The diagnostic and predictive accuracy of thyroglobulin to TSH ratio and TSH to thyroglobulin ratio in detecting differentiated thyroid carcinoma in normothyroid patients with thyroid nodules: A retrospective cohort study and systematic review of the literature

Evangelos Karvounis,[1] Ioannis Kappas,[1] Anna Angelousi,[2] George-Marios Makris,[3] Thomas D. Siamatras,[1] Eva Kassi[2,4]

[1]Department of Endocrine Surgery Center of Excellence, Euroclinic Hospital, Athens; [2]Department of Internal Medicine, Laiko hospital, National and Kapodistrian University of Athens; [3]Department of Gynecology, Euroclinic Hospital, Athens; [4]Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Abstract

The purpose of the present study is to examine the diagnostic and predictive accuracy of the thyroglobulin (Tg) to thyroid stimulating hormone (TSH) and TSH/Tg ratios in normothyroid patients with differentiated thyroid cancer (DTC). We conducted a retrospective cohort study evaluating the diagnostic accuracy of the serum Tg/TSH and TSH/Tg ratios in normothyroid patients with thyroid nodules. We also systematically searched the international literature using the Medline, Cochrane's CENTRAL, Scopus, Clinicaltrials.gov, EMBASE, and Google Scholar databases for evidence concerning the diagnostic and predictive accuracy of these ratios. Overall, 374 patients were identified in our cohort study of whom 240 were treated for benign disease and 134 were treated for DTC. Significant differences were noted in the Tg/TSH and TSH/Tg values among cases with malignant and benign disease (P=0.020). However, the diagnostic ROC curve did not confirm these results (Tg/TSH=0.572 and TSH/Tg=0.428). After searching the international literature, we identified 8 studies. The majority of the included data reported significant differences among patients with benign/malignant disease and those with successful iodine therapy compared to those with disease relapse. However, the clinical relevance was clearer among studies that investigated the usefulness of these ratios in predicting recurrent disease. The findings of our study support that the Tg/TSH ratio increases in patients with DTC and can, thus, become useful in the future as a predictive marker of ablative ^{131}I therapy success. However, given the significant variability of Tg its diagnostic accuracy remains to date minimal; thus, the actual cut-off value that can be used to discriminate cancer cases from benign disease has not been determined yet.

Correspondence: Evangelos Karvounis, Department of Endocrine Surgery Center of Excellence, Euroclinic Hospital, 9 Athanasiadou str, 11521 Athens, Greece.
Tel.: +302106416667. E-mail: karvounis18@gmail.com

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Introduction

Differentiated thyroid carcinoma (DTC) is a frequent form of cancer that is subdivided in the papillary (90%) and follicular (10%) histological type. Its overall annual incidence exceeds 10/10,000 cases and it is expected to increase further over the next decade[1] due to the higher levels of health care access; hence, developed countries will face this problem more frequently during the next decades.[2] Females are most commonly affected with a female to male ratio of 3:1. Both histological types have a generally favorable outcome and, although the course of the disease is not totally indolent, only 5% of cases are believed to be fatal.[3]

Total thyroidectomy remains the gold standard for the treatment of DTC with or without 131 Iodine ablation therapy according to histological criteria and the presence of residual microscopic disease.[4] Nevertheless, long-term follow up of patients with DTC remains crucial as there is a risk of recurrent disease that may exceed the boundaries of the 10-years follow-up period.[5]

Several factors have been described as predisposing for disease progression and relapse, including tumor size, patient age, positive lymph node ratio and pre-ablation stimulated thyroglobulin (Tg).[6-9] During the last decade several studies investigated the diagnostic value of the preoperative Tg/thyroid stimulating hormone (TSH) ratio and the TSH/Tg ratio in detecting the disease among patients with thyroid nodules and in predicting distant metastases as well as disease free survival (DFS). The purpose of the present study is to evaluate the diagnostic accuracy of these ratios among patients with thyroid nodules and in consecutive cohort of patients and to systematically review current evidence in the field in order to provide recommendations for current clinical practice and directions for future research in this field.

Methods of research

Methods of retrospective study

Patients, blood and tissue sampling

We retrospectively reviewed medical records and identified patients with thyroid nodules that were subjected to thyroidectomy (total or subtotal) between January 2013 and December 2016 at the Surgical Department of Euroclinic Hospital. The study was designed in agreement with both Greek and European Union Legislation as indicated in the Declaration of Helsinki for Human and Animal Rights and its later amendments and has received ethical approval by the Institutional Review Board of our Hospital.

