Original Article

Serum thyroid-stimulating hormone as a diagnostic marker for cancer in atypia of undetermined significance/follicular lesion of undetermined significance nodules

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Background: Several studies have assessed the efficacy of thyroid-stimulating hormone (TSH) as a diagnostic marker of thyroid cancer (TC), with inconsistent findings. However, few studies have investigated its role in indeterminate thyroid nodules (TNs), particularly in those with atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). The objective of this study was to evaluate preoperative TSH levels as a diagnostic marker for cancer in AUS/FLUS nodules.

Methods: A retrospective analysis was conducted on patients who underwent thyroidectomy with a primary cytological diagnosis of AUS/FLUS. The association between preoperative TSH levels and the final anatomopathological diagnosis (benign *vs.* differentiated TC) was examined.

Results: The analysis included 109 patients. The median TSH level was higher in patients with malignant nodules (2.32 mIU/L) than in those with benign pathology (1.60 mIU/L) (P=0.04). Receiver operating characteristic (ROC) curve analysis revealed that the TSH level was a potential indicator for the coexistence of thyroid malignancy, with a significant area under the curve of 0.61 (P=0.04). The optimal diagnostic cutoff point for TSH levels was ≥3.06 mIU/L.

Conclusions: This study demonstrated that TSH levels are an acceptable and useful marker to rule in rather than rule out TC in AUS/FLUS nodules.

Keywords: Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); differentiated thyroid cancer (differentiated TC); indeterminate thyroid nodules (indeterminate TNs); risk of malignancy (ROM); thyroid-stimulating hormone (TSH)

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Introduction

Background

The prevalence of thyroid cancer (TC) has markedly increased in recent years. This malignancy can manifest clinically as a nodule, which cannot be differentiated from benign lesions (1). In addition to clinical and radiological parameters, the management of thyroid nodules (TNs) is based on cytological assessments, as outlined in the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) (2). Although fine-needle aspiration cytology (FNAC) is a safe and informative technique for TN assessment, some FNACs have uncertain cytology, and choosing the most appropriate treatment remains challenging (3).

The risk of malignancy (ROM) in TNs diagnosed as atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), also known as Bethesda III, has been reported to be between 5% and 15% (4). However, the ROM ranges between 6% and 76% in surgically resected nodules (1). Most AUS/FLUS nodules are excised solely in the presence of concerning clinical or sonographic characteristics, an aberrant result on repeated aspiration, or an unfavorable outcome on molecular testing. In contrast, AUS/FLUS nodules that show a benign result on repeated FNAC and/or a benign outcome on molecular testing are not subjected to surgical removal (2).

Research is ongoing to identify a simple adjunct test for stratifying the ROM in cytologically indeterminate thyroid nodules (CITNs). Thyroid-stimulating hormone (TSH), which regulates thyroid function and hormone production, is of particular interest. Measuring serum TSH levels is essential for the biochemical evaluation of individuals with TNs as it is a valuable marker for detecting thyroid dysfunction (5). High TSH levels are known to cause the initiation and progression of differentiated TC, even if the levels are within the normal range (6-8). This may be mediated by TSH receptors, which can be found on cancer cell membranes and activate pathophysiological processes, stimulating TC growth (9).

Rationale and knowledge gap

Few studies have examined the role of TSH as a potential indicator of TC in CITNs, demonstrating the usefulness of TSH as a simple adjunct test while attempting to determine an appropriate cutoff value. Such a threshold can be utilized to predict the ROM in patients with TNs that have undergone surgical intervention (1,9-12). In contrast, other studies have found no correlation between TSH levels and malignant TNs (13-15). In addition to TSH levels, other biomarkers such as anti-thyroid antibodies (thyroid peroxidase and thyroglobulin antibodies) have been utilized as diagnostic and prognostic tools in CITNs (11).

Objective

This study aimed to ascertain whether serum TSH levels may serve as a potential indicator for TC in AUS/FLUS TNs. We present this article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-2024-520/rc).

