Original Article

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Surgery Section

Serum TSH Levels as a Predictor of Thyroid Malignancy in Euthyroid Patients with a Thyroid Nodule- A Cohort Study

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ABSTRACT

Introduction: Palpable thyroid nodules are a common disorder in the general population. In many cases, the initial presentation of thyroid cancers can be a thyroid nodule. Hence, this is important to distinguish between a benign and a malignant nodule. Fine Needle Aspiration Cytology (FNAC) is the gold standard for evaluating a thyroid nodule. Currently, FNAC is a much more reliable diagnostic technique. However, there are certain limitations of FNAC, which makes the serum Thyroid Stimulating Hormone (TSH) an essential marker in evaluating the thyroid nodule. It has been observed that the frequency of malignancy varies by the serum TSH levels within its normal range itself. Hence, in the present study, authors aim to assess the role of preoperative serum TSH in predicting the malignancy associated with thyroid nodules.

Aim: To evaluate the usefulness of preoperative serum TSH levels in patients with 'nodular thyroid disease', in prediction of malignancy.

Materials and Methods: This is a cohort study conducted over six years from January 2014 to December 2020 by the Department of Surgery of Gandhi Medical College and associated Hospital, Bhopal, India. A total of 50 patients with thyroid nodule(s) having preoperative serum TSH levels within the normal range were included in this study. Serum TSH levels were measured by Electrochemiluminscent Immunoassay (ECLIA). In addition, patients' postoperative tissue biopsies were analysed and associated with preoperative serum TSH levels statistically using student's t-test, Wilcoxon Mann Whitney U-test, Fisher's exact test, or Chi-square test.

Results: A total of 50 patients were included in the study. The age in years ranged from 19 to 70. Out of 50 patients who participated in the study, 46 (92%) were female. All 50 (100%) patients had thyroid swelling as their initial clinical presentation. Authors subdivided the sample into three groups by the TSH level distribution of the study (category A 0.4-1.4, category B 1.41-2.5, and category C 2.51-4.0 mIU/L). The serum TSH category C participants had the largest proportion of biopsy impressions as malignant (p-value <0.001). A cut off level of TSH 2.86 mIU/L showed a sensitivity of 58.8% and specificity of 100%.

Conclusion: In patients with thyroid nodule/s having serum TSH levels within their normal range, the higher limits of serum TSH levels are associated with an increased risk of thyroid cancer. Preoperative serum TSH levels can be used as an adjunctive diagnostic test for identifying the risk of malignancy associated with a thyroid nodule. It may aid in decision making on diagnostic approaches and may help in making the best therapeutic plans.

Keywords: Bethesda system, Nodular thyroid disease, Thyroid disease, Thyroid stimulating hormone

INTRODUCTION

Palpable thyroid nodules are a common disorder. In around 4-7% of adults in the general population and in around 19-67% undergoing high resolution Ultrasound (US) thyroid nodules are seen [1-5]. Thyroid carcinoma presents clinically as a nodule in many cases (solitary or multinodular), which is indistinguishable from the benign neoplasm. Therefore it is essential to have a clear distinction between the two conditions.

Fine Needle Aspiration Cytology (FNAC) is the gold standard investigation for thyroid nodule evaluation. It is currently the most reliable diagnostic method for thyroid nodules evaluation under the guidance of ultrasound [6-8]. The current approach to the patient with thyroid nodules detected by palpation or imaging is by taking a complete history, physical examination, and serum TSH level. In patients with low serum TSH, radionuclide scanning is done; if it shows a hyper functioning nodule, then evaluate and treat hyperthyroidism. If on radionuclide scanning (done for low serum TSH levels) nodule is non functioning or in thyroid nodules with normal to high serum TSH level, subsequent investigation diagnostic ultrasound with lymph node assessment is done. If nodule(s) is identified in the US, then FNAC is done based on US imaging features and size. Then further management depends on the results of FNAC cytology by Bethesda system [9] cytology reporting. The FNAC can be reported as non diagnostic, suspicious for PTC, malignant, follicular neoplasm, atypia, or follicular lesion of undetermined significance (AUS/FLUS), and benign. For non diagnostic, repeat US guided FNAC; if again reported as non diagnostic, then do close follow-up or surgery. For FNAC reported malignant and suspicious for PTC, surgery is indicated.