Patients with clinical or subclinical hypothyroidism and those with hyperthyroidism were preoperatively excluded from the study. Other exclusion criteria included prior history of head and neck radiation therapy and of prior thyroid surgery, treatment with antithyroid drugs or drugs that could affect thyroid function as well as thyroid hormone substitution therapy. Given the known effect of anti-Tg levels on measurement of serum Tg levels, patients with detectable anti-Tg levels, as well as those that did not have anti-Tg levels measured prior to thyroidectomy, were also excluded from our study.

Biochemical measurements

Serum thyroid hormone values [including TSH, triiodothyronine (T3) and thyroxine (T4)] as well as serum Tg were measured at 08:00 hours following an overnight fasting. All measurements were performed with by the ADVIA Centaur system with CV of 3.44%, 5.55%, 5.87%, 4.8% and 8.27 respectively.

Statistical analysis

We checked the distribution of continuous variables using the Kolmogorov-Smirnoff test and graphical methods. The Mann-Whitney U test was used to compare median values among patients with benign as well as those with malignant thyroid nodules as the distribution was abnormal. Continuous variables are presented as median (range) values. Quantitative variables are presented with absolute and relative frequencies. For the comparisons of proportions, we used the chi-square and Fisher's exact tests (when at least one field of variables had a count below 5). All reported analyses were designed as two-tailed. Logistic regression analysis was performed with the Enter method using histology (0 for benign pathology and 1 for malignant disease) as the predicted variable and patient and tumor characteristics as the predictive variables. The diagnostic accuracy of the Tg/TSH ratio was compared to that of TSH, fT3 and fT4 using receiver operating characteristics (ROC) curves. The level of statistical significance was set at $P<0.05$. The SPSS statistical package was used for the analysis of the retrospective cohort (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Methods of meta-analysis

Materials and methods

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] The methodological characteristics of included studies are summarized in Table 1.

Information sources and search methods

We used the Medline (1966-2018), Scopus (2004-2018), Cochrane`s CENTRAL (2004-2018), Clinicaltrials.gov (2008-2018), EMBASE (1980-2018), and Google Scholar (2004-2017) databases in our primary search along with the reference lists of electronically retrieved full-text papers. The date of our last search was set at December 31, 2018. Our search strategy included the text words 'thyroglobulin, anti-TG, TSH and thyroid cancer' and is presented in brief in Figure 1. We specifically searched Medline using the '('thyroglobulin'[MeSH Terms] OR 'thyroglobulin'[All Fields]) AND TSH[All Fields] AND ('Ratio (Oxf)'[Journal] OR 'ratio'[All Fields]) AND ('thyroid neoplasms'[MeSH Terms] OR ('thyroid'[All Fields] AND 'neoplasms'[All Fields]) OR 'thyroid neoplasms'[All Fields] OR ('thyroid'[All Fields] AND 'cancer'[All Fields]) OR 'thyroid cancer'[All Fields])' search terms.

The studies that were initially retrieved after performing the electronic search were then deduplicated and the titles and abstracts of all electronic articles were screened by two authors (EK and GM) to evaluate their eligibility for the inclusion in present systematic review. All articles that were held as eligible were retrieved in full text and read, along with their references to identify articles that could have been lost during the electronic search. Discrepancies in this latter stage were resolved by consensus from all authors.

Types of studies and patients

All observational studies (prospective and retrospective) that assessed the diagnostic accuracy of TSH/Tg and Tg/TSH ratios in cases of thyroid nodules were considered as eligible for inclusion. Articles that investigated the predictive accuracy of these ratios in terms of defining patients with distant metastases, advanced stage disease as well as predicting the progression free survival (PFS) and overall survival (OS) of patients with DTC were also included in the present systematic review. Case reports and animal experimental studies as well as previous reviews were excluded from tabulation and further analysis.

Outcome measures

Outcome measures were predefined during the design of the present systematic review. Differences in TSH/Tg and Tg/TSH ratios among patients with benign and malignant thyroid nodules as well as differences in these ratios among patients with advanced stage disease consisted the primary outcome of the present systematic review. The predictive accuracy of these ratios concerning the success of thyroidectomy and/or ablative ^{131}I therapy in terms of disease relapse was considered as a secondary outcome.