Highlight box

Key findings

- The preoperative level of thyroid-stimulating hormone (TSH) may be a useful diagnostic marker for ruling in rather than ruling out malignancy in thyroid nodules diagnosed as atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS).

What is known and what is new?

- The current literature has conflicting reports regarding the utility of TSH levels for predicting cancer in AUS/FLUS nodules.
- The current study confirmed that elevated TSH levels were associated with a higher risk of malignancy and can be used as a predictive marker.

What is the implication, and what should change now?

- Measuring preoperative TSH levels is a simple adjunct test that may help guide endocrine surgeons in developing a personalized treatment approach for patients with AUS/FLUS thyroid nodules.

Methods

This study is a retrospective analysis of the patients included in our previous report (16); patients with a primary cytological diagnosis of AUS/FLUS who underwent thyroidectomy between January 2011 and December 2014 at King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia were enrolled. Exclusion criteria included a final diagnosis of lymphoma (n=2) and unavailable preoperative TSH levels (n=4), resulting in a final cohort of 109 patients. Clinical and radiological data were collected from the medical records, and several factors were assessed, including age, sex, ultrasound features, preoperative serum TSH levels, and final pathological results (benign *vs.* differentiated TC). The final pathological diagnosis was

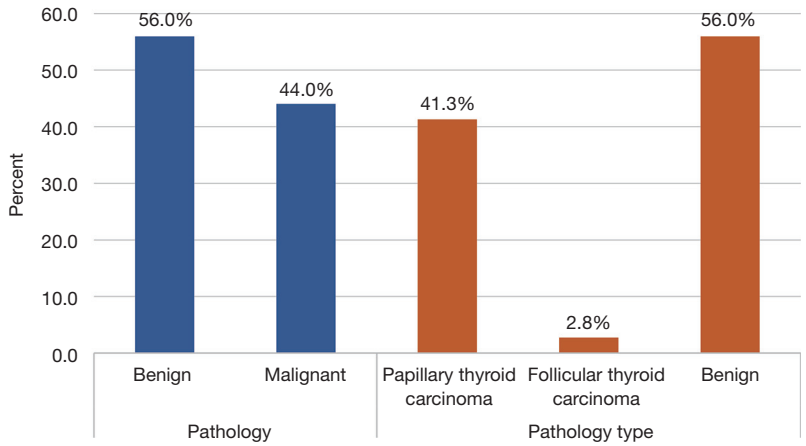

Figure 1 The final pathology results.

determined based on histopathological examination of surgical specimens using the World Health Organization criteria. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments and approved by the Office of Research Affairs at King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia (No. 2245263; date of approval, 29 May 2024). Patient consent was waived due to anonymous collection of patient data.

TSH levels

TSH levels were measured preoperatively with an electrochemiluminescence immunoassay (Roche Corporation, Indianapolis, IN, USA). The assay was performed according to the manufacturer's instructions, and TSH levels were categorized into four quartiles: 0.02–0.96, 0.97–2.0, 2.01–3.0, and 3.01–4.59 mIU/L.

Statistical analysis

We used SPSS (version 26; IBM, Armonk, NY, USA) for all calculations. All statistical analyses were two-tailed, with $P<0.05$ considered significant. Categorical variables are described as frequencies with percentages, whereas quantitative data are displayed as mean ± standard deviation or median and interquartile range (Q1–Q3), based on the distribution of the data. The normality of the distribution was determined using the Shapiro-Wilk test. The study groups (benign *vs.* malignant nodules) were compared using Fisher's exact, Student's *t*-, and the Chi-squared tests for normally distributed quantitative data and the Mann-Whitney *U* test for skewed quantitative data. Receiver operating characteristic (ROC) curves were constructed, and the area under the ROC curve (AUC), accuracy, specificity, sensitivity, and positive and negative predictive values were calculated to evaluate the performance of TSH as a diagnostic marker. The optimal diagnostic cutoff for TSH levels was determined using the Youden index, which maximizes sensitivity and specificity. Multiple logistic regression was utilized to identify predictors of TC, expressed as adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

The clinical information and reference standard results were available to the performers/readers of the index test.

