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Diagnostic Efficacy of Thyrotropin to Thyroglobulin Ratio in Correlation with Histopathology in a Euthyroid Patient with Thyroid Nodule

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Abstract: ***Introduction: With increasing rates of thyroid cancer in India, serum markers and their effectiveness in diagnosing the condition needs evaluation. The present study was conducted to compare thyrotropin with thyrotropin: thyroglobulin ratio with regards to their accuracy in the prediction of malignancy in patients with thyroid nodules. Methods: A prospective study was done. Forty-three patients presenting with thyroid nodules and undergoing thyroid surgery had their thyrotropin and thyroglobulin assessed during preoperative assessment. Post-thyroidectomy histopathology of tissue specimen was performed, and correlated between preoperative TSH, Tg, and TSH:Tg ratio. Results: Receiver operating characteristic (ROC) analysis yielded a cut off of 1.12 IU/g for TSH:Tg. The sensitivity, specificity, positive predictive value, positive likelihood ratio and negative likelihood ratio for this cutoff were 75%, 87.18%, 37.50%, 5.85, 0.29 respectively. The odds ratio for malignancy at the cut-off was 20.4. TSH cut-off was obtained at 1.31 micro-IU/ml with a sensitivity, specificity, PPV, PLR, NLR, and OR respectively as 50.0%, 33.33%, 7.14%, 0.75, 1.50, and 0.50. Conclusion: The present study showed that TSH:Tg ratio predicted thyroid malignancy in patients with thyroid nodules with fair accuracy. This ratio can therefore be reliably used in identification ofthyroid malignancies when combined with USG and FNAC.***

Keywords: Thyrotropin (TSH), Thyroglobulin (Tg), TSH; Tg ratio, Thyroid nodule

1. Introduction

Thyroid nodules are lesions which are discrete and radiologically distinct from parenchyma surrounding it.[1] It has been estimated that 4-5% of the general population has a thyroid nodule, with women having as high as 4 times the risk of developing it.[2] There has also been observed an association with age, with estimated prevalence of as much as 67% in the age group of 41 to 60 years.[3] Thyroid nodules are a commonly encountered condition in the daily clinical practice and represent a diagnostic challenge due to their potential for malignancy. Diagnosis of preoperative thyroid nodules can be made by USG and FNAC of the gland.[4]However, FNAC has certain drawbacks. It has been observed that in primary follicular neoplasms, cellular morphology is not a good indicator of malignancy. Thus, FNAC cannot accurately identify these lesions.[5]

Thyroid stimulating hormone is not widely utilized in the diagnostic and management protocols in place worldwide for thyroid nodules. This is despite the fact that TSH assessment is almost always the first step in the diagnosis of any thyroid dysfunction.[1] Serum TSH t has been linked to thyroid cancer formation and progression. A higher-than-normal TSH level has been observed to precipitate a higher risk of developing cancerous lesions.[6] It has been asserted that in a thyroid neoplasm, the tumor cells express thyrotropin receptor molecules, which respond to TSH stimulation by expressing several thyroid-specific proteins.[7] Of them, Thyroglobulin (Tg) has been found to be an important marker. It has been observed that there is a significantly higher expression of Tg in malignant thyroid lesions.[7, 8] However, very few studies have shown an association between the risk of malignancy and TSH: Tg concentration in a euthyroid patient with a thyroid nodule.

The present study was therefore performed to investigate the efficacy of Serum Thyrotropin to Thyroglobulin ratio for thyroid nodule evaluation in euthyroid subjects.

Aims:
To study the diagnostic efficacy of serum thyrotropin to thyroglobulin ratio in correlation with histopathology in a euthyroid patient with a thyroid nodule.

2. Methods

This was a hospital-based observational prospective study carried out on 43 euthyroid patients with thyroid nodules for a duration of one year.

Patients between the ages of 15 and 65 who presented to the department of otorhinolaryngology of the study institution

with a swelling in the anterior region of their neck and subsequently diagnosed with thyroid nodules were considered for the study. Those providing written informed consent were included in the study, while those having clinical or subclinical hypothyroidism or hyperthyroidism, on antithyroid drugs, and having a history of use of any medication that could affect thyroid function were excluded.

