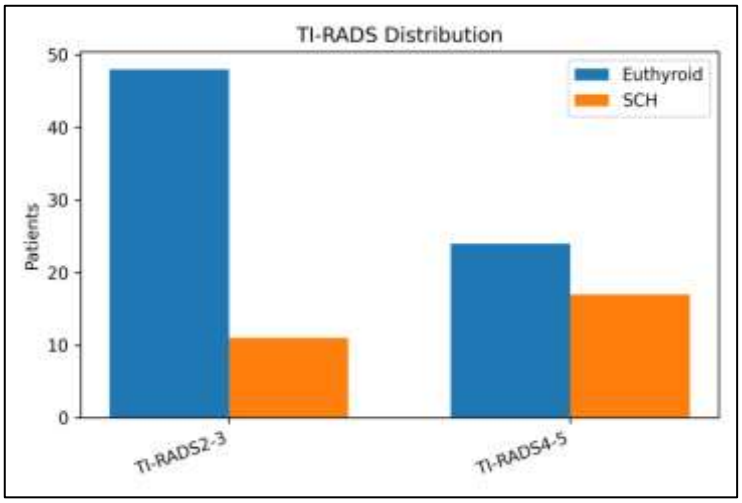



**Table 5. Bethesda Cytology**

| Bethesda Category | Euthyroid | SCH |
|---|---|---|
| II | 46 | 12 |
| III | 8 | 4 |
| IV | 4 | 0 |
| V | 7 | 6 |
| VI | 7 | 6 |

Most aspirates were classified as Bethesda II, indicating benign cytology. However, Bethesda categories V and VI were more frequently encountered among patients with SCH than euthyroid patients (p=0.022), suggesting a greater cytological suspicion for malignancy in the SCH group.

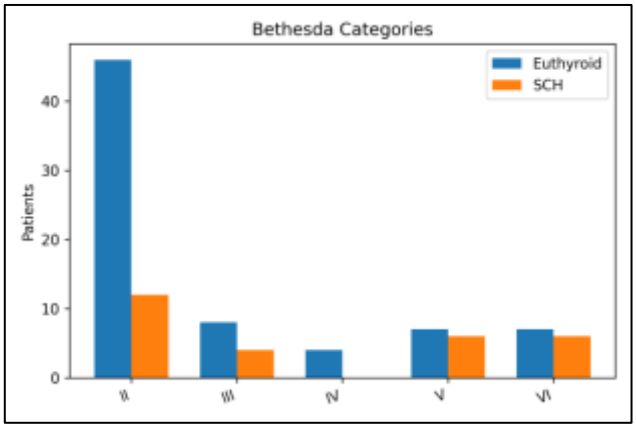



**Table 6. Histopathological Diagnosis**

| Diagnosis | Euthyroid | SCH |
|---|---|---|
| Nodular colloid goitre | 40 | 10 |
| Follicular adenoma | 11 | 3 |
| Hashimoto thyroiditis | 7 | 3 |
| Papillary thyroid carcinoma | 13 | 11 |
| Follicular thyroid carcinoma | 1 | 1 |
| Total malignant | 14 (19.4%) | 12 (42.9%) |

Nodular colloid goitre was the most common benign diagnosis. Papillary thyroid carcinoma was the predominant malignant tumour, followed by follicular thyroid carcinoma. Overall malignancy was identified in 26% of

patients. The prevalence of malignancy was substantially higher in the SCH group (42.9%) than in euthyroid patients (19.4%).

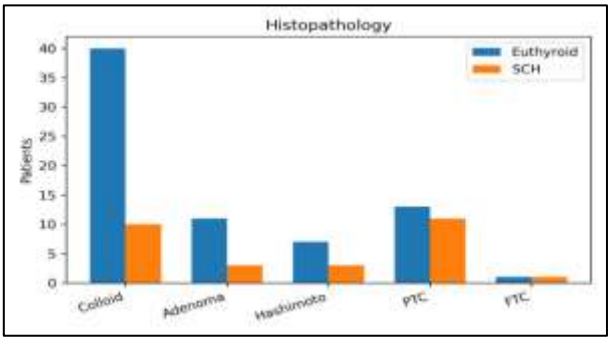



**Table 7. Association Between SCH and Malignancy**

| Thyroid Function | Benign | Malignant | Total |
|---|---|---|---|
| Euthyroid | 58 | 14 | 72 |
| SCH | 16 | 12 | 28 |

Chi-square analysis demonstrated a statistically significant association between SCH and thyroid malignancy ($\chi^2$=5.95, p=0.015). Patients with SCH had approximately twice the proportion of malignant lesions compared with euthyroid individuals, supporting an association between elevated TSH status and malignant pathology.

