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Research Article

Serum TSH Levels as a Predictor of Malignancy in Thyroid Nodules: a Retrospective Cross-Sectional Analytical Study

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ABSTRACT
Background: Thyroid nodules are common endocrine findings, with malignancy reported in 5–15% of cases. Although Fine Needle Aspiration Cytology (FNAC) remains the cornerstone of diagnosis, interest in biochemical predictors such as serum Thyroid Stimulating Hormone (TSH) has increased.
Aim: To evaluate the association between serum TSH levels and malignancy in thyroid nodules in a North Kashmir female cohort.
Methods: A retrospective cross-sectional analysis of 50 consecutive female patients with thyroid nodules undergoing FNAC and preoperative serum TSH estimation was performed. Cytology was classified according to the Bethesda System for Reporting Thyroid Cytopathology. Bethesda V–VI were considered malignant. TSH was analyzed as continuous and categorical (≤2.5 vs >2.5 µIU/mL). Statistical analysis included Student's t-test and chi-square test.
Results: Mean TSH in malignant cases (n=19) was significantly lower (1.58 µIU/mL) compared to benign/indeterminate cases (3.26 µIU/mL) ($p=0.003$). TSH ≤2.5 µIU/mL was significantly associated with malignancy ($x^2=4.99$, $p=0.026$).
Conclusion: Lower serum TSH levels were significantly associated with malignant thyroid nodules. TSH may serve as an adjunctive biomarker in malignancy risk stratification; however, larger prospective studies are required.

INTRODUCTION

Thyroid nodules represent one of the most common endocrine abnormalities encountered in clinical practice. Palpable nodules occur in approximately 4–7% of adults, while high-resolution ultrasonography detects nodules in up to 60–70% of the general population [1,2]. Despite this high prevalence, only 5–15% of nodules are malignant, necessitating accurate risk stratification to avoid unnecessary surgical intervention while ensuring timely diagnosis of thyroid cancer [3]. Fine Needle Aspiration Cytology (FNAC) remains the diagnostic standard and is reported according to the Bethesda System for Reporting Thyroid Cytopathology, which provides standardized malignancy risk categories [4]. However, indeterminate cytology (Bethesda III–IV) continues to present clinical challenges, often leading to diagnostic surgery [5]. Therefore, identifying reliable, cost-effective, and widely available biomarkers to improve preoperative risk assessment remains an important research priority.Thyroid Stimulating Hormone (TSH), secreted by the anterior pituitary gland, regulates thyroid hormone synthesis and has well-established trophic effects on thyroid follicular epithelium. Experimental data demonstrate that TSH stimulates thyroid cell proliferation through cyclic AMP (cAMP)–dependent pathways and activation of MAPK signaling cascades [6,7]. These proliferative effects have raised the possibility that TSH may contribute to thyroid carcinogenesis.Several clinical studies have suggested that higher serum TSH levels are associated with an increased likelihood of differentiated thyroid carcinoma [8–11]. Conversely, other investigations have reported conflicting or population-dependent findings [12,13]. Variations in iodine status, autoimmune thyroid disease prevalence, genetic factors, and laboratory assay differences may contribute to these discrepancies. Notably, data from South Asian populations remain limited despite a substantial burden of thyroid disorders in this region. The biological behavior of thyroid nodules and their hormonal associations may differ in iodine-variable settings. Therefore,

this study was designed to evaluate the association between serum TSH levels and malignancy in thyroid nodules in North Kashmir female cohort.

Materials and Methods

Study Design

Retrospective cross-sectional analytical study.

Study Area: Department of ENT and Head and neck Surgery in A Medical College in North Kashmir, conducted from September 2025 to January 2026

Study Population: Female patients attending OPD, with thyroid nodules who underwent FNAC and preoperative serum TSH estimation

Sample Size

Sample size was calculated using the formula for comparison of two independent means (unpaired t-test method) by a Epi Info. Assuming a mean TSH difference of 1.68 µIU/mL between malignant and benign groups and an estimated pooled standard deviation of 2.0 µIU/mL ,with 95% confidence level ($Z\alpha/2 = 1.96$) and 80% power ($Z\beta = 0.84$), the minimum required sample size was calculated as 23 patients per group (total 46). Therefore, the final sample size of 50 patients was considered statistically adequate.

Sampling Technique: By convenience type. Consecutive female patients with thyroid nodules evaluated by FNAC and pre-operative serum TSH levels where taken till the sample size was achieved

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Inclusion Criteria

- Female patients with thyroid nodules
- Availability of FNAC and serum TSH data

Exclusion Criteria

- Thyroid hormone therapy
- Anti-thyroid medication
- Known pituitary disorders

FNAC Classification

Cytology was categorized according to the Bethesda System for Reporting Thyroid Cytopathology [4].

