

The Role of Anti-Thyroglobulin Antibodies in Predicting Thyroid Cancers in Patients Undergoing Thyroidectomy

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Abstract

Background

Preoperative prediction of thyroid malignancy can help in risk stratification and perioperative management. It has been debated that anti-thyroglobulin antibody (TgAb) are more frequently elevated in patients with thyroid cancer than in general population.

Aim

To evaluate the predictive value of TgAb in predicting thyroid cancer in patients undergoing thyroidectomy.

Methods

This is a prospective single center study including 98 patients diagnosed with thyroid nodule and scheduled to have thyroidectomy. Demographic data and final histopathology reports were reported. Serum level of TgAb were measured by ready kit using competitive radioimmunoassay. Accordingly, patients were divided in to two groups: TgAb-positive and TgAb-negative groups.

Results

Thyroid malignancy was reported in 18 patients (18.37%), while the other 80 patients (81.63%) were found to have benign tumors. Twenty-one patients (21.43%) were TgAb-positive and 77

(78.57%) were TgAb-negative. The frequency of positive TgAbs among patients with thyroid malignancy was 61.11% compared to 12.5% among patients with benign tumors (OR= 11.0, 95%CI= 3.46-34.96, P< 0.001). The sensitivity and specificity of TgAbs was 61.11% and 87.5% respectively. The positive and negative predictive value of TgAbs were 52.38% and 90.91%, respectively Using receiver operating characteristic curve was used to find out the cut off value of TgAb in predicting thyroid malignancy. The area under curve was 0.681, 95%CI= 0.565-0.797, p= 0.048. The sensitivity and specificity of the test at the TgAb cut off value= 114.6 U/ml was 0.35 and 0.77 respectively.

Conclusion

Positive preoperative serum TgAb level was associated higher frequency of thyroid malignancy. The TgAb has poor sensitivity (61.11%) and good specificity (87.5%) in predicting thyroid malignancy in patients undergoing thyroidectomy.

Keywords:

Thyroid malignancy, anti-thyroglobulin antibodies, sensitivity and specificity

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1. Introduction

Thyroid cancer is the most common type of endocrine malignancy. About 90% of thyroid neoplasms are differentiated thyroid cancers (DTC) with low malignant potential and a very good prognosis [1].

Thyroid cancer has no established etiologic factors, although exposure to radiation has been implicated for several decades. The phenomenon of radiation exposure leading to increased incidence of thyroid cancer was documented following the atomic bomb exposure in Hiroshima and Nagasaki during World War II [2]. More recently, it was shown after the Chernobyl accident, which was followed by a steep rise in thyroid cancer among children exposed to the radiation fallout [3]. There is evidence that exposure to low-dose radiation during childhood (such as in patients receiving therapeutic radiation for leukemia/lymphoma) is associated with an increased incidence of thyroid cancer [4]. There is also evidence to show an increased risk of thyroid cancer in children treated with low-voltage radiation for acne. Although the incidence of thyroid cancer is higher after radiation exposure, the biological behavior of the disease is similar in both radiation-exposed and non radiation-induced thyroid cancer. Therefore, although radiation exposure is important for triggering the disease, it does not appear to play a role in determining the aggressiveness of the malignancy [5]. The objective of this study is to evaluate the predictive value of TgAb in predicting thyroid cancer in patients undergoing thyroidectomy.

Aim

To evaluate the predictive value of TgAb in predicting thyroid cancer in patients undergoing thyroidectomy.

2. Methods

Study design and Setting

This is a prospective single center study including 98 patients diagnosed with thyroid nodule and scheduled to have thyroidectomy by a single surgeon at the department of Surgery/ Baghdad Medical City during the period from January 2019 to January 2021. The study was approved by Iraqi Board of Medical Specialization.

Inclusion Criteria for Patients

- Patients presented with thyroid disease indicating for thyroid surgery (lobectomy or total thyroidectomy).

Exclusion Criteria

- Recurrent thyroid malignancy

Data Collection

Collected data included patients' demographic (age, gender, height, weight and body mass index (BMI), final histopathology reports, and preoperative TgAb measurements.

Biochemical Assay and Study Groups

Eligible patients were undergone thyroid ultrasonography, FNA, thyroid function test. CT scanning of the neck, Radioactive thyroid scan, Pet scan were indicated to few patients.