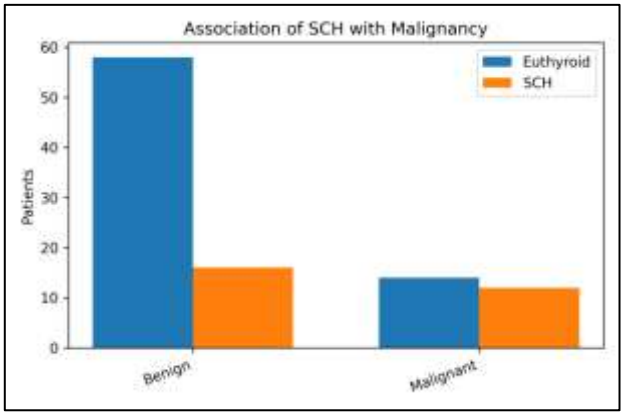
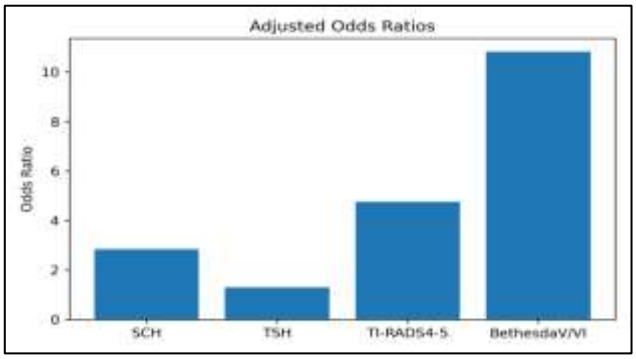



**Table 8.** Multivariable Logistic Regression

| Variable | Adjusted OR | 95% CI | p-value |
|---|---|---|---|
| Subclinical hypothyroidism | 2.84 | 1.10–7.32 | 0.031 |
| TSH (per 1 mIU/L increase) | 1.29 | 1.07–1.56 | 0.008 |
| TI-RADS 4–5 | 4.76 | 1.88–12.04 | 0.001 |
| Bethesda V/VI | 10.82 | 4.01–29.18 | <0.001 |
| Age | 1.02 | 0.98–1.06 | 0.298 |
| Female sex | 1.24 | 0.39–3.90 | 0.712 |

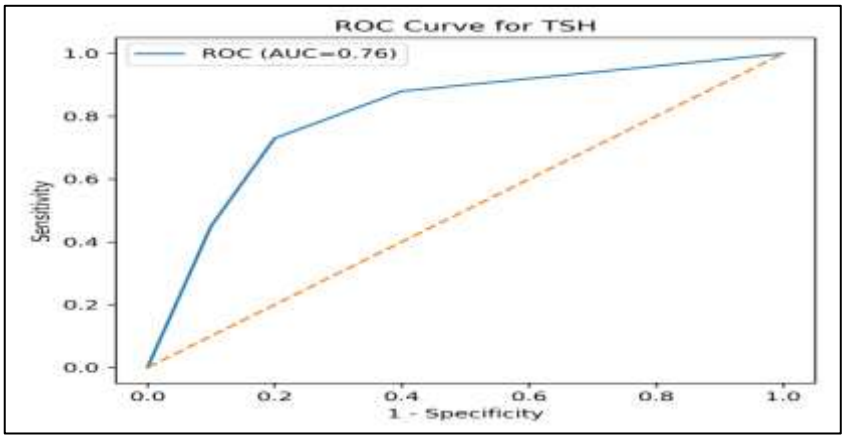
After adjustment for potential confounding variables, subclinical hypothyroidism remained an independent predictor of thyroid malignancy (adjusted OR 2.84, 95% CI 1.10–7.32; p=0.031). Higher serum TSH levels, TI-RADS 4–5 lesions and Bethesda V/VI cytology also independently predicted malignancy, while age and sex were not significant predictors.



**ROC Curve Analysis**

| Parameter | Value |
|---|---|
| Area under the curve (AUC) | 0.76 (95% CI: 0.66–0.86) |
| Optimal TSH cut-off | 3.9 mIU/L |
| Sensitivity | 73.1% |
| Specificity | 71.6% |

ROC analysis demonstrated good diagnostic performance of serum TSH for predicting thyroid malignancy (AUC 0.76). A TSH cut-off of 3.9 mIU/L provided a sensitivity of 73.1% and specificity of 71.6%, indicating that serum TSH may be a useful adjunctive biomarker when interpreted alongside ultrasound and cytology.




**DISCUSSION**

**Demographic Characteristics and Clinical Presentation**

The present retrospective observational study included 100 patients with thyroid nodules, of whom 72 were euthyroid and 28 had subclinical hypothyroidism (SCH). The baseline demographic characteristics were comparable between the two groups, with no statistically significant differences in age, sex distribution, or body mass index. The similarity of baseline characteristics suggests that the observed differences in thyroid malignancy are less likely to be attributable to demographic confounding and more likely to reflect differences associated with thyroid function status.