Quality and risk of bias analysis

The risk of bias and methodological quality of included studies was evaluated with the Newcastle-Ottawa Scale (NOS), which takes into account the selection of the study groups, the comparability of the groups and the ascertainment of the exposure or outcome of interest (Table 2).[11]

Results

Results of the retrospective analysis

Overall, 685 patient records were screened to assess their eligibility for inclusion in the present study. After excluding patients with incomplete data and those that did not meet the inclusion criteria as previously described, 374 patients were identified, 240 of whom were treated for benign disease and 134 were treated for malignancy (Figure 1). All patients that were treated for malignant disease had papillary carcinoma, whereas one patient was diagnosed with concurrent myeloid carcinoma as well. Epidemiological characteristics are described in Table 3. No differences were noted in terms of smoking habits, patient age, number of nodules (solitary or multiple) maximum diameter of the lesion and tumor weight (Table 3). Male sex, high Tg value as well as increased Tg/TSH ratio were significantly associated, with increased risk of DTC. The logistic regression analysis identified female sex as a protective factor of malignancy (OR 0.421) whereas Tg and Tg/TSH values as predictive indices of thyroid cancer (Table 4). ROC curve analysis identified (Figure 2) Tg value and

Table 1. Methodological characteristics of included studies.

Year; author	ratio	Study type	Outcome Patient n	Inclusion criteria	Outcome reporting measures
2018; Tam[13]	TSH/Tg Tg/TSH	Retrospective	Malignant *vs* benign (244 *vs* 370)	Patients with detectable levels of Tg without high anti-Tg levels and with no evidence of clinical or subclinical hypothyroidism or hyperthyroidism, radiation to head and neck, history of thyroid surgery, and previous or current use of anti-thyroid or thyroid hormone replacement therapy	Median (min-max), diagnostic AUC
2016; Yazici[14]	TSH/Tg Tg/TSH	Prospective	Malignant *vs* benign (68 *vs* 134)	Patients that underwent thyroid surgery without medullary thyroid cancer or elevated anti-Tg levels or TSH.	Median (min-max)
2016; Trevizam[15]	Tg/TSH	Retrospective	Success *vs* fail of ablative ^{131}I (48 *vs* 16)	Patients with DTC that underwent radioactive iodine ablation that were not under thyroid hormone replacement therapy and had a cervical US, WBS and STg measurement at one-year follow-up	Median (min-max), diagnostic AUC
2016; Livhits[16]	Tg/TSH	Retrospective	Presence *vs* absence of pulmonary M (8 *vs* 36)	Pediatric patients that underwent surgery for DTC followed-up by radioactive iodine ablation that were not under thyroid hormone replacement therapy and that had negative TSH-stimulated Tg value measured at the time of 131I administration	Mean±SD values, diagnostic AUC
2015; Orlov[12]*	Tg/TSH	Retrospective	Disease free survival	Patients with DTC that underwent total thyroidectomy did not receive T3 at least for 9 days and T4 22 days. Radioactive iodine ablation was performed when indicated	Sensitivity, specificity, AUC
2015; Wang17	TSH/Tg	Retrospective	Malignant *vs* benign (242 *vs* 158)	Patients with no evidence of clinical or subclinical hypothyroidism or hyperthyroidism, previous or current use of anti-thyroid or thyroid hormone replacement therapy, with no previous FNA during the past 4 weeks or ALT ≥80 IU/ml	False positive/ negative true positive/negative
2014; Zubair Hussain[18]	Tg/TSH	Retrospective	Success *vs* fail of ablative ^{131}I (45 *vs* 30)	Adult patients with DTC that underwent thyroidectomy and had stimulated TSH (sTSH), sTg, and Anti-Tg antibodies (Anti-Tg) 3-4 weeks after thyroidectomy without thyroxine replacement, received RRA, underwent WBIS, neck US, diagnostic WBIS, and sTg; and anti-Tg at 6–12 months after RRA. Patients with anti-Tg >40IU/ml prior to RRA were excluded	Median (IQR), False positive/ negative true positive/negative
2011; Lin[19]	Tg/TSH	Retrospective	Presence vs absence of M (47 *vs* 197)	Patients with DTC that underwent total thyroidectomy followed by ^{131}I therapy	Median (min-max), diagnostic AUC

*Data were retrieved from conference abstract.

Table 2. Newcastle-Ottawa scale of case control studies.