After the pandemic of COVID 19, screening for COVID-19 was conducted for all patients.

Blood samples were collected from all patients. after enrollment in the study.

A ready commercial kit (ZenTech, Angleur, Belgium) was used to measure serum level

of TgAb using competitive radioimmunoassay with a functional sensitivity of <15 IU/mL. According to the instructions of the manufacturer, TgAb \geq 70 IU/mL was defined as positive and below this level was considered negative result. Accordingly, patients were divided in to two groups: TgAb-positive and TgAb-negative groups.

Histopathology

All thyroid tissue samples obtained by surgical resection were examined histopathologically in different specialized laboratories; all results were classified into malignant or benign regardless to the subclassifications

Data Analysis

Data were analyzed by statistical package for social sciences (SPSS) version 25 and Microsoft Excel 2016 using descriptive statistics. Continuous variables were expressed and mean and standard deviation (SD) and analyzed with Student t-test. Binomial variables were expressed as frequency and percentage and analyzed with Chi square. The sensitivity, specificity, positive predictive value, negative predictive value, relative risk and odds ratio of TgAb as a diagnostic test for thyroid malignancy were calculated. Univariate and multivariate logistic regression analysis was performed to evaluate the association between thyroid malignancy and risk factors, such as age, sex, nodule size, TSH, TgAb-positivity. A value of $P < 0.05$ was considered statistically significant.

3. Results

Demographic Characteristics of the

Patients

Mean age of the patients was 51.26 ± 11.3 years (range 30-76 years). The age class 43-55 years was the most frequent accounting for more than half of the patients followed by age class 56-68 years (28.58%). About three quarters of the patients were females. The majority of patients (63.27%) were overweight having BMI between 25 and 30 kg/m^2 . Most patients (60.2%) had no comorbidity, while 26.53% of them were suffering from DM and/or hypertension. Mean serum level of TSH was 1.87 ± 1.3 mU/L (Table 1).

Table 1: Patients' characteristics and demographic data (n=98)

Variables	Frequency	%
Age, years		
30-42	11	11.22%
43-55	54	55.1%
56-68	28	28.58%
69-80	5	5.1%
Gender		
Male	25	25.51%
Female	73	74.49%
Body mass index, kg/m^2		
< 25	24	24.49%
25-29.9	62	63.27%
≥ 30	12	12.24%
Comorbidities		
No comorbidity	59	60.2%
DM and/or HTN	26	26.53%
Chronic renal insufficiency	8	8.16%
Others	5	5.1%
TSH, mU/L		
Mean \pm SD	1.87 ± 1.3	-----
Range	0.92-3.43	

DM: diabetes mellitus, HTN: hypertension.

Histopathological Study

Thyroid malignancy was reported in 18 patients (18.37%), while the other 80 patients (81.63%) were found to have benign tumors (figure 1).

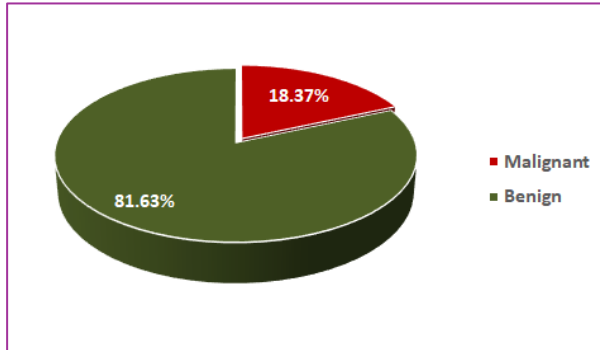


Figure 1: The proportion of thyroid malignancy

Serum Concentration of Thyroglobulin Antibodies

Mean serum concentration of TgAb in patients with thyroid malignancy was 184.8 ± 22.7 U/ml which was higher than that of patients with benign tumor (93.2 ± 31.9 U/ml) with a significant difference (figure 2).