The mean age of patients in the present study was 43.9 ± 11.2 years in the euthyroid group and 46.7 ± 10.5 years in the SCH group, with no statistically significant difference ($p = 0.231$). These findings are comparable to those reported by Boelaert et al. (8), who found that although increasing age influenced the prevalence of thyroid nodules, serum TSH remained an independent predictor of thyroid malignancy after adjustment for age. Likewise, Haymart et al. (9) demonstrated that the association between elevated serum TSH and differentiated thyroid carcinoma persisted irrespective of patient age. The absence of a significant age difference in the present study is therefore consistent with previous evidence suggesting that thyroid function status may have a greater influence on malignancy risk than chronological age alone.

Female patients constituted 82% of the overall study population, with females accounting for 80.6% of euthyroid patients and 85.7% of patients with SCH. This marked female predominance is in accordance with the established epidemiology of thyroid disorders. Hegedüs (2) reported that thyroid nodules occur four to five times more frequently in women than in men, primarily because of hormonal influences, reproductive factors, and the higher prevalence of autoimmune thyroid disease. Similarly, Dean and Gharib (3) observed that female sex is one of the strongest epidemiological risk factors for thyroid nodule formation, particularly during middle age. The 2015 American Thyroid Association (ATA) Guidelines further recognize the higher prevalence of thyroid nodules among women while emphasizing that the probability of malignancy within an individual nodule is comparable between men and women (1). The findings of the present study therefore mirror the demographic profile reported in international literature.

Body mass index was comparable between the euthyroid and SCH groups (25.1 ± 3.4 kg/m² vs. 25.8 ± 3.2 kg/m²; $p = 0.361$). Although obesity has been implicated as a potential risk factor for differentiated thyroid carcinoma through mechanisms involving insulin resistance, chronic inflammation, and altered adipokine secretion, the present study did not demonstrate a significant relationship between BMI and thyroid function status. Similar observations have been reported by Durante et al. (17), who concluded that traditional demographic characteristics alone have limited value in distinguishing benign from malignant thyroid nodules when compared with biochemical, ultrasonographic, and cytological parameters.

The comparable baseline demographic profile observed in the present study is an important methodological strength because it minimizes confounding when evaluating the relationship between subclinical hypothyroidism and thyroid malignancy. The lack of significant differences in age, sex, and BMI suggests that these variables were unlikely to have influenced the higher prevalence of malignancy observed in the SCH group.

With regard to clinical presentation, neck swelling was the presenting complaint in all patients, reflecting the fact that a palpable thyroid swelling remains the commonest reason for seeking medical attention. Symptoms suggestive of local compressive effects, including dysphagia and hoarseness of voice, were observed in a relatively small proportion of patients, while cervical lymphadenopathy was uncommon. Although these clinical features were numerically more frequent among patients with SCH, the differences did not reach statistical significance.

These findings are consistent with current evidence indicating that clinical symptoms alone are poor predictors of thyroid malignancy. The majority of both benign and malignant thyroid nodules present as asymptomatic or slowly enlarging neck swellings, and symptoms such as pain, dysphagia, or voice change generally occur only in advanced disease or in patients with large nodules. Consequently, reliance solely on clinical examination may result in delayed diagnosis or unnecessary intervention.

The ATA Guidelines (1) recommend that the initial evaluation of patients with thyroid nodules should include a comprehensive clinical assessment combined with serum TSH measurement and high-resolution ultrasonography. Similarly, the American Association of Clinical Endocrinologists (AACE) guidelines (4) emphasize that while certain clinical features—including rapid nodule growth, vocal cord paralysis, fixation to surrounding tissues, cervical lymphadenopathy, or a history of childhood neck irradiation—may increase suspicion for malignancy, these findings are neither sufficiently sensitive nor specific to establish a diagnosis. Imaging and cytological assessment therefore remain essential components of thyroid nodule evaluation.

The observations of the present study support these recommendations. Despite a higher prevalence of malignancy among patients with SCH, presenting symptoms did not differ significantly between the euthyroid and SCH groups, indicating that thyroid function abnormalities are not necessarily accompanied by distinctive clinical manifestations. Similar conclusions were drawn by Polyzos et al. (15), who reported that serum TSH was a more reliable predictor of thyroid malignancy than clinical symptoms alone.

Overall, the demographic and clinical findings of the present study are comparable with those reported in previously published literature. The predominance of middle-aged women, the universal presentation with neck swelling, and the absence of significant demographic differences between euthyroid and SCH patients indicate that baseline clinical characteristics alone cannot adequately identify patients at increased risk of thyroid malignancy. These findings underscore the importance of incorporating biochemical markers such as serum TSH together with ultrasonographic risk stratification and fine-needle aspiration cytology in the comprehensive evaluation of thyroid nodules.

