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Thyrotropin/Thyroglobulin ratio in combination with thyroid u/s to assess malignancy risk stratification of thyroid nodules

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***Abstract*---**Objective: we aimed to asses if thyrotropin/thyroglobulin ratio has a significant value in detection of malignant thyroid nodules. Design: Retrospective analysis. Material and Methods: This study included finally 100 subject collected as outpatient's endocrinology clinic of ALHuessine university hospital or admitted at oncology institute of Tanta. Patients who had history of thyroid diseases or surgery, those with abnormal levels of anti- thyroglobulin antibodies, cases without simultaneous measurement of serum anti Tg., with history of current use of thyroid hormone replacement therapy were excluded from this study. Clinico pathological features, as well as serumTSH, Tg, and TSH/Tg were compared between histopathologically benign and malignant groups. Results: Data

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related to 100 subjects (40%) normal and 60(60%) patients with thyroid nodules were analyzed, 30 patients (50%) were malignant thyroid nodules and 30 patients (50%) were benign.The malignant patients exhibited significantly higher TSH, TSH/Tg, , and a lower Tg compared to the benign patients ($p<0.05$ for each). Conclusion: Preoperative TSH/Tg could be used as a predictive marker for differentiating between benign and malignant thyroid nodules.

***Keywords*---**Thyrotropin/Thyroglobulin, thyroid, stratification, thyroid nodules.

Introduction

Thyroid nodules have been defined by the American Thyroid Association (ATA) as "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma. [(1)] Thyroid nodules are common, their prevalence being largely dependent on the identification method. The estimated prevalence by palpation alone ranges from 4% to 7%,[(3,4)] whereas US detects nodules in 20% to 76% of the adult population,[(2,3,4)] particularly with the current use of high-resolution US techniques.[(5)]. The reported frequencies detected by US correlate with the prevalence reported at surgery and autopsy with ranges between 50% and 65%.[(6)].

Thyroid nodules are 4 times more common in women than men and their frequency increases with age and low iodine intake.[(2)] More than 50% of the population has at least one thyroid nodule under ultrasonography examination. [(7)] However, along with increased detection rates of non-palpable thyroid nodules, the incidence rate of thyroid cancer has been raised [(8,9)] and the absolute number of indeterminate thyroid nodule cytology results has also markedly increased. Although fine needle aspiration cytology (FNAC) is a primary method for detecting malignant nodules, 10%-25% of thyroid nodules are categorized as indeterminate nodules [(10)]. Classifications for indeterminate nodules are defined as "atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)" and "follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN)" under the Bethesda classification systems, and the risk of malignancy of the FN/SFN category nodules is approximately 15%-30% [(11)]. Thyroglobulin (Tg) is a glycoprotein produced specifically in the thyroid follicular cells, regardless of whether they are of malignant or benign nature [(12)].It is a well-known marker for persistent or recurrent differentiated thyroid cancer [(13)]. Although the role of Tg in the post-operative period has been clearly defined, its use as a predictive marker in the preoperative period is debatable [(12,14,15)].Routine Tg measurement is not recommended as an initial laboratory investigation for thyroid nodules. It is not sensitive or specific for thyroid cancer as it exhibits increased levels in several other thyroid diseases [(16)].Majority of the nodules with indeterminate cytology are surgically excised due to their malignancy potential, which confronts the patients with risks of morbidity and complications related to unnecessary surgeries [(6)]. Therefore, it is comprehensible that in addition to cytology, certain other parameters are required to predict malignancy preoperatively. Gender, age, nodule diameter, exposure to radiation, and certain ultrasonography(US) features

have been demonstrated to be associated with the risk of malignancy in previous reports [3,7]. Preoperative high serum thyrotropin (TSH) has also been demonstrated to increase the risk of malignancy in various studies. Boelaert et al. [8] evaluated serum TSH in patients with nodular or diffuse goiter, and observed that even though within normal ranges, high serum TSH was associated with thyroid malignancy.