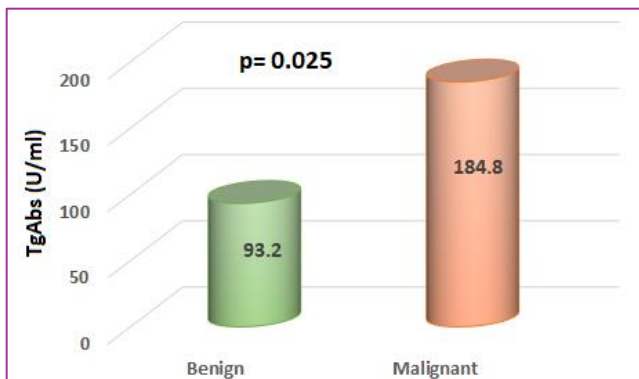


Figure 2: Mean serum concentration of thyroglobulin antibodies in patients with benign and malignant tumours

Frequency of malignancy According to TgAb Positivity

According to Tg level, patients were categorized in to two groups: Those positive

for $TgAb \geq 70$ U/ml (21 patients (21.43%) and those negative for $TgAb < 70$ U/ml (77 (78.57%). Out of 21 patients positive for TgAb, 11 (52.38%) had thyroid malignancy. In contrast, out of 77 patients negative for TgAb, 7 (9.09%) had thyroid malignancy, while 70 (90.91%) had benign tumor. Statistically, there was a significant difference (figure 3).

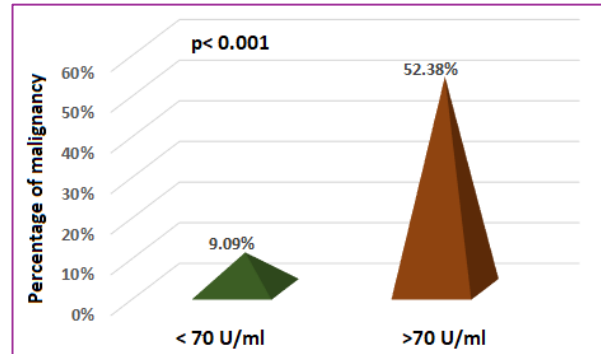


Figure 3: Frequency of malignancy in TgAB positive and negative patients Predictors of Malignancy in patients with thyroid nodules

Out of six factors included in the study, only TgAbs positivity was significantly associated with the occurrence of thyroid malignancy. The frequency of positive TgAbs among patients with thyroid malignancy was 61.11% compared to 12.5% among patients with benign tumors (OR= 11.0 95%CI= 3.46-34.96, $p < 0.001$). as shown in table 2.

Table 2: Association of demographic and clinical factors with thyroid malignancy

Variables	Malignant (n=18)	Benign (n=80)	p-value	OR(95%CI)
Age, years				
≤ 50	13(72.22%)	59(73.75%)	0.894	1.0
>50	5(27.78%)	21(26.25%)		1.08(0.34-3.4)
Gender				
Male	6(33.33%)	13(16.25%)	0.098	1.0
Female	12(66.67%)	67(83.75%)		0.39(0.12-1.22)
BMI, kg/m ²				
≤ 25	6(33.33%)	20 (25%)	0.469	1.0
>25	12(66.67%)	60(75%)		0.67(0.22-2.0)
Comorbidities				
No comorbidity	11(61.11%)	46(57.5%)	0.779	1.0
DM and/or HTN	6(33.33%)	19(23.75%)	0.399	0.62(0.21-1.88)
Renal insufficiency	3(16.67%)	7(8.75%)	0.316	0.48(0.34-5.6)
Others	2(11.11%)	3(3.75%)	0.200	0.31(0.05-2.02)
TSH, mu/L				
≤2	15(83.33%)	66(82.5%)	0.993	1.0
>2	3(16.67%)	14(17.5%)		0.94(0.24-3.7)
TgAbs, U/L				
Negative	7(38.89%)	70(87.2%)	<0.001	1.0
Positive	11(61.11%)	10(12.5%)		11.0(3.46-34.96)

A patient can have more than one comorbidities

Sensitivity and Specificity of TgAbs in Predicting Thyroid Malignancy

Out of 18 patients having thyroid malignancy according to histopathological finding, 11 was positive for TgAbs. On the other hand, 10 patients out of 80 patients having benign thyroid tumor according to histopathology

were also found be positive for TgAbs. Accordingly, the sensitivity and specificity of TgAbs was 61.11% and 87.5% respectively. The positive and negative predictive value of TgAbs were 51.38% and 90.91%, respectively (Table 3).