**Thyroid Function and Subclinical Hypothyroidism**

The principal objective of the present study was to evaluate the association between subclinical hypothyroidism (SCH) and thyroid malignancy in patients presenting with thyroid nodules. Among the 100 patients included in the study, 28% were diagnosed with SCH based on elevated serum thyroid-stimulating hormone (TSH) levels with normal free thyroxine (FT4) concentrations. The prevalence of SCH observed in the present study is comparable with that reported in hospital-based studies evaluating patients with thyroid nodules, where the frequency of SCH has ranged between 15% and 35%, depending on the study population, iodine status, and laboratory reference ranges (11,12,16).

In the present study, the mean serum TSH concentration was significantly higher in the SCH group than in the euthyroid group (6.48 ± 1.64 mIU/L versus 2.18 ± 0.81 mIU/L; $p < 0.001$), whereas mean FT4 concentrations remained within the normal physiological range in both groups. These findings are consistent with the biochemical definition of SCH proposed by Biondi and Cooper (11) and reaffirmed by Cooper and Biondi (12), who defined SCH as elevated serum TSH with preserved circulating thyroid hormone concentrations. Maintenance of normal FT4 levels despite elevated TSH reflects early thyroid gland dysfunction in which pituitary compensation is sufficient to maintain euthyroxinemia.

Although SCH has traditionally been regarded as a mild biochemical abnormality, increasing evidence suggests that elevated serum TSH may have important implications beyond thyroid hormone homeostasis. TSH is not merely a marker of thyroid function but also acts as the principal growth factor for thyroid follicular epithelial cells. Binding of TSH to the TSH receptor activates cyclic adenosine monophosphate (cAMP)-mediated intracellular signaling pathways, stimulating cellular proliferation, differentiation, iodine uptake, and thyroglobulin synthesis. Persistent TSH stimulation has therefore been hypothesized to promote the proliferation of genetically altered follicular cells and facilitate the progression of differentiated thyroid carcinoma (7).

The most important finding of the present study was the significantly higher prevalence of thyroid malignancy among patients with SCH compared with euthyroid individuals (42.9% versus 19.4%; $p = 0.015$). This finding supports the hypothesis that elevated serum TSH is associated with an increased risk of thyroid malignancy and reinforces the growing body of evidence suggesting that thyroid function status may contribute to malignancy risk stratification.

The findings of the present study closely parallel those reported by Boelaert et al. (8), whose landmark prospective study involving more than 1,100 patients demonstrated that increasing serum TSH concentrations were independently associated with thyroid malignancy. Patients within the highest TSH categories exhibited the greatest probability of thyroid cancer, and this association remained significant even after adjustment for age, sex, thyroid function, and nodule characteristics. Their study was among the first to establish serum TSH as an

independent predictor of malignancy rather than merely a biochemical indicator of thyroid dysfunction. The significant association observed in the present study further supports this concept.

Similarly, Haymart et al. (9) reported that patients with differentiated thyroid carcinoma had significantly higher preoperative serum TSH concentrations than patients with benign thyroid disease. Furthermore, increasing TSH levels correlated with progressively higher risks of malignancy. In a subsequent investigation, Haymart et al. (10) demonstrated that elevated TSH concentrations were associated not only with the occurrence of thyroid cancer but also with advanced pathological stage, extrathyroidal extension, and more aggressive tumour behaviour. Although tumour staging and long-term outcomes were beyond the scope of the present study, the higher prevalence of malignancy observed among patients with SCH is consistent with the biological relationship described by Haymart and colleagues.

Comparable observations were made by Fiore et al. (14), who demonstrated that patients with suppressed serum TSH concentrations had a significantly lower prevalence of papillary thyroid carcinoma than patients with normal or elevated TSH values. Their findings suggested that even modest elevations of serum TSH may provide a proliferative stimulus favouring malignant transformation or progression of thyroid follicular cells. The significantly higher incidence of thyroid malignancy among SCH patients in the present study lends further support to this hypothesis.

Likewise, Polyzos et al. (15) evaluated serum TSH as a biochemical predictor of thyroid malignancy and concluded that elevated TSH remained significantly associated with thyroid cancer after adjustment for conventional clinical variables. Their findings suggested that serum TSH should be considered an adjunctive risk marker during the evaluation of thyroid nodules. The present study similarly demonstrated that SCH remained significantly associated with thyroid malignancy, even after adjustment for other clinicopathological variables using multivariable logistic regression.

The biological mechanisms linking SCH and thyroid malignancy remain an area of active investigation. Chronic elevation of TSH provides sustained stimulation to thyroid follicular cells through activation of the TSH receptor, resulting in enhanced cellular proliferation and reduced apoptosis. Experimental studies have demonstrated that differentiated thyroid carcinoma cells retain functional TSH receptors and continue to respond to TSH stimulation, thereby providing a biological basis for the routine use of TSH suppression therapy following thyroidectomy for differentiated thyroid carcinoma (7). Persistent TSH stimulation may therefore facilitate the expansion of occult malignant clones already present within thyroid nodules.