Material and Methods

This study included finally 100 subjects collected as out patients endocrinology clinic of AL Hussein university hospital or admitted at oncology institute of Tanta.At the beginning of the study 180 subjects meeting both the inclusion and the exclusion criteria were enrolled , (40) subjects were normal without thyroid nodules as control group ,then 80 patients were excluded from the study for various causes as (45 cases without simultaneous measurement of serum anti Tg., 28 cases with high anti Tg ,7 cases with history of current use of thyroid hormone replacement therapy). All patients who had thyroid nodule by thyroid ultrasound who collected during the duration of the study were included except who met exclusion criteria as patients with high anti-Tg., patients without simultaneous measurement of serum anti-Tg., clinical or subclinical hypothyroidism or hyperthyroidism., radiation to head and neck, history of thyroid surgery or previous or current use of anti-thyroid or thyroid hormone replacement therapy. All the patients had been subjected to history taking and demographic data collection, general and local examination of thyroid gland to detect any abnormality by palpation.

Vital data collection included temperature, mean arterial blood pressure in the highest limb, pulse, respiratory rate and investigations included Complete blood picture, thyroid function test, thyroglobulin and thyroglobulin antibodies , thyroid ultrasound to detect thyroid nodules using TIRADS assessment , fine needle aspiration biopsy (FNAB) for cytology of nodular pathology depend on BETHESDA classification, Excisional biopsy for cases of suspected malignancy by FNAC across thyroidctomy syrgery and detection of thyrotropin to thyroglobulin ratio and its significance in predicting malignancy of thyroid nodules compared with FNAC and results of excisional biopsy post-surgery. Cases were categorized into 3 groups:

Patients with thyroid nodules who met the criteria of malignancy by cytology and effect of ratio of thyrotropin to thyroglobulin in prediction of malignancy risk, Patients with thyroid nodules who didn't meet the criteria of malignancy by cytology and effect of ratio of thyrotropin to thyroglobulin in prediction of malignancy risk and subjects who were normal without thyroid nodules by thyroid ultrasound and study of any effect for thyrotropin to thyroglobulin ratio for those patients compared with results of both two previous groups.

Statistical analysis

Recorded data underwent analysis using the statistics of social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). Pooled quantified data underwent presentation as mean ± standard deviation and the ranges when their distribution

was parametric (normal) while the non-normally distributed variables (non-parametric data) were shown as the mean with the interquartile range (IQR). Also qualitative variables were presented inform of numbers and percentages. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk Test.

The following tests were done

Independent-samples t-test of significance was used in comparison between two means & Mann Whitney U test: for two-groups comparisons in non-parametric data. The Comparison between groups with qualitative data was done by using Chi-square test and Fisher's exact test instead of Chi-square test only when the expected count in any cell less than 5.

Multivariate logistic regression analysis: Odds ratios (OR) with 95% confidence intervals were computed to assess the overall association between each factor and the occurrence of Malignancy Risk Stratification of Thyroid Nodules Receiver operating characteristic (ROC curve) analysis was used to find out the over all predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.

- Sensitivity = (true +ve)/ [(true +ve) + (false –ve)].
- Specificity = (true –ve) / [(true –ve) + (false +ve)].
- PPV = (true +ve) / [(true +ve) + (false +ve)].
- NPV = (true –ve)/ [(true –ve) + (false –ve)].
- Accuracy = (TP+TN)/[TP+FP+TN+FN]

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant, P-value>0.05wasconsideredinsignifi-cant.

Results

Data related to 100 subjects, 60 euthyroid patients with nodular thyroid disease were analyzed. Histopathological diagnosis was benign in 30 patient (50%) and malignant in 30 patient (50%) patients and control group of 40 subjects. Table (1) describes the age and the sex distribution of total study population. Age ranged from 14 to 65 years with mean± SD of 39.06±13.43. As regards sex distribution, there was female predominance with 51 females with percentage 51% and 49 males with percentage 49%.