Table 3: Sensitivity and specificity of TgAbs in prediction of thyroid malignancy

		Histopathology		Total
		Positive	Negative	
TgAbs	Positive	11	10	21
	Negative	7	70	77
	Total	18	80	98

Sensitivity = $11 / (11+7) \times 100 = 61.11\%$

Specificity = $70 / (70+10) \times 100 = 87.5\%$

Positive predictive value= $11 / (11+10) \times 100 = 52.38\%$

Negative predictive value= $70 / (70+7) \times 100 = 90.91\%$

Cut off Value of TgAb that Predict Thyroid Malignancy

Receiver operating characteristic (ROC) curve was used to find out the cut off value of TgAb in predicting thyroid malignancy. The area under curve (AUC) was 0.681(95%CI= 0.565-0.797), $p= 0.048$. The sensitivity and specificity of the test at the TgAb cut off value= 114.6 U/ml was 0.35 and 0.77 respectively (Figure 4).

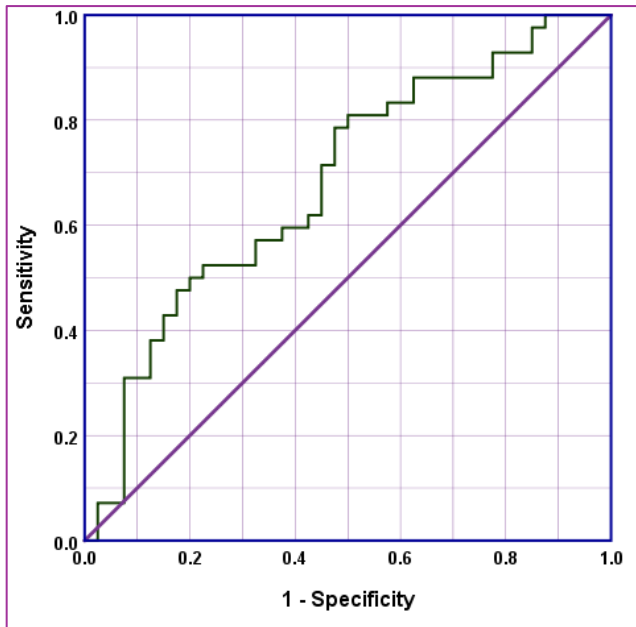


Figure 4: receiver operating characteristic curve for TgAb in the context of predicting thyroid malignancy.

4. Discussion

This study aimed to evaluate the diagnostic value of TgAb in predicting thyroid cancer in patients undergoing thyroidectomy. To the best of our knowledge, this is the first study in Iraq that addressed the role of anti TgAb in predicting thyroid cancer.

The most interesting finding in the present study was that mean serum concentration of TgAb in patients with thyroid malignancy was 184.8 ± 22.7 U/ml which was higher than that

of patients with benign tumor (93.2 ± 31.9 U/ml) with a significant difference.

This result is in accordance with many previous studies. Barin et al. retrospectively assessed a total of 2088 patients with thyroid nodules who received FNA, and found that thyroid cancer was significantly associated with positive TgAb (OR=1.61) [6]. Almost similar results were obtained by Vasileiadis et al. [7], who found that in patients undergoing thyroidectomy for any causes, preoperative TgAb positivity was more common in patients with thyroid malignancy than in those with benign thyroid tumors (38.2% vs. 19.8%). Grani et al. enrolled a total of 2562 patients who underwent FNAC and found that malignant cases were detected more commonly in TgAb-positive patients than in those TgAb-negative (9.4% vs 5.7%). The study considered TgAb as a mild risk factor for thyroid cancer (OR= 1.74) [8].

Hosseini et al. [9] categorized a group of patients based on TgAb level and found out that the prevalence of malignancy was higher in the positive TgAb group than negative TgAb (65.38% vs. 50.42%). Qin et al. [10] also classified patients according to TgAb level (0, 4, 11, 40, 100, and 500 IU/mL), and found that the prevalence of differentiated thyroid cancer was significantly higher in the high TgAb groups (≥ 100 IU/mL) than in the low TgAb groups (< 100 IU/mL).