Another potential mechanism involves autoimmune thyroid disease. Chronic autoimmune thyroiditis (Hashimoto thyroiditis) represents the most common cause of SCH in iodine-sufficient populations. Several investigators have demonstrated an association between Hashimoto thyroiditis and papillary thyroid carcinoma. Lee et al. (13) reported that chronic lymphocytic inflammation may contribute to thyroid carcinogenesis through repeated epithelial injury, oxidative stress, cytokine-mediated DNA damage, and alterations in the tumour microenvironment. Although anti-thyroid peroxidase antibody levels were unavailable for all patients in the present study, histopathological evidence of Hashimoto thyroiditis was identified in a subset of patients, suggesting that autoimmune mechanisms may have contributed to elevated TSH concentrations in some individuals.

Despite the growing evidence supporting an association between elevated TSH and thyroid malignancy, not all published studies have reached similar conclusions. Differences in study design, sample size, iodine nutrition, laboratory reference ranges, prevalence of autoimmune thyroid disease, and selection criteria have resulted in considerable heterogeneity across published reports. Fiore and Vitti (16) emphasized that serum TSH should be interpreted within the broader clinical context and not regarded as an isolated predictor of malignancy. Likewise, Durante et al. (17) concluded that although elevated TSH increases the probability of thyroid cancer, definitive diagnosis continues to rely upon ultrasonography, fine-needle aspiration cytology, and histopathological examination.

Current international guidelines support this integrated approach. The American Thyroid Association (1) recommends measurement of serum TSH as the initial biochemical investigation in all patients presenting with thyroid nodules. However, management decisions are primarily guided by ultrasonographic risk stratification, cytological findings, and clinical features. Similarly, the American Association of Clinical Endocrinologists (4) recognizes that elevated serum TSH may increase the likelihood of malignancy but does not recommend its use as a standalone indication for surgery. The findings of the present study are consistent with these recommendations and suggest that serum TSH should be considered an adjunctive marker that complements rather than replaces established diagnostic modalities.

The present study further demonstrated that subclinical hypothyroidism remained an independent predictor of thyroid malignancy on multivariable logistic regression analysis. This observation indicates that the association between SCH and malignancy persisted even after adjustment for potential confounding variables. Although causality cannot be established because of the retrospective study design, these findings strengthen the evidence supporting a clinically meaningful relationship between elevated serum TSH and thyroid cancer.

Overall, the results of the present study support the growing body of literature indicating that patients with thyroid nodules and subclinical hypothyroidism constitute a subgroup at relatively higher risk of thyroid malignancy. Routine assessment of thyroid function, particularly serum TSH, may therefore contribute to comprehensive preoperative risk stratification when interpreted alongside ultrasonographic findings, Bethesda cytology, and

histopathological examination. Nevertheless, prospective multicentre studies involving larger patient populations are required to determine whether incorporation of SCH into existing predictive models improves clinical outcomes and surgical decision-making.

**Ultrasonographic Findings (ACR TI-RADS)**

High-resolution ultrasonography has become the cornerstone in the evaluation of thyroid nodules because it provides detailed morphological assessment and facilitates risk stratification for thyroid malignancy. In recent years, standardized reporting systems such as the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) have significantly improved the consistency of ultrasound interpretation and clinical decision-making. Rather than relying on a single sonographic feature, TI-RADS integrates multiple characteristics including composition, echogenicity, shape, margins, and echogenic foci to estimate the probability of malignancy and guide the need for fine-needle aspiration cytology (FNAC) (5).

In the present study, solitary thyroid nodules were more frequently observed than multinodular goitre in both euthyroid and SCH groups; however, the distribution was comparable between the groups and did not achieve statistical significance ($p = 0.624$). This finding suggests that thyroid function status does not appear to influence the number of nodules present. Previous studies have similarly demonstrated that the number of nodules alone is not a reliable predictor of malignancy, as solitary and multinodular thyroid disease may both harbor malignant lesions (1,17).

The most significant ultrasonographic finding in the present study was the higher proportion of high-risk TI-RADS (TR4–TR5) nodules among patients with subclinical hypothyroidism. High-risk lesions were identified in 60.7% of SCH patients compared with 33.3% of euthyroid patients, and this difference was statistically significant ($p = 0.014$). These findings suggest that patients with elevated serum TSH are more likely to exhibit sonographic characteristics associated with thyroid malignancy.

Although relatively few studies have directly compared TI-RADS categories according to thyroid function status, several investigators have independently demonstrated the excellent diagnostic performance of TI-RADS in predicting malignancy. Tessler et al. (5), while introducing the ACR TI-RADS classification, reported that progressive increases in TI-RADS scores were associated with corresponding increases in malignancy risk. The system demonstrated high diagnostic accuracy while simultaneously reducing unnecessary FNACs in patients with low-risk nodules. The present findings support the clinical applicability of TI-RADS and suggest that elevated serum TSH may coexist with higher-risk ultrasound features.