Detailed history and clinical examination were performed for each patient. Patients underwent FNAC, USG, and serum TSH and Tg assay in their preoperative period. All the patients subsequently underwent surgery to remove the nodule by either hemithyroidectomy or total thyroidectomy. Subsequently, the tissue obtained was sent for HPE in the Department of Pathology for histopathological examination (HPE), which was the gold standard of consideration for the present study.

After obtaining HPE reports, the findings were correlated with findings of the Serum TSH and TSH to Tg ratio. The sensitivity, specificity and diagnostic accuracies for each of the two markers were evaluated using appropriate statistical methods.

Statistical Analysis

The statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) software v.25. Comparisons of outcome proportions between the groups were made using Mann Whitney Test and a 2-tailed P value < 0.05 was considered significant.

The optimum cut-off point values for serum TSH and TSH: Tg ratio were determined by a receiver -operating-characteristic curve (ROC) analysis. A cut-off point value was selected at which the sum of sensitivity and specificity was maximum.

3. Results

A total of 54 patients presented to the study institution in the study period with a diagnosis of thyroid nodules. Of them, 43 provided written informed consent, and were recruited into the present study. It was observed that the median age of the study participants was 32 years, and the mean age was32.33±10.81 years. Of the participants, 38 (88.37%) were female, with a male-to-female ratio of 1:7. Ultrasonography of the swellings revealed that 40 (93.02%) of the patients had benign lesions and 3 (6.98%) had malignant ones. (Table 1) On FNAC, it was seen that benign thyroid nodules were the commonest (76.45%), followed by follicular lesion of undetermined significance (13.95%), follicular neoplasm (4.65%), and suspicious of malignancy (4.65%). (Table 2) The mean preoperative TSH levels of the study participants was 2.07±1.40 microIU/ml, and the mean preoperative Tg levels of the study participants was 895±1590.91 ng/ml. The mean TSH: Tg ratio in the participants was 29.57±49.81 IU/g. (Table 3) Confirmatory histopathology revealed that 39 (90.70%) of the patients had benign thyroid nodules, while the rest had malignancies.(Figure 1)

ROC curve analyses were performed to obtain the optimal cut-off value for TSH and TSH: Tg ratios. The area under the curve (AUC) for TSH was found to be 0.590(95% CI, 0.384, 0.796), and for the TSH: Tg ratio was found to be 0.885, (95% CI, 0.765, 1.000). (Figure 2) The cut-off value of TSH was found to be 1.31 micro-IU/mL, with the calculated sensitivity, specificity, Positive Predictive Value (PPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR), being50%, 33.33%, 7.14%, 0.75, and 1.50 respectively. The Odds Ratio (OR) indicating malignancy for TSH at this cut-off was was 0.50. On the other hand, the cut-off value for TSH:Tg ratio was calculated to be 1.12 IU/gm. The accuracy of the TSH: Tg ratio was 86.05 %, specificity, sensitivity, PPV, PLR, and NLR was respectively 87.18%, 75%, 37.5%, 5.85, and 0.29. The OR indicating malignancy for the TSH: Tg ratio was 20.4. (Table 5).

Based on this cut-off thyroid nodule evaluation of study participants was done in comparison to histopathological diagnosis. Out of 43 cases, 28 cases had TSH values that were higher than the cut-off indicating a risk of malignancy, but only two were determined to be malignant on HPE. While TSH was below the cut-off in 2 patients with HPE-proven malignancy. (Table 4)

4. Discussion

Duccini K et al. reported that patients with nodular thyroid disease (NTD) and having relatively higher preoperative serum TSH have a higher risk of developing differentiated thyroid carcinoma (DTC).[9] On the other hand, **Rinaldi S et al.** could demonstrate no significantly improved accuracy of either TSH or Tg as markers for thyroid cancer.[10]Although several studies have evaluated postoperative serum Tg as a prognostic marker in the long-term follow-up of patients with DTC, the conclusions remain unclear.[11, 12, 13]