For follicular neoplasm on FNAC, consider molecular testing and then surgery if indicated. For atypia or follicular lesion of undetermined significance, repeat US guided FNAC or consider molecular testing and surgery if indicated. Benign nodules on FNAC may be monitored by ultrasound for growth, and one may consider repeating FNAC if the nodule enlarges [8]. In Bethesda III patients, the predicted probability of cancer is 5-10%, in Bethesda IV patients, it is 20-30%, and in patients with Bethesda V, it is 50-75%, but different centers have shown variability [9,10]. Several studies have evaluated TSH's role in predicting the malignancy of thyroid nodules. A study by Boelaert has shown a parallel increase in the risk of malignancy and serum TSH levels [11]. Many other authors have also studied the relationship between serum TSH levels and thyroid cancer [12,13]. In a recent meta-analysis, it is shown that there exists a positive association between increased risk of thyroid cancers with high serum TSH levels [14]. The basic idea behind this approach is that TSH is the primary regulator of thyrocyte differentiation and growth, and this capacity is retained in cancer cells of Differentiated Thyroid Carcinoma (DTC). In the

present study, it included only finally biopsy proven DTCs. Here, authors have aimed to evaluate the role of preoperative serum TSH levels in patients who had undergone surgery for nodular thyroid disease. The levels of TSH were associated with the final histological diagnosis, defined as benign and malignant. Therefore, only serum TSH levels within the normal range (0.4-4.0 mIU/L, ECLIA) were studied in this study.

The current study aims to evaluate the usefulness of preoperative serum TSH levels in predicting malignancy in patients with 'nodular thyroid disease'.

MATERIALS AND METHODS

It is a cohort study conducted over six years from January 2014 to December 2020 by the Department of Surgery of Gandhi Medical College and associated Hospital, Bhopal, India. A total of 78 were evaluated during this period, and 28 were excluded who did not meet inclusion criteria. Based on eligibility criteria and time frame a total of 50 patients who met the study's inclusion criteria were selected and thoroughly examined, evaluated, and followed-up on average for 2 years. The Ethical Clearance was obtained from the Committee (36142-44/2018).

Inclusion criteria:

- Patients with normal preoperative serum TSH levels (0.4 to 4 mIU/L).
- Patients with nodular thyroid disease.
- Patients with postoperative biopsy suggestive of DTC.

Exclusion criteria:

- Patients with already diagnosed thyroid cancers.
- Patients having a history of hypothyroidism/hyperthyroidism.
- Patients with no clinical or radiological thyroid nodule.
- Patients with final histological report other than DTC (medullary and anaplastic thyroid cancers).

Study Procedure

All the patients were evaluated with full history, general examination, and examination of the neck, thyroid gland, and cervical lymph nodes. In additaion, serum TSH levels were measured in all the patients at least one month before the surgery by the Electrochemiluminscent Immunoassay (ECLIA) method. Only euthyroid patients 0.4 to 4 mIU/L were included in the study. All the patients were subjected to thyroid US to confirm the nodular thyroid disease, defined as a discrete lesion within the thyroid gland that is palpably or radiologically distinct from the surrounding thyroid parenchyma [15]. The number of thyroid nodules, US characteristics (presence of microcalcifications), and the presence of cervical lymphadenopathy were documented.

Fine Needle Aspiration Cytology (FNAC) was performed for thyroid nodules greater than 1 cm or the nodules <1 cm with suspicious US findings [16]. It was carried out with aseptic precautions using a 23G needle, a non aspiration technique. Material obtained was smeared on two glass slides, air dried, and stained with Leishman's stain. The remaining wet slides were fixed by using alcohol and were stained with Hematoxylin and Eosin (H&E) stains. A thyroid FNAC specimen was considered satisfactory if at least six groups of follicular cells were present and each group comprising at least ten cells.

Thyroidectomy was performed for patients with malignant, suspicious or repetitive indeterminate nodules as per the FNAC results. Surgery was also indicated for benign diseases with local symptoms or cosmetic reasons.

Total, subtotal, and hemithyroidectomy were performed according to the type of thyroid swelling. After surgery specimens were sent for histopathological examination. Biopsy reports followed-up to decide the final diagnosis of benign and differentiated thyroid carcinoma (papillary and follicular).