Results

Of the 109 patients that met the inclusion criteria, 48 (44%) had malignant pathology; 45 were diagnosed with papillary TC (PTC) and 3 with follicular TC (*Figure 1*). *Table 1* lists the demographic, clinical, and ultrasound characteristics; only sex, the presence of a peripheral halo, and TSH levels were significantly different between the benign and malignant groups. In total, 70.8% and 83.6% of the malignant and benign nodules, respectively, were diagnosed in women ($P=0.05$). Additionally, 60.4% of malignant nodules had a peripheral halo, whereas only 47.5% of benign nodules showed this characteristic ($P=0.05$). The median TSH level was 2.32 (range, 0.02–16.1) mIU/L for patients with malignant nodules and 1.60 (range, 0.02–31.2) mIU/L for patients with benign nodules ($P=0.04$).

Figure 2 displays the distribution of TSH quartiles based on nodule pathology. Patients with malignant TNs were

Table 1 Demographics and ultrasound findings of patients with benign and malignant AUS/FLUS nodules

Factor	Total	Pathology		P value
		Benign	Malignant	
Age (years), mean ± SD [range]	41.2±11.6 [15–71]	41.9±11.3 [16–68]	40.3±12.0 [15–71]	0.46†
Sex				0.05*
Male	24 (22.0)	10 (16.4)	14 (29.2)	
Female	85 (78.0)	51 (83.6)	34 (70.8)	
Content				0.52‡
Solid	74 (67.9)	40 (65.6)	34 (70.8)	
Predominantly solid (>50% solid)	27 (24.8)	15 (24.6)	12 (25.0)	
Predominantly cyst-like (>50% cystic)	8 (7.3)	6 (9.8)	2 (4.2)	
Shape				0.77
Ovoid	71 (65.1)	39 (63.9)	32 (66.7)	
Irregular	38 (34.9)	22 (36.1)	16 (33.3)	
Margins				0.44
Smooth	66 (60.6)	35 (57.4)	31 (64.6)	
Ill-defined	43 (39.4)	26 (42.6)	17 (35.4)	
Size (mm)				0.95†
Range	6–130	6–100	7–130	
Mean ± SD	34.5±23.0	34.4±21.1	34.6±25.4	
Echogenicity				0.28
Hypoechoic	60 (55.0)	34 (55.7)	26 (54.2)	
Isoechoic	17 (15.6)	12 (19.7)	5 (10.4)	
Hyperechoic	32 (29.4)	15 (24.6)	17 (35.4)	
Calcification				0.50
Yes	24 (22.0)	12 (19.7)	12 (25.0)	
No	85 (78.0)	49 (80.3)	36 (75.0)	
Echotexture				0.21
Homogenous	45 (41.3)	22 (36.1)	23 (47.9)	
Heterogenous	64 (58.7)	39 (63.9)	25 (52.1)	
Vascularity				0.96
Hypervascular	61 (56.0)	34 (55.7)	27 (56.3)	
Hypovascular	48 (44.0)	27 (44.3)	21 (43.8)	
Lymphadenopathy				0.72‡
Yes	8 (7.3)	4 (6.6)	4 (8.3)	
No	101 (92.7)	57 (93.4)	44 (91.7)	
Peripheral halo				0.05*
Yes	58 (53.2)	29 (47.5)	29 (60.4)	
No	51 (46.8)	32 (52.5)	19 (39.6)	
TSH (mIU/L), median (range)	2.03 (0.02–31.2)	1.60 (0.02–31.2)	2.32 (0.02–16.1)	0.04*§

Data are presented as n (%) unless otherwise specified. *, P<0.05. P values were calculated using the Pearson χ^2 test, unless otherwise noted. †, independent samples *t*-test; ‡, exact probability test; §, Mann-Whitney *U* test. AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; SD, standard deviation; TSH, thyroid-stimulating hormone.