	Selection				°	Exposure			
Year; author	Case definition	Representativeness	Controls selection	Controls definition	Comparability	Ascertainment of exposure	Same method	Non-response rate	Total score
2018; Tam[13]	*	*	*	*	*	*	*	*	8
2016; Yazici[14]	*	*	*	*	**	*	*	*	9
2016; Trevizam[15]	*	*	*	*	**	*	*	-	8
2016; Livhits[16]	*	*	*	*	**	*	*	*	9
2015; Orlovn[12#]	*	*	-	-	**	*	*	-	6
2015; Wang[17]	*	*	*	*	-	*	*	*	7
2014; Zubair Hussain[18]	*	*	*	*	**	*	*	*	9
2011; Lin[19]	*	*	*	*	**	*	*	*	9

°Comparability based in exclusion of anti-Tg antibodies, second star was given if all case referred to differentiated thyroid cancer; #data were retrieved from conference abstract.

Table 3. Clinical and hormonal profile of our studied population.

	Benign (240)	Malignant (134)	P-value
Age	71 (60-85)	72 (62-79)	0.771
Sex			0.003
Male	52	48	
Female	188	86	
Smoking	54	22	0.161
Number of nodules			0.257
Solitary	53	23	
Multiple	187	111	
Positive lymph nodes	0/240	28/134 (range 5-14)	<0.001
Surgical procedure			0.015
Lobectomy	18 (4*)	2*	
Thyroidectomy	222	134	
Max tumor diameter (mm)	18 (7, 32) [9-22]	17 (5, 24) [7-17]	0.850
Tumor weight (gr)	63 (13, 113) [28-86]	59 (3, 78) [15-66]	0.358
TSH	1.89 (1.21, 3.28) [1.26-2.75]	1.93 (1.20, 3.40) [1.21-3.06]	0.541
fT3	2.61 (2.10, 3.99) [2.12-3.09]	2.71 (2.23, 3.16) [2.32-2.84]	0.227
fT4	1.35 (0.88, 1.67) [0.89-1.79]	1.39 (0.80, 2.10) [0.82-1.77]	0.874
Tg	29 (5, 548) [6-119]	35.5 (5, 1227) [10-724]	0.039
Tg/TSH	15.6 (1.5, 268) [3.09-50.67]	27.8 (12.9, 776) [15.10-416]	0.020
TSH/Tg	0.06 (0.00, 0.66) [0.02-0.32]	0.06 (0.02 , 0.53) [0.05-0.45]	0.020

*These patients underwent completion thyroidectomy; Parentheses include min max values; square brackets include 95% confidence interval.

Table 4. Logistic regression for the prediction of thyroid cancer.

	Exp(B) (95% CI)	P-value
Female sex	0.421 (0.214, 0.828)	0.012
Smoking	0.758 (0.424, 1.352)	0.348
Tumor diameter	1.009 (0.982, 1.037)	0.504
Tumor weight	0.997 (0.989, 1.005)	0.514
Multiple nodules	1.359 (0.726, 2.544)	0.337
TSH	0.946 (0.582, 1.538)	0.824
fT3	1.167 (0.525, 2.591)	0.705
fT4	1.357 (0.614, 2.997)	0.450
Tg	0.979 (0.959, 0.999)	0.038
Tg/TSH	1.058 (1.012, 1.107)	0.014
TSH/Tg	5.813 (0.280, 120.5)	0.255

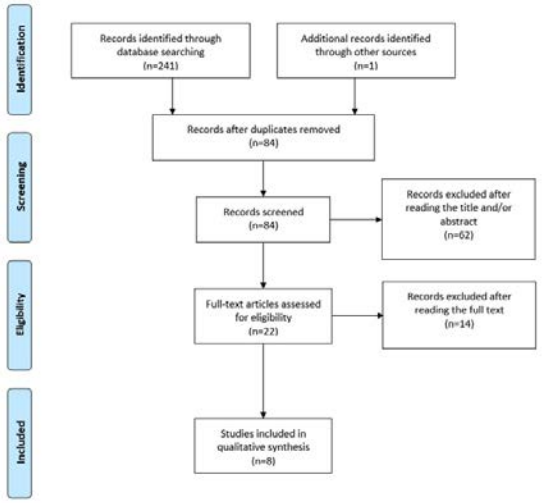
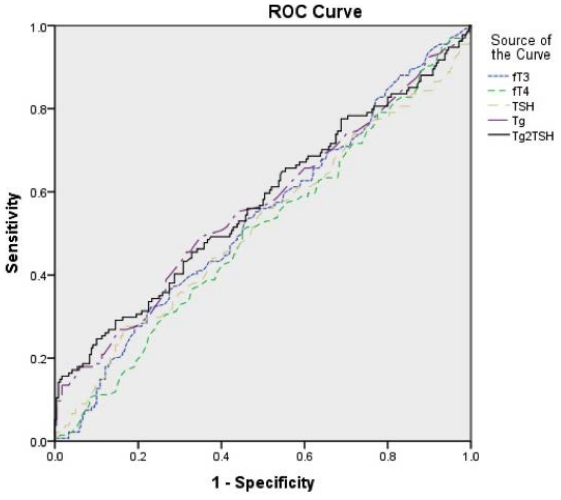


Figure 1. Flow diagram.