STATISTICAL ANALYSIS

The clinical findings, laboratory reports, ultrasonography findings, and cytological data, which are reported as mean, standard deviation values, median with percentiles, or absolute numbers and percentages, were compared using various tests like an unpaired student's t-test, Wilcoxon Mann Whitney U-test, Fisher's exact test, or Chi-square test, as appropriate. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software version 21.0 to determine whether or not there were differences in TSH levels between patients diagnosed with benign and malignant lesions in the biopsy. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 78 cases were studied in the present study for over six years. Out of them, 28 were excluded under the exclusion criteria. The remaining 50 patients were included in the study. The mean age of the studied patients was 39.34±12.29 years. The age in years ranged from 19 to 70. Of the 50 patients who participated in the study, 46 (92%) were female. All 50 (100%) patients had thyroid swelling as their initial presentation.

Ultrasonography microcalcification: In the ultrasonography of the thyroid gland, microcalcifications were found in 20 (40%) of the patients, and the rest 30 (60%) showed no microcalcifications.

The association between FNAC findings and histopathology report is shown in [Table/Fig-1].

Parameters	Biopsy impression		p-value
	Benign pathology; n=33	Malignant pathology; n=17	
Age (years); (mean±SD)	36.61±12.19	44.65±10.95	0.015[a]
Male gender; n (%)	4 (12.1)	0	0.285[b]
Serum TSH (mIU/L); (mean±SD)	1.61±0.62	2.76±0.70	<0.001
TSH category (mIU/L); n (%)			
A. 0.4-1.4	13 (39.4)	1 (5.9)	<0.001[c]
B. 1.41-2.5	14 (42.4)	4 (23.5)	
C. 2.51-4.0	6 (18.2)	12 (70.6)	
Microcalcification (present); n (%)	4 (12.1)	16 (94.1)	<0.001[c]
FNAC findings (N=50)			
Benign; n (%)	23 (69.7)	0	<0.001[b]
Suspicious; n (%)	3 (9.1)	5 (29.4)	
Follicular; n (%)	7 (21.2)	0	
Malignant	0	12 (70.6)	

[Table/Fig-1]: Parameters with benign and malignant nodules.
a: Wilcoxon Mann Whitney test; b: Fisher's exact test; c: Chi-square test

Postoperative biopsy: Out of all the 50 patients who underwent various types of thyroidectomy, the biopsy reports suggested that 33 (66%) of them had benign pathology and 17 (34%) had malignant pathology. Microcalcification was present in 12.1% of benign lesions and 94.1% of malignant lesions with a p-value <0.001, which is statistically significant. The presence of microcalcification on ultrasound shows a relative risk of 24 for malignant lesions and a relative risk of 0.2 for benign lesions.

The mean age in years for benign lesions was 36.61±12.19. The mean age in years for malignant lesions was 44.65±10.95, the p-value=0.015.

Serum TSH and the thyroid malignancy: To evaluate the role of preoperative serum TSH levels as a predictor of thyroid cancer, It was subdivided the sample into three groups by the TSH level distribution of the study (category A 0.4-1.4, category B 1.41-2.5, and category C 2.51-4.0 mIU/L). Authors statistically compared the biopsy results (benign and malignant) with each TSH group. Interestingly, it was observed that the frequencies of malignancy

in each group of TSH vary by TSH levels (p<0.001). There is a statistically significant difference between the various groups in terms of the distribution of TSH (χ^2=14.173, p<0.001). The Serum TSH category C participants had the largest proportion of biopsy impressions as malignant [Table/Fig-1].

Multivariate regression analysis of the significant variables is shown in [Table/Fig-2].