Table (1)
Demographic data distribution among study group (n=100)

Demographic data	Total (n=100)
Age (years) Range Mean±SD	 14-65 39.06±13.43
Sex Female	 51 (51.0%)

Male	49 (49.0%)

According to laboratory data in the study group, it was median of TSH [2.2 (1.5-3)]; median of FT3 [3.29 (2.9-3.9)]; median of FT4 [1.32 (1.1-1.5)] and median of Thyroglobulin [30.2 (16.38-43.5)]. (table2)

Table (2)
Laboratory data descriptive among study group (n=100)

Laboratory data	Range	Mean±SD
TSH#	0..5-4.8	2.2 (1.5-3)
FT3#	1.1-5.9	3.29 (2.9-3.9)
FT4#	0.7-1.8	1.32 (1.1-1.5)
Thyroglobulin#	0.93-500	30.2 (16.38-43.5)

Table (3)
Assessment of thyroid by U/S and among study group (n=100)

Assessment of thyroid by U/S	No.	%
Normal	40	40.0%
thyroid nodules	60	60.0%
Thyroid noduleTIRAD2	51	51.0%
Multible nodules TIRAD 3	6	6.0%
Thyoid nodule TIRAD 5	1	1.0%
Thyroid nodule TIRAD 3	1	1.0%
Thyroid nodule TIRAD 4	1	1.0%

Table (4)
Assessment of thyroid by pathology among abnormality thyroid nodules by U/S (n=60)

Assessment of thyroid by Pathology (n=60)	No.	%
Benign nodule	30	50.0%
Malignancy	30	50.0%
Papillary carcinoma BETHESDA 4	19	31.6%
follicular carcinoma BETHESDA 3	5	8.3%
Papillary carcinoma BETHESDA 5	4	6.6%
Papillary carcinoma BETHESDA 3	2	3.3%

Median of Thyrotropin/ Thyroglobulin Ratio was 0.059(0.028-0.093) for the normal group compared to 0.122(0.074-0.172) for the thyroid nodules groups, there was statistically significant higher mean of Thyrotropin/ Thyroglobulin Ratio in thyroid nodules groups compared to normal group with p-value ($p<0.05$). This indicates that when the value is increased, it is expected that there are thyroid nodules (Table5).

Table (5)
Comparison between normal and thyroid nodules by U/S according to Thyrotropin/ Thyroglobulin Ratio

Thyrotropin/ Thyroglobulin Ratio	U/S		Test value	p-value
	Normal (n=40)	thyroid nodules (n=60)		
Median (IQR)	0.059(0.028-0.093)	0.122(0.074-0.172)	-3.715	<0.001**
Range	0.01-0.30	0.0-3.66		

Median of Thyrotropin/ Thyroglobulin Ratio was 0.051(0.032-0.087) for the Benign group compared to 0.073(0.034-0.449) for the malignant group, there was statistically significant higher mean of Thyrotropin/ Thyroglobulin Ratio in malignant group compared to Benign group with p-value ($p<0.05$). This indicates that when the value is increased, it is expected that there are malignant tumors.(Table6). Table (6): Comparison between benign and malignant by pathology according to Thyrotropin/ Thyroglobulin Ratio.

Thyrotropin/ Thyroglobulin Ratio	Pathology		Test value	p-value
	Benign (n=30)	Malignant (n=30)		
Median (IQR)	0.051(0.032-0.087)	0.073(0.034-0.449)	-5.274	<0.001**
Range	0.02-0.29	0.001-3.66		

Multivariate regression analysis demonstrated that TLC, TSH, thyroglobulin, Thyrotropin/Thyroglobulin Ratio and Thyroglobulin/ Thyrotropin Ratio were the best independent predictors of malignancy of thyroid nodules with [OR (C.I.95%), p-value] [1.860 (1.427-4.259), p=0.018]; [2.489(1.909-5.700), p=0.027]; [0.934 (0.716-2.139), p=0.030]; [3.378 (2.591-7.736), p<0.001] and [4.952 (3.031-12.051), p<0.001] respectively.(Table7) Table (7): Multivariate logistic regression analysis for independent factors as predictors for Malignancy of Thyroid Nodules.