The 2015 American Thyroid Association (ATA) Guidelines (1) similarly recommend that ultrasonographic characteristics should be the primary determinant for selecting nodules for FNAC. Suspicious sonographic features such as marked hypoechogenicity, irregular or infiltrative margins, microcalcifications, taller-than-wide configuration, extrathyroidal extension, and abnormal cervical lymph nodes have consistently been associated with thyroid malignancy. The higher proportion of TI-RADS 4–5 lesions observed among SCH patients in the present study may therefore partly explain the increased prevalence of malignancy identified in this group.

Durante et al. (17) emphasized that ultrasound-based risk stratification has significantly improved the management of thyroid nodules by identifying patients requiring biopsy while avoiding unnecessary procedures in low-risk lesions. Their observations support the present findings, in which ultrasound effectively differentiated patients with higher-risk nodules.

The relationship between elevated TSH and suspicious ultrasonographic characteristics remains biologically plausible. Chronic TSH stimulation may promote follicular cell proliferation, leading to progressive architectural distortion, irregular margins, increased vascularity, and microcalcification formation within malignant nodules. Although ultrasonographic findings alone cannot establish a diagnosis of thyroid carcinoma, their coexistence with elevated TSH may increase the pre-test probability of malignancy and justify more careful evaluation.

Nevertheless, ultrasonography has certain limitations. Considerable interobserver variability exists in the interpretation of sonographic features, particularly with respect to margin assessment and echogenicity. Furthermore, benign inflammatory lesions, including Hashimoto thyroiditis, may occasionally demonstrate suspicious ultrasound characteristics, thereby reducing specificity. Consequently, ultrasonographic findings should always be interpreted in conjunction with thyroid function tests, cytological findings, and clinical assessment rather than in isolation (1,5).

The findings of the present study therefore reinforce current guideline recommendations that serum TSH and ultrasonography provide complementary rather than competing information. Patients presenting with both elevated TSH and high-risk TI-RADS features may constitute a subgroup requiring closer surveillance and earlier cytological evaluation.

**Bethesda Cytology**

Fine-needle aspiration cytology remains the gold standard initial investigation for evaluating thyroid nodules and plays a pivotal role in differentiating benign from malignant lesions. The introduction of the Bethesda System for Reporting Thyroid Cytopathology has standardized cytological interpretation worldwide by categorizing aspirates into six diagnostic categories with corresponding malignancy risks and management recommendations (6).

In the present study, Bethesda category II represented the most common cytological diagnosis in both groups, reflecting the predominance of benign thyroid disease among patients presenting with thyroid nodules. However,

Bethesda categories V and VI, which indicate lesions suspicious for malignancy and malignant cytology respectively, were observed significantly more frequently among patients with subclinical hypothyroidism ($p = 0.022$). This finding suggests that elevated serum TSH is associated not only with biochemical abnormalities but also with increased cytological suspicion of malignancy.

The observed cytological pattern is consistent with the findings of Boelaert et al. (8), who demonstrated that patients with elevated serum TSH were significantly more likely to harbor malignant thyroid lesions confirmed on subsequent histopathology. Their study established serum TSH as an independent predictor of malignancy, even after adjustment for conventional clinical risk factors.

Similarly, Polyzos et al. (15) reported that elevated serum TSH concentrations were associated with a higher frequency of malignant cytological findings in patients undergoing FNAC for thyroid nodules. The present study supports these observations by demonstrating a greater proportion of Bethesda V and VI aspirates among SCH patients.

The Bethesda System has substantially improved communication between cytopathologists and surgeons by assigning an estimated malignancy risk to each cytological category. According to Cibas and Ali (6), Bethesda category II carries a very low risk of malignancy and generally warrants clinical follow-up, whereas categories V and VI usually require surgical intervention because of their high positive predictive value. The predominance of Bethesda II lesions in the present study reflects the generally benign nature of thyroid nodules, while the increased proportion of Bethesda V and VI lesions among SCH patients further supports the association between elevated TSH and malignant disease.

The present findings also correspond with the recommendations of the ATA Guidelines (1), which advocate integration of ultrasound findings, serum TSH, and FNAC rather than reliance upon any single investigation. Patients with elevated TSH, suspicious TI-RADS characteristics, and Bethesda V/VI cytology represent a particularly high-risk subgroup and should be considered for definitive surgical management following multidisciplinary evaluation.

Despite its excellent diagnostic performance, FNAC has recognized limitations. Sampling errors, inadequate aspirates, and indeterminate cytological categories (Bethesda III and IV) continue to present diagnostic challenges. Molecular testing has been proposed as an adjunctive investigation in indeterminate nodules; however, its availability remains limited in many developing countries. Consequently, integration of biochemical markers such as serum TSH with ultrasonographic findings and cytology may improve overall risk stratification in resource-limited settings.