It was indicated that a TgAb count ≥ 70 IU/ml may be specific for DTC. However, lower levels should not be used to rule out malignancy. Some authors have suggested that elevated TgAb levels could be an indicator for increased risk for malignancy [9]. A study conducted by Kim et al. [11] was the

first to report that a positive TgAb test was an independent predictor of thyroid nodule malignancy, regardless of the presence of chronic lymphocytic thyroiditis. A more recently, Grani et al. [8] showed that TgAb positivity could be a mild risk indicator for thyroid cancer, as opposed to Hashimoto's thyroiditis.

Although most studies indicated the significance of TgAb-positivity in predicting thyroid cancer, a marked variation does occur between different studies. This variation is mainly attributed to the methods used for diagnosis of thyroid malignancy. Kim et al. [11] and Grani et al. [9] used FNAC for final diagnosis of thyroid cancer, with only a minority of diagnoses confirmed by histological follow-up. The major limitation of FNAC is that the cytological findings seen in the sample are not necessarily reflect of the entire thyroid tissue and cannot consequently offer a confirmed diagnosis. Thus, many cases of malignancy can be missed.

According to the results of the current study, each of patient's age, gender, BMI, presence or absence of comorbidities, and TSH level are poor predictors for the presence of thyroid malignancy.

In a Brazilian study, Girardi et al. [12] tried to introduce a model for predicting thyroid cancer. Accordingly, the authors recruited 204 benign and 57 malignant thyroid nodules in a retrospective study. Variables including age, gender and ultrasonographic features were examined using univariate and multivariate models. In univariate model, each of lower mean age ($p = 0.031$), lower diameter ($p = 0.004$), solid content ($p < 0.001$), irregular or lobulated shape ($p < 0.041$), hypoechoic texture ($p < 0.001$), and

ill-defined margins ($p = 0.001$) were significantly associated with cancer. Like in the present study, there was no effect of gender or TSH level. Hulikal et al. [13] also stated that age and gender were not significant variables influencing the differences between benign and malignant groups in their study. Almost similar results were obtained by two other studies [14,15].

In contrast, Petric et al. [16] reported that patient age, solitary tumor, and preoperative serum level of thyroglobulin were independent predictors of follicular neoplasms of thyroid gland. Strazisar et al. [17] reported that patient age and preoperative serum level of TgAb were independent predictors of malignancy in Hurthle cell neoplasms. Furthermore, Kim et al. [11] reported that a positive TgAb test is an independent predictor of thyroid nodule malignancy along with TSH results, regardless of autoimmune thyroiditis.

Until now, there is no defined threshold of what is considered an elevated TgAb titer in thyroid malignancy. Most studies published set their cut-off values according to the recommendations of the assay kit provided by the manufacturer, which are calculated for its use in the diagnosis of CLT [45]. In fact, two studies suggested that up to 20 % of samples may be misclassified as TgAb negative when the manufacturer's cut-off levels are used, as they are set too high [11, 18]. In the present study, 114.6 U/ml was determined as a compromising cut off value between benign and malignant tumors.

The failure for determining a particular cut off value for TgAb related to many reasons.

Cut-off value for laboratory test is typically determined as the level at which as low as

2.5% of normal people are having abnormal value. For TgAb, this excludes individuals with autoimmune thyroid disease from being classified as “normal”. However, studies showed that TgAb detected using this cut off are not always correlate with thyroid dysfunction [54]. In a study by Spencer *et al.* [19], many samples that are classified as TgAb negative did, in fact, have measurable TgAb; 50–80% of these had interference TgAb measurement, and 20% of these had undetectable TgAb.

Another factor is the complexity of the Tg as an antigen. Tg has a molecular weight of around 660 kDa with many sites that are immunogenic when given to an experimental animal. Antibodies differ in their ability to recognize different epitopes on the molecule [20]. Accordingly, it is difficult to make

standards that can be used for TgAb detection. Madureira *et al.* [21] reported that different forms of Tg have different pattern of interference with sera containing TgAbs. In some cases, a known TgAb-positive samples show no reactivity with one form of Tg.

Conclusion

1. Positive preoperative serum TgAb level is associated higher frequency of thyroid malignancy.
2. The TgAb has low sensitivity (61.11%) and very good specificity (77%) in predicting thyroid malignancy in patients undergoing thyroidectomy.
3. None of demographic and clinical characteristics of the patients has a significant prediction value for the occurrence of thyroid malignancy.

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