Parameters	β	Wald	Sig.	Odds ratio	95% C.I. for OR	
					Lower	Upper
Age (years)	0.170	1.259	0.200	0.844	0.647	1.933
Sex	0.518	1.661	0.198	0.596	0.457	1.365
Hb.	-0.165	0.464	0.363	0.848	0.650	1.942
TLC	1.151	6.589	0.018*	1.860	1.427	4.259
PLT	0.187	0.266	0.606	0.829	0.636	1.898
TSH	1.682	5.012	0.027*	2.489	1.909	5.700
FT3	0.291	0.026	0.872	0.695	0.533	1.592
FT4	0.580	1.034	0.309	0.705	0.541	1.614
Thyroglobulin	-1.290	4.735	0.030*	0.934	0.716	2.139
Thyrotropin/Thyroglobulin Ratio	2.274	11.795	<0.001**	3.378	2.591	7.736
Thyroglobulin/ Thyrotropin Ratio	2.061	8.081	<0.001**	4.952	3.031	12.051

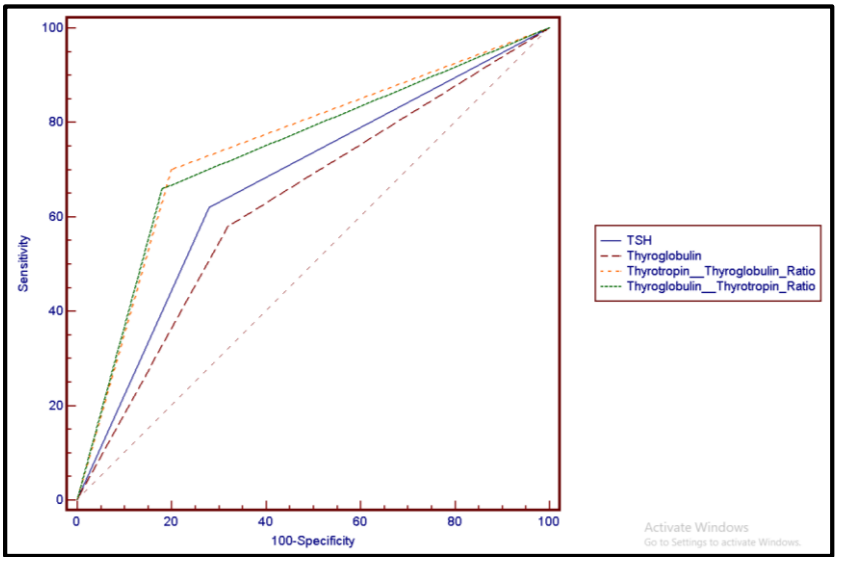

Fig. (1)Receiver-operating characteristic (ROC) curve for prediction malignancy using the risk factors

Table (8)
Receiver operator characteristics (ROC) curves were constructed for TSH, Thyroglobulin, Thyrotropin/ Thyroglobulin Ratio and Thyroglobulin/ Thyrotropin Ratio

Parameters	Cut-off	Sen.	Spe.	PPV	NPV	AUC
TSH	≥4.00	62.0%	72.0%	68.9%	65.5%	67.0%
Thyroglobulin	≤10.60	58.0%	68.0%	64.4%	61.8%	63.0%
Thyrotropin/ Thyroglobulin Ratio	≥0.105	70.0%	80.0%	77.8%	72.7%	75.0%
Thyroglobulin/ Thyrotropin Ratio	≤9.40	66.0%	82.0%	78.6%	70.7%	74.0%

Discussion

Thyroid nodules are common signs, often discovered in clinical practice, either during thyroid examination, or incidentally during imaging procedures. Their importance is due to the possibility of being malignant nodules [17].Clinical follow up mostly is sufficient for the thyroid nodules after exclusion of malignancy but the major concerns to identify malignant lesions preoperatively.[18].Many studies search about the optimum way to investigate thyroid nodules and susceptibility to be malignant or benign according to many parameters including thyrotropin effect and the relation between its level and increased suspicion of malignancy (17).TSH has an important role in the regulation of thyroid differentiation genes, growth factors, and receptors [19].