In the present study, 33 patients presented with a solitary thyroid nodule, of which 4 were identified as malignant via HPE, thus giving a malignancy incidence rate of 12.1%. The rest of the 10 patients presented with multiple nodules, none of which were identified as malignant. These observations were lower than the incidence rates of 20.83%, 35.29%, and 24.6% reported by **Sharma VK et al., Rok P et al.,** and **Lei S et al.** in their studies exploring the topic.[14, 15, 16]

In the present study, the TSH cut-off value was determined to be 1.31 micro-IU/mL. Our findings are similar to the study performed by **Lei S et al.,** who reported a preoperative serum TSH level of 1.17 micro-IU/mL in patients with malignancy and 1.08 micro-IU/mL in those with benign pathology. However, the observed differences were statistically non-significant, indicating a poor accuracy of the marker in the prediction of malignancy.[16]On the other hand, **Wang L et al.** found that patients with benign and malignant thyroid nodules exhibited significantly varied serum TSH concentrations (P<0.001), and at a cut-off of 1.525 micro-IU/ml, TSH had a sensitivity, specificity, positive predictive value,

positive likelihood ratio, negative likelihood ratio of 74%, 53.2%, 70.8%, 1.58, and 0.49 respectively.[17]

As per ROC curve analyses, in the present study, the cut-off for TSH:Tg ratio was determined to be 1.12 IU/gm, with those patients having the TSH:Tg ratio below it being at a higher risk of developing malignancies. The cut-off point value of TSH: Tg in the studies conducted by **Wang L et al.** was 24.97 IU/gm and **Sharma VK et al.** was 25.02 IU/gm respectively, both of which are substantially higher than the present study.[14, 17]Furthermore, in contrast to our study, in both of these studies, malignancy was suspected in patients with thyroid nodules, when the ratio of TSH to Tg was higher than the specified cut-off.

In our study the Odds Ratio (OR) of the TSH: Tg ratio was 20.4, indicating that when the ratio is lesser than 1.12 IU/gm, the risk of malignancy is elevated by 20.4-fold in comparison to cases with values more than the cut-off (1.12 IU/gm). Therefore, it can be said that the TSH: Tg ratio can be a reliable predictor of malignancy, which can be utilized as a diagnostic tool to predict thyroid malignancy preoperatively.

The primary limitations of our study were the smaller sample size and shorter study duration, which may have an impact on the generalizability of the findings and call for additional research with larger sample size.

5. Conclusion

The risk of development of thyroid carcinoma can be reliably predicted by the TSH: Tg ratio. On the other hand, TSH alone had poor accuracy in diagnosing malignancy.However, combining preoperative tests including USG, FNAC, and TSH: Tg ratio can help to predict malignancy more accurately.

Table 1: USG characteristics of the study population

USG Characteristics	Number of cases	Percentage %
	Nodularity	
Solitary	33	76.74
Multiple	10	23.26
	USG-based probable diagnosis	
Benign	40	93.02
Malignant	3	6.98

Table 2: Distribution of patients according to FNAC based on Bethesda Category

FNAC findings (Bethesda)	Number of cases	Percentage %
Category 1	0	0
Category 2	33	76.45
Category 3	06	13.95
Category 4	02	4.65
Category 5	02	4.65
Category 6	0	0
Total	43	100

Table 3: Quantitative statistics of the Thyroid Hormones

Values	TSH(micro IU/ml)	Tg(ng/ml)	TSH: Tg Ratio (IU/gm)
Minimum	0.16	3.69	0.39
Maximum	6.63	7300	209.3
Mean± SD	2.07 ± 1.40	895±1590.91	29.57±49.81

Table 4: Comparisons of Thyroid Nodule Evaluations Based on the TSH: Tg Ratio and TSH with Histopathological Diagnoses.

		HPE diagnosis		Total
		Malignant	benign	
TSH based evaluation	Malignant	2	26	28
	Benign	2	13	15
Total		4	39	43
TSH:Tg Ratio based evaluation	Malignant	03	05	8
	Benign	01	34	35
Total		4	39	43

Table 5: Statistical parameters and comparison of TSH with TSH: Tg ratio.