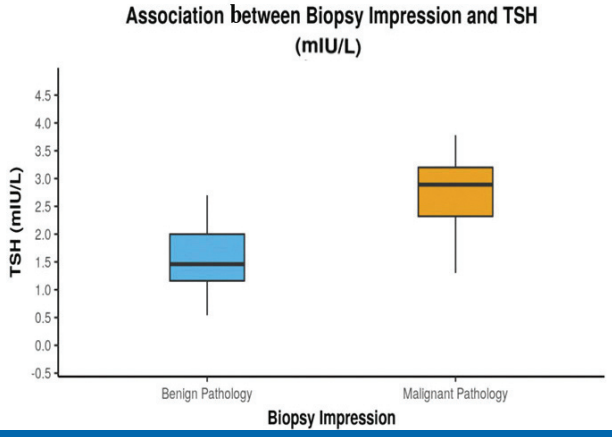
Variable	Odds ratio	95% CI	p-value
Age	1.494	0.967-2.306	0.07
TSH level	43.521	1.065-1777.68	0.046
Microcalcification	386798.3	1.466-1.02×10^{11}	0.043

[Table/Fig-2]: Multivariate regression analysis.
CI: Confidence interval

In the present study, It was considered that all possible FNAC findings were without exclusion and shows a sensitivity of 58.8% (95% CI: 33-82), specificity of 100% (95% CI: 89-100), a positive predictive value of 100% (95% CI: 69-100), negative predictive value 82.5% (95% CI: 67-93) and diagnostic accuracy 86% (95% CI: 73-94) for the cut off value of TSH level ≥2.86 mIU/L, shown in results in [Table/Fig-3]. The mean serum TSH level (mIU/L) for benign lesions was 1.62±0.62, and the mean serum TSH level (mIU/L) for malignant lesions was 2.76±0.70, the p-value <0.001 [Table/Fig-4].

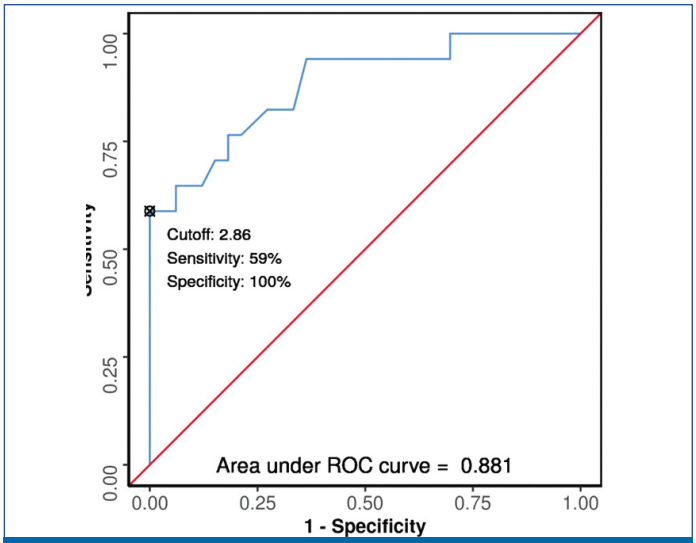
Parameter	Value (95% CI)
Cut off (mIU/L) (p-value)	≥2.86 (<0.001)
Area under ROC CURVE (AUROC)	0.881 (0.778-0.984)
Sensitivity	58.8% (33-82)
Specificity	100% (89-100)
Positive predictive value	100% (69-100)
Negative predictive value	82.5% (67-93)
Diagnostic accuracy	86% (73-94)
Positive likelihood ratio	Inf (NaN-Inf)
Negative likelihood ratio	0.41 (0.23-0.73)
Diagnostic odds ratio	Inf (NaN-Inf)

[Table/Fig-3]: Table showing the accuracy of the study.
Inf (NaN-Inf): infinity (not a number)



[Table/Fig-4]: Box plot showing biopsy impression and mean TSH values (mIU/L).

The ROC curve [Table/Fig-5] shows TSH (mIU/L) cut off for differentiating between benign and malignant nodule was 2.86.



[Table/Fig-5]: ROC curve analysis showing diagnostic performance of TSH in predicting biopsy impression.

DISCUSSION

In various other studies, thyroid nodules were common in the 3rd and 4th decades [17-19]. In the present study, the age of the patients ranged from 19-70 years. The mean age was 39.34±12.29 years in the present study which is similar to Martinek A et al., [18].

In the present study, 92% of the patients were female and only 8% were male with a male to female ratio of 1:0.086. Sex distribution was comparable to the study by Sinna EA et al., showed an M:F ratio of 1:5.2 and Screaton NJ et al., which showed 1:5.2 [20,21]. It has been well documented in every study that all types of thyroid lesions occur more commonly in females [21,22].