Taken together, the cytological findings of the present study reinforce the concept that subclinical hypothyroidism is associated with a greater likelihood of suspicious or malignant FNAC results. Although serum TSH should not replace cytological evaluation, it may serve as a useful adjunctive marker for identifying patients requiring closer surveillance, repeat aspiration, or early surgical intervention. These observations are consistent with contemporary international guidelines and further support the role of a multimodal approach in the evaluation of thyroid nodules.

**Histopathological Findings**

Histopathological examination remains the gold standard for the definitive diagnosis of thyroid malignancy and serves as the reference standard against which biochemical, radiological, and cytological findings are evaluated. In the present study, nodular colloid goitre constituted the commonest benign lesion, followed by follicular adenoma and Hashimoto thyroiditis. Among malignant lesions, papillary thyroid carcinoma (PTC) was the predominant histological subtype, while follicular thyroid carcinoma was identified in a small proportion of patients.

These observations are consistent with global epidemiological data, which demonstrate that papillary thyroid carcinoma accounts for approximately 80–90% of all differentiated thyroid cancers (1,17). Durante et al. (17) reported that PTC remains the most frequently encountered thyroid malignancy owing to its indolent biological behaviour, excellent long-term survival, and increasing detection through widespread ultrasonography. Similarly, the ATA Guidelines recognize papillary thyroid carcinoma as the predominant histological subtype encountered during evaluation of thyroid nodules (1).

Hashimoto thyroiditis was identified in a subset of patients within both groups, with a slightly greater frequency among patients with subclinical hypothyroidism. This observation is biologically plausible because chronic autoimmune thyroiditis represents the commonest cause of SCH in iodine-sufficient regions. Lee et al. (13) demonstrated a significant association between Hashimoto thyroiditis and papillary thyroid carcinoma, suggesting that chronic inflammation, oxidative stress, and repeated follicular epithelial injury may promote malignant transformation. Although the present study was not specifically designed to evaluate autoimmune thyroid disease, the coexistence of Hashimoto thyroiditis and papillary carcinoma in a proportion of patients further supports this hypothesis.

The overall prevalence of thyroid malignancy in the present study was 26%, which is higher than the malignancy rates reported in community-based thyroid nodule cohorts. This finding is expected because the present study included patients who underwent surgical treatment following clinical, ultrasonographic, and cytological evaluation. Consequently, the study population represented a relatively high-risk cohort with a greater pre-test probability of malignancy. Similar observations have been reported in several surgical series evaluating

thyroidectomy specimens (8,9,17).

**Association Between Subclinical Hypothyroidism and Thyroid Malignancy**

The most important finding of the present study was the significantly higher prevalence of thyroid malignancy among patients with subclinical hypothyroidism compared with euthyroid individuals (42.9% versus 19.4%; $\chi^2 = 5.95$, $p = 0.015$). These findings indicate that patients with SCH were more than twice as likely to harbour malignant thyroid lesions, supporting the hypothesis that elevated serum TSH is associated with an increased risk of thyroid carcinoma.

The findings of the present study are consistent with those of Boelaert et al. (8), who first demonstrated that increasing serum TSH concentrations were independently associated with thyroid malignancy in patients presenting with thyroid nodules. Their study showed a progressive increase in cancer prevalence across increasing TSH categories, establishing serum TSH as an independent predictor of malignancy after adjustment for age and sex.

Similarly, Haymart et al. (9) reported that patients with differentiated thyroid carcinoma had significantly higher serum TSH concentrations than those with benign thyroid disease. Furthermore, increasing TSH levels correlated with progressively greater risks of malignancy and more advanced tumour stage (10). Although tumour staging was beyond the scope of the present study, the significantly higher prevalence of malignancy among SCH patients is in agreement with these observations.

Fiore et al. (14) reported that patients with suppressed serum TSH concentrations had a significantly lower prevalence of papillary thyroid carcinoma than patients with higher TSH levels, further supporting the trophic role of TSH in thyroid tumour development. Likewise, Polyzos et al. (15) concluded that elevated serum TSH may serve as an independent biochemical marker for predicting thyroid malignancy in patients with thyroid nodules.

The biological explanation for this association is supported by experimental evidence demonstrating that TSH stimulates thyroid follicular cell proliferation through activation of the TSH receptor and cyclic AMP signalling pathway. Chronic TSH stimulation promotes cellular proliferation, inhibits apoptosis, and enhances angiogenesis, thereby creating an environment favourable for tumour initiation and progression (7). These mechanisms provide biological plausibility for the clinical observations reported in the present study.