Statistical Analysis

Data was entered in Microsoft Excel. Then was analyzed by Jamovi software 2.7.18. (a free to use statistical software). Categorical associations were assessed using chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 50 female patients with thyroid nodules were included in the study. Based on cytological classification, 19 cases (38%) were categorized as malignant (Bethesda V–VI), while 31 cases (62%) were classified as benign or indeterminate (Bethesda II–IV). The mean serum TSH level in the malignant group was 1.58 µIU/mL, which was significantly lower than the mean TSH level of 3.26 µIU/mL observed in the benign/indeterminate group ($p = 0.003$), indicating a statistically significant difference between the two groups.

When analyzed categorically, 16 of 19 malignant cases (84.2%) had TSH levels ≤2.5 µIU/mL, compared to 15 of 31 benign cases (48.4%). Conversely, TSH levels >2.5 µIU/mL were observed in only 3 malignant cases (15.8%) versus 16 benign cases (51.6%). This association between lower TSH levels (≤2.5 µIU/mL) and malignancy was statistically significant ($\chi^2 = 4.99$, $p = 0.026$). Receiver Operating Characteristic (ROC) curve analysis demonstrated moderate discriminatory ability of serum TSH in predicting malignancy, with an Area Under the Curve (AUC) of 0.74 (95% CI: 0.60–0.88, $p = 0.004$). At the cutoff value of ≤2.5 µIU/mL, serum TSH showed a sensitivity of 84.2% and specificity of 51.6%, suggesting good screening potential but moderate specificity

Categorical TSH Analysis

TSH Category	Benign (n=31)	Malignant (n=19)	
>2.5 µIU/mL	16	3	Chi-square = 4.99 p = 0.026
≤2.5 µIU/mL	15	16	

Patients with TSH ≤2.5 µIU/mL demonstrated a significantly higher proportion of malignancy.

Graphical Analysis

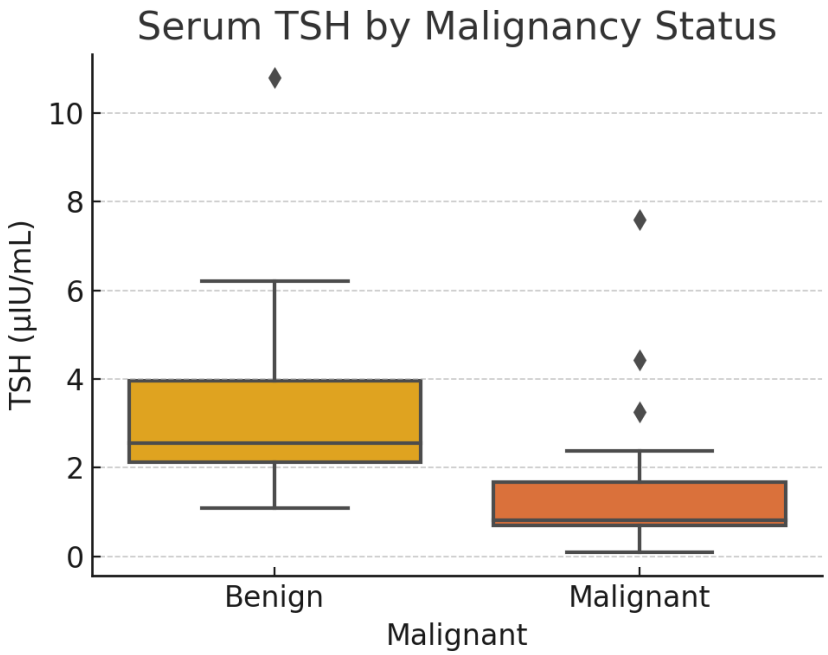

Figure 1: Boxplot of TSH by Malignancy Status

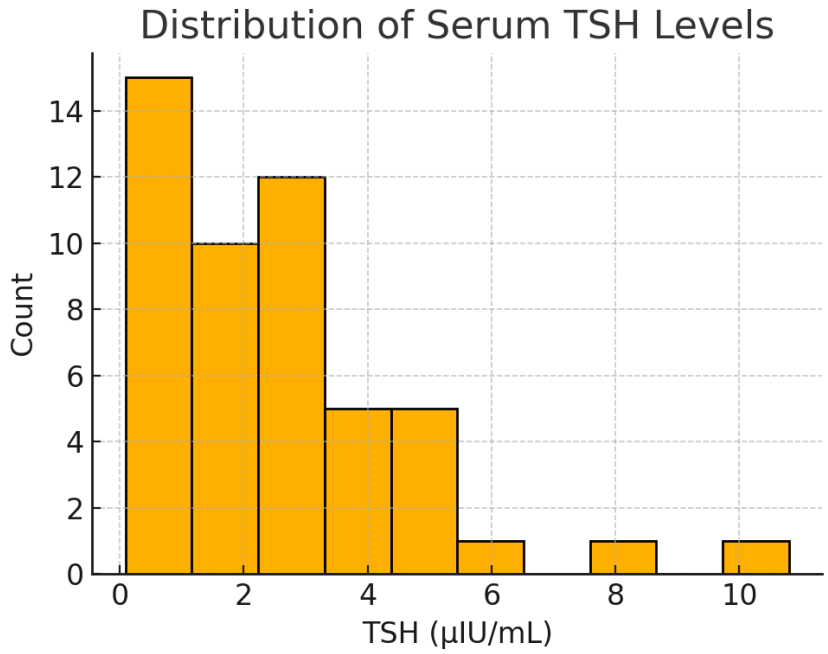

Figure 2: Histogram of TSH Distribution

The histogram illustrates an overall right-skewed distribution of TSH values. Malignant cases predominantly cluster in the lower TSH range, whereas benign cases show a broader distribution extending into higher TSH values.