In this current study, authors could demonstrate that the patients with the malignant thyroid disease showed higher serum TSH levels within the normal range than those with benign nodules. As defined via ROC curve analyses, the prevalence of malignancy was higher in subjects with TSH levels >2.86 mIU/L. Remarkably, additional analyses using TSH levels as a categorical variable showed that the risk of malignancy was higher in patients with TSH levels in category C (TSH 2.51-4 mIU/L) than category B (TSH 1.41-2.5 mIU/L) and category A (TSH 0.4-1.41 mIU/L). Accordingly, TSH suppression is an important therapeutic tool for clinical thyroid cancer management. A previous study has addressed the role of TSH as a predictor of malignancy of thyroid nodules, but the results are still open for discussion [8]. Here, authors have demonstrated that patients with higher TSH levels within the normal range have an increased malignancy risk. The relative risk (95% confidence index) for biopsy specimen malignant pathology when TSH >2.86 mIU/L was 5.12 (2.94-9.77). The observations found similar with the previous studies [12,13]. That the mean TSH level was higher in the malignant group [13], (5.5 MIU/mL vs 1.4 MIU/mL, p<0.0001), and on both univariate and multivariate analyses. The risk of malignancy correlated with higher TSH levels (p=0.007) [12]. Although in contrast with the data from the EPIC study, which showed that the thyroid carcinoma risk was negatively associated with TSH level [23]. (OR=0.56; 95% CI=0.38 to 0.81; p=0.001). However the EPIC was a case-control study that included only cancer free subjects, which might be limiting when compared to the current study. The consistent association between higher TSH levels and malignant nodules is shown in most series, including the previous study by Golbert L et al., found the TSH cut off value (2.26 MIU/mL) using the best point of a ROC curve for TSH assay used during the study period, and showed that the malignancy risk was approximately three fold higher with TSH level >2.26 mIU/L [24]. Haymart MR et al., suggested that TSH may play a key role in optimising surgical interventions when aspirates are suspicious of malignancy [12]. These recommendations might support TSH levels as having an adjunctive role while evaluating thyroid nodules. There are several strengths in this study, as it included patients with thyroid nodules with TSH within normal limits who were examined and evaluated at a single institution and also excluded those patients with abnormal TSH levels, which enhances the external validity of its findings and increases the clinical applicability of its data. Also, TSH was calculated by a single method Electro Chemiluminscent Immumoassay Analyser (ECLIA) to define the relation between TSH level and malignancy accurately.

The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the serum TSH are studied. In the present study, 33 patients were diagnosed as benign on histopathology reports and 17 patients as malignant. The mean TSH level (mIU/L) for benign lesions was 1.62±0.62, and the mean TSH level (mIU/L) for malignant lesions was 2.76±0.70, the p-value <0.001 [Table/Fig-4].

Currently, FNAC is the most simple, safe, accurate, and cost effective method of identifying malignant thyroid nodules [5,8,25]. But,15-30% of aspirations fall in the grey zone of indeterminate findings in which malignancy cannot be ruled out nor be confirmed. In this present study also, 30% of patients were not able to be differentiated as benign or malignant. Serum TSH levels are used as a diagnostic tool can be useful in avoiding unnecessary surgeries in these patients. In FNAC, 69.7% of benign biopsy pathology reported benign, 0% reported malignant, 9.1% reported suspicious, and 21.2% follicular and malignant biopsy pathology was reported by FNAC as 0% benign, 70.6% malignant, 29.4% suspicious and 0% reported follicular.

The TSH (mIU/L) cut off was ≥2.86 in the present study is comparable with a study by Carlo C et al., [8], showing a serum TSH level of >2.7 mIU/L which predicted thyroid malignancy with a 61% sensitivity and 65% specificity. It was a cohort study performed on patients with indeterminate cytology on FNAC.

Limitation(s)

Less sample size is the main limitation of the current study. Authors would recommend further studies with a large sample size for a deeper understanding of the association between TSH levels and thyroid malignancy.

CONCLUSION(S)

From the present study, authors could conclude with statistical results that in patients with thyroid nodule/s having serum TSH levels within their normal range, the higher limits of serum TSH levels are associated with an increased risk of thyroid cancer. Therefore, preoperative levels of serum TSH can be used as an adjunctive diagnostic test for identifying malignancy risk associated with a thyroid nodule. It may aid in decision making on diagnostic approaches.

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