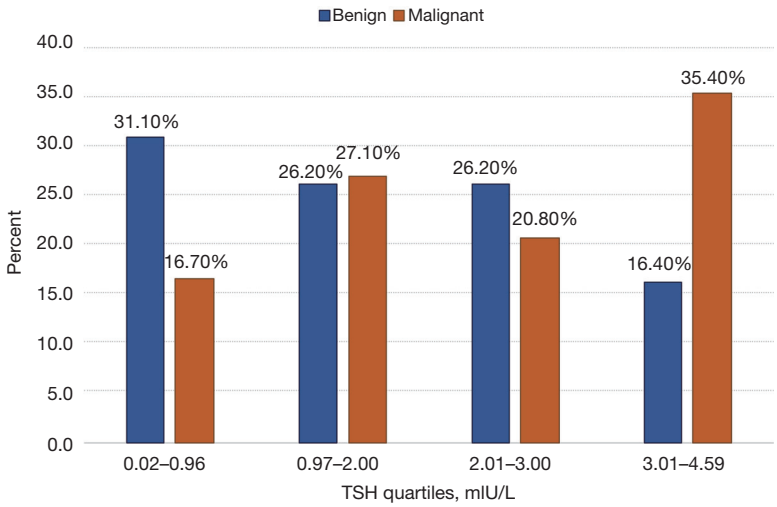

Figure 2 Distributions of benign and malignant nodules based on TSH quartile. TSH, thyroid-stimulating hormone.

Table 2 The potential of TSH levels as a diagnostic marker for thyroid malignancy

ROC statistics	Values
AUC (95% CI)	0.61 (0.51–0.72)
P value	0.04*
Youden index cut-off	≥3.06 mIU/L
Sensitivity	35%
Specificity	87%
PPV	84%
NPV	41%

*, P<0.05. AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; TSH, thyroid-stimulating hormone.

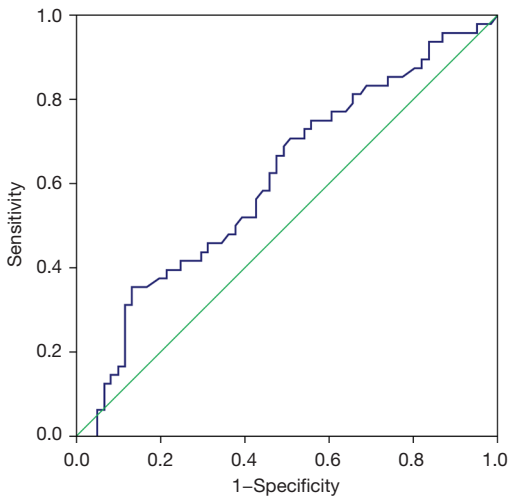

Figure 3 ROC curve analysis for TSH levels in patients with malignancy. ROC, receiver operating characteristic; TSH, thyroid-stimulating hormone.

significantly more likely to have TSH levels in the highest quartile than those with benign pathology; patients with benign nodules were significantly more likely to have serum TSH levels in the lowest quartile than those with malignant pathology (P=0.05).

As shown in *Table 2* and *Figure 3*, the ROC analysis demonstrated that TSH levels showed average potential as a marker for the presence of TC, with an AUC of 0.61 (95% CI: 0.51–0.72; P=0.04). The optimal diagnostic cut-off value was ≥3.06 mIU/L, with a sensitivity of 35% and specificity of 87%, indicating that TSH was more useful as a marker to rule in rather than rule out TC.

Multiple logistic regression analysis was performed to determine predictors of TC in AUS/FLUS TNs (*Table 3*). Of the parameters considered, only TSH levels were associated with the ROM, with a 12% increase in risk at higher TSH levels (OR, 1.12; 95% CI: 1.014–2.047; P=0.05).