Mitogenic effect of thyrotropin hormone on thyroid malignant cells has been well described previously Varying levels of TSH-receptor mRNA are expressed in nearly

all malignant thyroid lesions [20].Increasing serum thyrotropin levels, even within normal limits, have been reported to have risky role of malignancy in patients with thyroid nodules [21].From our study results, we observed higher serum thyrotropin (within normal ranges) in histo pathologically malignant patients in being compared to benign patients as median of TSH was 1.64(1.15-2.75) for the benign group compared to 1.89(1.175-3.025) for the malignant group, in addition to there was statistically significant lower mean of TSH in benign group compared to malignant group with p-value ($p<0.05$).In agreement with the results of our research, there were other studies that confirmed the importance of thyrotropin hormone in predicting the presence of malignant tumors in the thyroid gland. Shi et al. study demonstrated significant increase of the prevalence of differentiated thyroid cancer (DTC) as the serum TSH levels increased. A serum TSH level of 1.9-4.8 mIU/L and a serum TSH level >4.8mIU/L were observed to be associated with 1.57 (95% CI: 1.03-2.40; p=0.038) times and 5.71 (95% CI: 2.31-14.14; p=0.0002) times of the possibility of malignancy respectively, compared to a serum TSH level of 1.0-1.9 mIU/L. [18].Haymart MR et al. study observed an association between increased levels of serum TSH and significantly high risk of DTC. The risk of malignancy increased by 25% when the TSH levels were in the range of 0.40-1.39 mIU/L, while the increase was 35% when the TSH levels were in the range of 1.40-4.99 mIU/L (p=0.002)[22].Abbas et al. study suggested increased serum TSH levels (within normal ranges) in histo- pathologically malignant thyroid nodules compared to benign patients [23]. Similar to these findings, we also observed increased serum TSH levels (within normal ranges) in histo- pathologically malignant thyroid nodules compared to benign patients. In contrast to these findings, Kim et al. reported similar serum TSH levels in both papillary thyroid cancer (PTC) and benign nodules. There are also additional studies that reported lack of association between TSH and malignancy [24]. According to KIM study most of included cases were under hormone replacement therapy without exclusion of auto immune effect by exclusion of positivity of anti thyroglobulin antibodies in addition to selection of his cases only for Hashimoto's thyroiditis only which may made differences between the two study results. Thyroglobulin is directly associated with the process of synthesis and deposition of the hormones of thyroid gland with release of small amounts of physiological thyroglobulin into the peripheral circulation in healthy people. Detection of thyroglobulin in serum after total thyroidectomy in patients with DTC is highly suggestive of recurrent or persistent disease [26].In the present study, we observed Tg was risk factor for malignancy in euthyroid patients with thyroid nodules, as median of thyroglobulin was 37.5(20.5-63.5) for the Benign group compared to 28.4(10.5-40.75) for the malignant group, there was statistically significant higher mean of Thyroglobulin in Benign group compared to malignant group with p-value ($p<0.05$).In agreement with the results of our research, there were other studies that confirmed the importance of thyroglobulin hormone in predicting the presence of malignant tumors in the thyroid gland.Abbas et al. study observed that both TSH and Tg represented risk factors for malignancy in euthyroid patients with thyroid nodules [23].Lee EK et al study suggested a possible role of Tg in the preoperative diagnosis of malignancy[27]. Similar to these findings, we also observed statistically significance higher mean of Thyroglobulin in Benign group compared to malignant group with p-value ($p<0.05$).Youn I et al study examined the role of preoperative thyroglobulin, in addition to the characteristic features of ultrasound, in predicting malignancy in thyroid nodules suggested