Area under the curve

Variables	AUC	SE	P-value	95% confidence interval Lower	Upper
fT3	0.538	0.031	0.227	0.477	0.599
fT4	0.505	0.031	0.874	0.444	0.566
TSH	0.519	0.032	0.541	0.456	0.582
Tg	0.564	0.032	0.039	0.502	0.627
Tg/TSH ratio	0.572	0.032	0.020	0.509	0.635

The test result variable(s): fT3, fT4, TSH, Tg, Tg2TSH has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption;
b. Null hypothesis: true area =0.5.

Figure 2. ROC curve analysis.

Tg/TSH ratio as predictive of thyroid cancer [area under the curve (AUC) of 0.564 and 0.572 respectively]. The optimal cut-off value in our study for the Tg/TSH ratio was set at 15.6 ng/mIU (sensitivity 58%, specificity 50%). We also tested the optimal cut-off value suggested by Orlov *et al.* (sTg/TSH <0.07μg/IU);[12] however in our analysis it was associated with a very high specificity but extremely low sensitivity (92% and 13% respectively) (Figure 2).

Results of the systematic review

Eight studies were included in the present systematic review that involved a total of 1,643 patients.[12-19] The methodological characteristics of included studies are summarized in Table 1. Briefly, three studies investigated differences in serum Tg/TSH and/or TSH/Tg levels among patients with malignant and benign thyroid nodules, two studies assessed the accuracy of Tg/TSH ratio in predicting success of ablative ^{131}I therapy, one study investigated the correlation of this ratio with the DFS of patients with DTC and two studies investigated whether this ratio could predict distant metastases. Significant heterogeneity was observed in terms of inclusion criteria and outcome reporting measures that precluded meta-analyses of aggregated data that were presented in these studies. The methodological quality of included studies was evaluated as high and the results of the Newcastle-Ottawa scale are presented in Table 2.

Primary outcomes

The three studies that evaluated the differences concerning the TSH/Tg ratio among patients with malignant and benign disease reported that these were significantly different (P<0.05). However, the median values in both groups were extremely close in the two studies. Specifically, Tam *et al.* reported that the median and range values in the benign and malignant group were 0.02 μIU/ng (0.001-1.09) and 0.04 (0.001-2.24) respectively (P<0.001).[13] Similar results were reported by Yazici *et al.* (0.02 (0.004-8.6) *vs* 0.04 (0.002-19) μIU/ng respectively, P=0.024).[14] Wang *et al*. reported that patients with benign nodules had a TSH/Tg ratio of 19.9, 95% confidence interval (CI): (11.8-29.5) IU/g, whereas patients with malignant disease had a significantly larger ratio 86.2, 95%CI: 56.2-129.6) IU/g.[17] On the other hand, data concerning differences of the Tg/TSH ratio were conflicting as Yazici *et al*. failed to observe a significant difference among patients with benign and malignant disease [43 (1-9100) *vs* 17 (1-5200) ng/μIU, P=0.072], whereas Tam *et al*. reported that the differences were significant [53.1 (0.92-1587.3) *vs* 23.8 (0.45-2137.5) ng/μIU, P<0.001].

Concerning distant metastases, the only study published in adults revealed that differences in Tg/TSH values among patients with metastatic disease and those with local disease were different [7.747 (1.733–13.340) *vs* 0.066 (0.017–0.21) ng/μIU, P=0.021].[19] The diagnostic area under the curve of this ratio was 0.916 (95% CI 0.858, 0.973) and was comparable to that of Tg as a single marker (0.913, 95% CI 0.854, 0.971). Similarly, Livhits *et al.* observed that the pre-ablation Tg/TSH was higher in children and adolescents with DTC and pulmonary metastases (12.5±18.8 *vs* 0.7±1.8 μg/mU, P<0.01).[16] The area under the curve for the Tg/TSH ratio was 0.83 and for Tg as a single index 0.85.