Discussion

Key findings

In our previous studies, we found that clinical and

Table 3 Multiple logistic regression analysis for predictors of malignancy in AUS/FLUS nodules

Factor	P value	AOR	95% CI	
			Lower	Upper
Age (years)	0.28	0.979	0.942	1.017
Female	0.15	0.470	0.168	1.312
TSH	0.049*	1.12	1.014	2.047
Size (mm)	0.84	1.002	0.984	1.021
Predominantly solid	0.67	1.251	0.441	3.548
Predominantly cyst-like	0.66	0.660	0.107	4.086
Irregular shape	0.69	1.268	0.401	4.015
Ill-defined margin	0.50	0.683	0.228	2.047
Hyperechogenic echogenicity	0.68	1.113	0.671	1.847
Calcification	0.27	1.800	0.634	5.115
Heterogenous echotexture	0.22	0.543	0.206	1.427
Hypervascularity	0.49	1.363	0.564	3.293
Lymphadenopathy	0.72	1.328	0.281	6.285
Peripheral halo	0.62	1.271	0.487	3.318

*, P<0.05. AOR, adjusted odds ratio; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; CI, confidence interval; TSH, thyroid-stimulating hormone.

radiological characteristics were ineffective predictors of cancer in AUS/FLUS nodules (16,17). Therefore, this study aimed to examine the utility of TSH levels as a simple biochemical marker for predicting TC in AUS/FLUS nodules. Our findings demonstrated that TSH levels were moderately effective as a diagnostic marker, with greater utility in ruling in malignancy than in ruling it out.

Strengths and limitations

One of the strengths of our study is that all the included patients had a final pathological diagnosis (benign *vs.* differentiated TC). Additionally, it is one of the few studies to explore the effectiveness of TSH levels as a cancer predictor in AUS/FLUS nodules. However, its limitations should be acknowledged and include the retrospective methodology and small sample size. Furthermore, as a single-institution study where only surgically resected nodules were included, selection bias was unavoidable. Lastly, our study did not include data on cancer stage, disease-free survival, or anti-thyroid antibody levels.

Comparison with similar researches

A prospective study demonstrated that, in conjunction with an individual's age, sex, and specific type of goiter, the TSH level at the time of diagnosis was an independent predictor of TC, even if it fell within the normal range (18). Another study involving 236 patients without thyroid dysfunction revealed that mean TSH levels were lower in individuals with benign lesions than in those with lesions diagnosed as differentiated TC (5). Correspondingly, TSH suppression has been shown to be beneficial for individuals with differentiated TC (10). In addition, patients with higher TSH levels, even within the normal range, were found to have a heightened risk of developing differentiated TC; therefore, FNAC was recommended for TNs that fell within the biopsy threshold when TSH levels were elevated within the normal range (5).

Cappelli *et al.* found a correlation between TSH levels in the upper normal range and heightened ROM in patients with CITNs. They concluded that measuring serum TSH levels is a simple supplementary test to support decision-

Table 4 Cut-off value for TSH (mIU/L) from different studies for indeterminate thyroid nodules

Study	Cut-off value for TSH (mIU/L)	Cytological diagnosis
Cappelli *et al.* [2020] (10)	≥2.7	TIR3A and TIR3B
Adhami *et al.* [2020] (11)	≥1	Bethesda III, IV, or V
Amado *et al.* [2022] (1)	≥2.68	Bethesda III
Kaliszewski *et al.* [2022] (9)	2.5	Bethesda III
Vinod *et al.* [2022] (12)	>2.185	Bethesda III
Present study [2024]	≥3.06	Bethesda III

TSH, thyroid-stimulating hormone.

making in individuals with indeterminate nodules (10). Similarly, Amado *et al.* found a correlation between elevated TSH levels in CITNs and increased ROM (1). Therefore, TSH levels have the potential to become a useful diagnostic tool for stratifying ROM and assisting in the management of these nodules. In 2020, Adhami *et al.* reported that a TSH level ≥1 mIU/L and high levels of anti-thyroid antibodies were both associated with heightened ROM in patients with CITNs (11). In addition, TSH levels >2.185 mIU/mL have been reported as a reliable indicator of TC in CITNs. Our results identified a cut-off value of ≥3.06 mIU/L, which is higher than those previously reported. *Table 4* compares the cut-off values for TSH found in different studies on CITNs.