Parameter	Accuracy	Sensitivity	Specificity	PPV	PLR	NLR	OR
TSH	34.88	50%	33.33%	7.14%	0.75	1.50	0.50
TSH:Tg ratio	86.05 %	75%	87.18%	37.50%	5.85	0.29	20.4

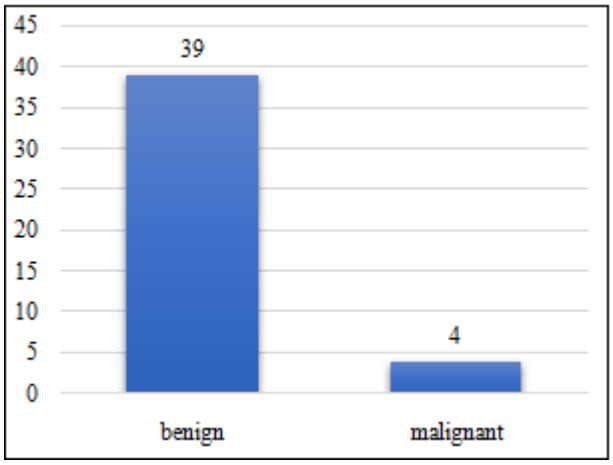

Figure 1: HPE findings

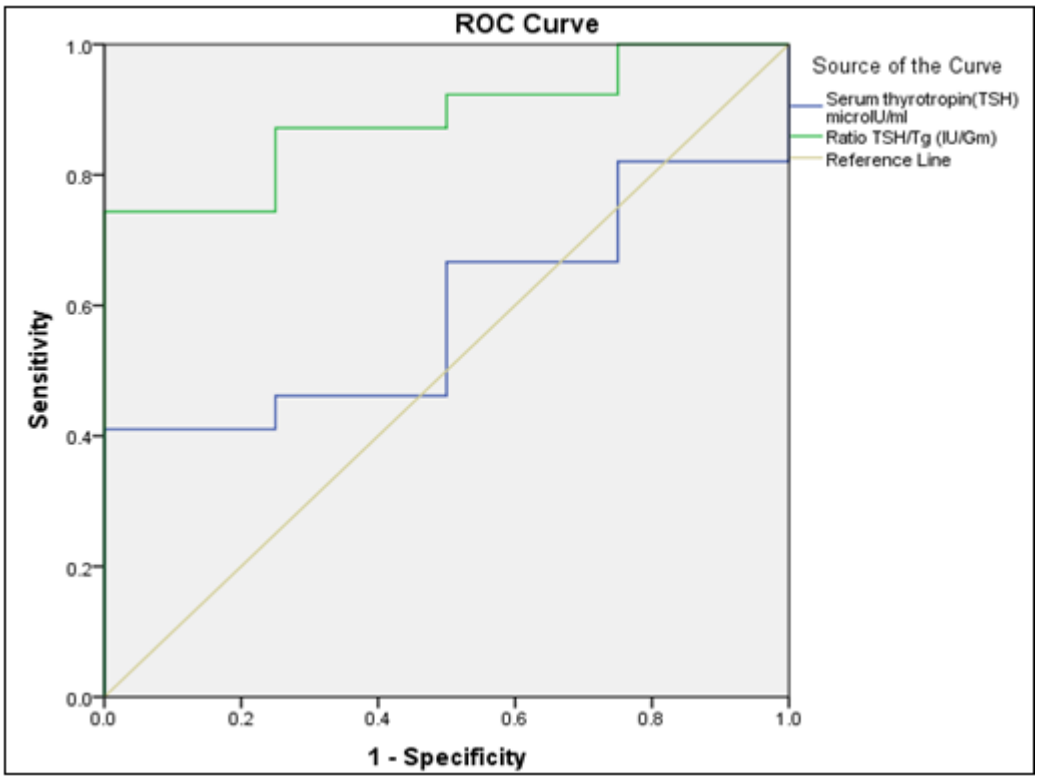

Figure 2: ROC curves for TSH and TSH: Tg ratio.

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