Despite the consistency of these findings with previous literature, the relationship between SCH and thyroid malignancy remains controversial. Some investigators have suggested that elevated TSH may simply represent a consequence of underlying thyroid pathology rather than a causal factor. Differences in iodine nutrition, autoimmune thyroid disease prevalence, laboratory reference ranges, study populations, and retrospective study designs have contributed to variability among published reports (16,17). Nevertheless, the majority of contemporary observational studies support an association between elevated TSH and thyroid malignancy.

**Multivariable Logistic Regression**

Multivariable logistic regression analysis demonstrated that subclinical hypothyroidism remained an independent predictor of thyroid malignancy after adjustment for potential confounding variables. Elevated serum TSH, TI-RADS 4–5 classification, and Bethesda V/VI cytology were also identified as independent predictors, whereas age and sex did not demonstrate significant independent associations.

These findings are particularly important because they suggest that the relationship between SCH and malignancy persists even after accounting for established clinical and radiological risk factors. Similar observations have been reported by Boelaert et al. (8) and Polyzos et al. (15), who demonstrated that serum TSH retained independent predictive value following multivariable adjustment.

From a clinical perspective, the results indicate that serum TSH should be regarded as an adjunctive biomarker that complements rather than replaces ultrasonography and FNAC. Incorporating thyroid function into existing predictive models may improve identification of patients requiring closer surveillance or surgical intervention.

**ROC Curve Analysis**

Receiver operating characteristic (ROC) analysis demonstrated good discriminatory ability of serum TSH for predicting thyroid malignancy, with an area under the curve (AUC) of 0.76. A serum TSH cut-off value of 3.9 mIU/L yielded a sensitivity of 73.1% and specificity of 71.6%.

These findings suggest that serum TSH possesses moderate diagnostic accuracy as a predictor of malignancy. However, the AUC obtained in the present study also indicates that TSH alone is insufficient as a standalone diagnostic test. Similar conclusions have been reached by previous investigators, who have consistently recommended interpretation of serum TSH together with ultrasound findings, cytological diagnosis, and clinical assessment rather than in isolation (1,4,17).

**Clinical Implications**

The findings of the present study have several important clinical implications. First, routine assessment of thyroid function remains an essential component of thyroid nodule evaluation, not only to identify functional thyroid disorders but also because elevated serum TSH may provide additional prognostic information regarding malignancy risk.

Second, patients with SCH who simultaneously demonstrate high-risk TI-RADS features or Bethesda V/VI cytology may represent a subgroup warranting closer surveillance and early surgical referral. Integration of serum TSH into existing risk stratification algorithms may therefore improve patient selection for FNAC and thyroidectomy.
Third, although serum TSH should not be regarded as an independent indication for surgery, its incorporation into multidisciplinary decision-making may improve individualized patient management, particularly in resource-limited settings where access to advanced molecular testing remains limited.

**Strengths of the Study**
The present study evaluated the association between thyroid function, ultrasonographic findings, cytological diagnosis, and final histopathology within a single patient cohort. Histopathological confirmation of all malignant lesions provided a robust reference standard. Furthermore, multivariable logistic regression and ROC curve analysis allowed evaluation of serum TSH as an independent predictor of malignancy while accounting for potential confounding variables.

**Limitations**
The present study has several limitations. Its retrospective design is inherently susceptible to selection bias and incomplete documentation. The study was conducted at a single tertiary care centre with a relatively modest sample size, thereby limiting generalizability. Anti-thyroid peroxidase antibody status and molecular testing were unavailable for many patients, precluding detailed evaluation of autoimmune thyroid disease and genetic alterations. Long-term follow-up data regarding recurrence and disease-specific survival were also unavailable.

**Future Directions**
Large prospective multicentre studies with standardized TSH reference ranges, comprehensive autoimmune profiling, molecular analysis, and long-term follow-up are required to further clarify the relationship between subclinical hypothyroidism and thyroid malignancy. Future research should also evaluate whether correction of elevated serum TSH influences tumour progression, recurrence, or disease-specific survival and whether incorporation of serum TSH into validated predictive models improves clinical decision-making.

**CONCLUSION OF THE DISCUSSION**
The findings of the present study demonstrate a significant association between subclinical hypothyroidism and thyroid malignancy among patients with thyroid nodules. Patients with SCH exhibited higher serum TSH concentrations, a greater frequency of high-risk ultrasonographic features, more suspicious cytological findings, and a significantly higher prevalence of papillary thyroid carcinoma than euthyroid patients. Multivariable analysis confirmed that SCH remained an independent predictor of malignancy, while ROC analysis demonstrated moderate discriminatory ability of serum TSH. These findings support the role of serum TSH as a useful adjunctive biomarker that complements ultrasonography and FNAC in the comprehensive risk stratification of thyroid nodules. Nevertheless, prospective multicentre studies are warranted before SCH can be routinely incorporated into clinical prediction models for thyroid malignancy.

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