Conversely, Gudmundsson *et al.* showed that low TSH levels may elevate the risk of malignant cell transformation in the context of three distinct genetic variations found at 2q35, 8p12, and 14q13.3 (19). Furthermore, Castro *et al.* (20) showed that TSH levels did not predict ROM in cytologically suspicious TNs, although the ROM was elevated among patients who received thyroid hormone replacement therapy.

Explanations of findings

TSH is widely recognized to have a substantial influence on the proliferation of thyroid cells, and thyrotropin-activated signaling pathways are known to affect TC occurrence. Notably, a high TSH level, even if within the normal range, is correlated with an increased ROM (9). A study involving 27,914 patients found a strong correlation between the prevalence of PTC and serum TSH levels, with a lower frequency of PTC in individuals with TSH levels <0.4 µU/mL than in those with TSH levels >3.4 µU/mL (21). Furthermore, high TSH levels have been observed in advanced stages of TC (9) and correlate with poor disease-free survival in individuals with PTC (22). A recent study showed that patients who had TSH levels >4.5 mIU/L, together with specific ultrasound findings, demonstrated elevated ROM (23). Although the results obtained in this study did not reach statistical significance (23), similar findings have been reported in other studies (24,25).

Implications and actions needed

One of the challenges associated with ambiguous nodules is the potential for patients with benign conditions to undergo unnecessary surgical procedures, whereas patients with malignant conditions may not receive timely and optimal therapy (12). Repeated FNAC is recommended for CITNs in the updated versions of TBSRTC (2,26), and Jooya *et al.* demonstrated that repeated FNAC in CITNs can result in more definite categorization (27). The updated guidelines from the American Thyroid Association (2) and the latest version of TBSRTC identify molecular testing as a useful alternative (26); however, the limited accessibility of molecular testing in most facilities restricts its use.

The current literature remains contentious regarding the appropriate degree of thyroidectomy, highlighting the potential risks of both under- and over-treatment (3). Some investigators believe that total thyroidectomy is the best option for CITNs because it enables a comprehensive assessment of the entire thyroid gland. Conversely, other researchers argue that lobectomy alone is satisfactory for such patients (3). Despite this ongoing debate, adopting personalized approaches for therapy is generally advised, incorporating TSH levels with demographic, radiological, pathological, and molecular data (9,23,28).

For surgeons, the challenge of decision-making in the context of AUS/FLUS may be effectively addressed by assessing TSH levels. This simple measurement can provide valuable insights into the likelihood of malignancy

and offers a cost-effective alternative to more expensive molecular testing methods, particularly when used in conjunction with clinical evaluations and ultrasound findings (12).

Importantly, the purpose of investigating the relationship between TSH and malignancy was not to use TSH levels as the only diagnostic indicator to determine the optimal therapeutic strategy for patients with AUS/FLUS nodules. Rather, together with patient characteristics, cytological findings, and ultrasound data, including TSH levels in the assessment process may allow for the classification of patients into high- or low-risk categories. This classification can help prevent unnecessary thyroidectomies and guide clinical decision-making.

Conclusions

In conclusion, elevated TSH levels are a moderately effective diagnostic marker for ROM in AUS/FLUS nodules. Therefore, other factors, including clinical evaluation, ultrasound findings, and cytological assessment, should also be considered. Evaluating additional biochemical tests, such as those for thyroid antibodies, may also be beneficial for the ongoing care of patients with these nodules. Furthermore, prospective multicenter studies are imperative to definitively identify TSH levels as a useful indicator for cancer and define the role of this analyte in the clinical management of CITNs.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments and approved by the Office of Research Affairs at King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia (No. 2245263; date of approval, 29 May 2024). Patient consent was waived due to anonymous collection of patient data.

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