that it could not be a marker to differentiate between malignant nodules and the benign ones. The authors concluded that the only predictive factor for suspicion malignancy was suspicious US features [28]. According to Youn I et al study it was a retrospective study performed on 374 thyroid nodules (363 benign and 11 malignant) It is clear that the number of patients with malignant thyroid cancer is low compared to the number of benign tumor, which may affect the emergence of a difference between the results of the two studies. Guarino et al. study did not find any diagnostic or prognostic value of preoperative Tg measurement in thyroid nodules. [29].In our study we aimed to assess TSH/Thyroglobulin ratio in combination with thyroid U/S to assess malignancy risk stratification of thyroid nodules and we applied our study on 100 cases, with the same inclusion and exclusion criteria.Age ranged from 14 to 65 years with mean± SD of 39.06±13.43. As regards sex distribution, there was female predominance with 51 females with percentage 51% and 49 males with percentage 49%.Many risk factors were studied to assess their malignancy risk stratification of thyroid nodules as regard to laboratory data in the study group, it was mean of Hb. (12.47±2.34); mean of TLC (7.58±3.60); mean of PLT (220.10±75.62); median of TSH [2.2 (1.5-3)]; median of FT3 [3.29 (2.9-3.9)]; median of FT4 [1.32 (1.1-1.5)] and median of Thyroglobulin [30.2 (16.38-43.5)].This study showed that according to ratio between Thyrotropin/ Thyroglobulin in the study group, it was median of Thyrotropin/ Thyroglobulin Ratio 0.077 (0.040-0.138), as for the Thyroglobulin/ Thyrotropin Ratio 13.03 (7.23-24.83).Additionally, median of TSH was 1.75(1.18-2.83) for the normal group compared to 2.80(2.03-3.00) for the thyroid nodules group, there was statistically significant lower mean of TSH in normal group compared to thyroid nodules group with p-value ($p<0.05$).While median of thyroglobulin was 34.50(21.00-53.25) for the normal group compared to 23.00(13.25-33.75) for the thyroid nodules group, there was statistically significant higher mean of Thyroglobulin in normal group compared to thyroid nodules group with p-value ($p<0.05$).Median of Thyrotropin/ Thyroglobulin Ratio was 0.059(0.028-0.093) for the normal group compared to 0.122(0.074-0.172) for the a thyroid nodules group, there was statistically significant higher mean of Thyrotropin/ Thyroglobulin Ratio in abnormality thyroid nodules group compared to normal group with p-value ($p<0.05$). This indicates that when the value is increased, it is expected that there are thyroid nodules.Median of thyroglobulin/ thyrotropin ratio was 16.60 (10.05-35.65) for the normal group compared to 8.23 (5.81-13.42) for the abnormality thyroid nodules group, there was statistically significant lower mean of thyroglobulin/ thyrotropin ratio in thyroid nodules group compared to normal group with p-value ($p<0.05$). This indicates that when the value is decreased, it is expected that there are abnormality thyroid nodules.As regard Comparison between benign and malignant by pathology according to Thyrotropin/ Thyroglobulin Ratio the study showed that Median of Thyrotropin/ Thyroglobulin Ratio was 0.051(0.032-0.087) for the Benign group compared to 0.073(0.034-0.449) for the malignant group, there was statistically significant higher mean of Thyrotropin/ Thyroglobulin Ratio in malignant group compared to Benign group with p-value ($p<0.05$). This indicates that when the value is increased, it is expected that there are malignant tumors.Multivariate regression analysis demonstrated that TLC, TSH, thyroglobulin, Thyrotropin/Thyroglobulin Ratio and Thyroglobulin/ Thyrotropin Ratio were the best independent predictors of malignancy of thyroid nodules with [OR (C.I.95%), p-value] [1.860 (1.427-4.259), p=0.018]; [2.489 (1.909-5.700), p=0.027]; [0.934 (0.716-2.139), p=0.030];

[3.378 (2.591-7.736), p<0.001] and [4.952 (3.031-12.051), p<0.001] respectively. Receiver operator characteristics (ROC) curves were constructed for TSH, Thyroglobulin, Thyrotropin/ Thyroglobulin Ratio and Thyroglobulin/ Thyrotropin Ratio as predictors of malignancy in included patients. All variable were significant predictors as represented by the significantly large area under the curves (AUCs); with Thyrotropin/ Thyroglobulin Ratio being the most significant predictor.

Conclusion

High serum TSH has a significant role in predicting the risk of thyroid malignancy of thyroid nodules patients. In addition to TSH/Tg ratio promising to be noninvasive predictor marker of malignancy of thyroid nodules patients. TSH/Tg could serve as a practical and applicable index for risk stratification of thyroid nodules, and with combination with other factors, it could aid physicians to take important decisions regarding the management of thyroid nodules.

Recommendation

Further prospective and large-scale research are required to support these findings.

Ethics

Ethics Committee Approval and Informed Consent: Ethical review board of AlAzhar University, AL-Hussein University Hospital approved the study protocol.

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