DISCUSSION

The present study demonstrates a statistically significant association between lower serum TSH levels and malignant thyroid nodules in a North Kashmir female cohort. Malignant nodules exhibited significantly lower mean TSH values compared to benign and indeterminate nodules, and a TSH cutoff of ≤2.5 µIU/mL was significantly associated with malignancy. These findings suggest that serum TSH may have predictive utility in preoperative risk stratification.

Several landmark studies from Western populations have reported contrasting findings. Boelaert et al. observed that increasing serum TSH concentrations were independently associated with a higher likelihood of thyroid malignancy in patients with nodular thyroid disease [8]. Similarly, Haymart et al. reported that higher preoperative TSH levels were associated not only with malignancy but also with advanced tumor stage in differentiated thyroid carcinoma [9]. Additional studies by Fiore et al. and Polyzos et al. supported a positive association between elevated TSH and cancer risk [10,11]. These observations are biologically plausible, given the well-established trophic effects of TSH on thyroid follicular cells.

However, the relationship between TSH and thyroid cancer appears to be complex and potentially population-dependent. Some investigations have demonstrated weak, non-linear, or inconsistent associations [12, 13]. Differences in iodine nutrition, genetic background, autoimmune thyroiditis prevalence, and environmental exposures may significantly influence the hormonal milieu and tumor biology [14, 15]. In iodine-variable regions, alterations in thyroid physiology may modify TSH dynamics, potentially explaining the inverse association observed in our cohort.

From a mechanistic perspective, TSH stimulates follicular cell proliferation through activation of cyclic AMP (cAMP), protein kinase A, and downstream MAPK signaling pathways [6, 7]. While chronic TSH stimulation has been implicated in tumorigenesis, malignant transformation may also result in altered thyroid hormone synthesis and feedback regulation. Suppressed TSH levels in malignant cases, as observed in our study, may reflect partial tumor autonomy, subclinical hyperfunction, or altered hypothalamic–pituitary–thyroid axis feedback mechanisms. It is conceivable that early neoplastic changes disrupt normal regulatory control, leading to subtle reductions in circulating TSH.

Clinically, these findings suggest that serum TSH, a widely available and cost-effective test, may serve as an adjunctive biomarker in evaluating thyroid nodules—particularly in settings where molecular testing is not readily accessible. In resource-limited regions, biochemical markers that assist in refining malignancy risk could reduce unnecessary surgical interventions and improve patient counseling. However, TSH alone should not replace cytological or radiological assessment but may complement established diagnostic algorithms.

An important implication of this study is the need for region-specific validation of TSH cutoff values. Most existing recommendations are derived from Western populations, and endocrine dynamics may differ in South Asian cohorts. Establishing population-adjusted reference ranges and risk thresholds could enhance diagnostic precision.

Additionally, our findings raise the possibility that the association between TSH and malignancy may not be strictly linear. Rather than a simple "higher TSH–higher cancer risk" model, the relationship may follow a more complex pattern influenced by tumor biology, iodine status, and host endocrine regulation. Future studies incorporating multivariate logistic regression, larger sample sizes, and histopathological confirmation are necessary to determine whether TSH is an independent predictor after adjustment for confounders such as age, nodule size, autoimmune thyroiditis, and ultrasonographic risk features.

Limitations

- Small sample size
- Retrospective design
- Female-only cohort
- FNAC rather than histopathology as definitive diagnosis

Prospective multicenter studies with histopathological confirmation are recommended to validate these findings and define optimal predictive thresholds.

CONCLUSION

In this retrospective cross-sectional study of female patients with thyroid nodules from North Kashmir, serum TSH levels demonstrated a statistically significant association with cytologically diagnosed malignancy. Malignant nodules were characterized by lower mean TSH values compared to benign and indeterminate lesions, and a cutoff of ≤2.5 μIU/mL showed moderate discriminatory performance on ROC analysis. These findings suggest that serum TSH may have potential utility as an adjunctive biochemical marker in preoperative risk stratification of thyroid nodules. However, given the limited sample size and retrospective design, larger prospective studies with histopathological confirmation and multivariate adjustment are required to validate these observations and clarify the role of TSH in

malignancy prediction within region-specific populations.

Ethical Consideration: Ethical clearance was sought from the Instructional Review Board(IRB).

Conflict of interest: Nil

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