The only study that attempted to evaluate the accuracy of the Tg/TSH ratio in predicting long term DFS was published Orlov *et al*.[12] They suggested an optimal cut-off value of <0.07 μg/mIU and reported that its sensitivity was 68% and its specificity 71%.

Secondary outcomes

Two studies investigated the accuracy of the Tg/TSH ratio in predicting success of ablative ^{131}I therapy. Specifically, Trevizam *et al.*[15] observed that patients with successful ablative therapy had significantly lower Tg/TSH levels compared to patients with treatment failure [0.02 (0.00; 0.32) 0.20 (0.00; 4.40), P<0.001).[15] The same authors concluded that the use of the optimal cut-off value of 0.093 had a sensitivity of 80% and a specificity of 79.2% in predicting the success of ablative ^{131}I therapy. Zubair Hussain *et al.*[18] also observed that pre-ablation Tg/TSH ratio was significantly associated with the outcome of patients with DTC.[18] They suggested that a Tg/TSH ratio of 0.35 was associated with a relatively high specificity (81.5%) and sensitivity (81.4%).

Discussion

Thyroglobulin is a glycoprotein that is explicitly produced by thyroid cells. Its expression is not affected by the malignant or benign nature of these cells. This may explain its clear association with the adequacy of ^{131}I ablative therapy. Given that both malignant and benign cells can produce this protein, it would be reasonable to argue its prognostic significance among patients with thyroid nodules. Current guidelines do not suggest the use of serum Tg for the detection of DTC in patients with thyroid nodules.[4] On the other hand, the altered genomic profile of thyroglobulin in thyroid[20] cancer has been already mentioned.[21] Since TSH is the trigger factor that directly affects the expression of Tg, one could assume that cancer cells may respond differently to TSH compared to healthy thyroid cells. Thus, Tg/TSH and /or TSH/Tg ratios could be a better biomarker for the detection of thyroid cancer that Tg alone.

In our retrospective cohort we observed that both Tg/TSH and TSH/Tg ratios differed between the two groups in the univariate analysis. However, this finding was not replicated in the multivariate analysis or the diagnostic ROC curves indicating that their impact in current clinical practice would have been debated. Reviewing the data of the literature we observed that at least two studies reported significant differences in TSH/Tg ratios between patients with benign and malignant disease, although they were discrete with a very large range.[13,14] This latter observation significantly hinders the application of this ratio to clinical practice as a diagnostic and surveillance biomarker. Most of the studies failed to report actual 95% confidence intervals with their results being potentially affected by significant outliers; hence, it remains unknown whether the range of the true value of these ratios is associated with clinical relevance.[22,23] The main reason for these outliers is the extreme variability of Tg expression in thyroid cells.[24] The biological variability of the existing analytes remains also an issue as the reported coefficients of variation of the protein may reach a value of 16.2%.[25]

Strengths and limitations of our study

The main strength of our study relies on the very strict exclusion criteria eliminating potential confounders that could affect thyroid function. Moreover, we performed an in-depth review of the literature that allowed us to minimize potential article losses that would limit the findings of our systematic review. The studies that were included, although case control in nature, were rated with high scores.

On the other hand, the retrospective nature of our study partially limits the interpretation of our findings, given the fact that selection bias is always an issue in retrospective studies. Moreover, despite the fact that we used an optimal test for the assessment of Tg values its coefficient of variation may partially limit the diagnostic value of the studied ratio as it reached performances of

approximately 10%. Moreover, the heterogeneity that was observed in terms of reported outcomes and measurements (mean values, AUCs, true and false positive/negative results) did not permit the conduct of a meta-analysis. Lastly, the methodological heterogeneity of the included studies (Table 1) and the small number of studies that were retrieved per reported outcome do not permit the introduction of specific guidelines in current clinical practice.

Conclusions

The findings of our study support that the Tg/TSH ratio may help determine the success of ablative ^{131}I therapy as the two studies that investigated this biomarker suggested that it seems to have clinical relevance to the studied outcome. In our study we observed a positive correlation of increased Tg/TSH with the risk of having DTC; however, the method does not seem to perform well. This is why we believe that current data concerning its diagnostic accuracy of are not sufficient to support its clinical applicability in every day practice. Future studies are needed for more firm conclusions focusing not only in the differences of absolute values among the studied groups, but also on predefined optimal cut-off values with high diagnostic and predictive accuracy.

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