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Concordance of TI-RADS Scores with Thyroid Histopathology and Its Relationship with TSH, T3, and T4 Levels in Thyroid Nodule Patients at Prof dr. I.G.N.G Ngoerah General Hospital

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ABSTRACT

Background: Thyroid gland disorders are the second most common endocrine disorder worldwide after diabetes. Ultrasonography (USG) with TI-RADS scoring is an essential modality for assessing the malignancy risk of thyroid nodules, while Fine Needle Aspiration Biopsy (FNAB) is used to determine the histopathological characteristics of the nodules. This study aims to assess the correlation between TI-RADS scores and histopathological results and their relationship with thyroid hormone levels in patients with thyroid nodules. ***Method:*** This is an observational analytic study with a cross-sectional design. The study uses the results of TI-RADS score measurements, histopathological findings, and thyroid hormone levels in patients with thyroid nodules. These three variables were measured simultaneously at the time of diagnosis. The collected data were processed and presented in the form of frequency distribution tables. All data obtained were statistically analyzed using the SPSS 24.0 for Windows, including descriptive statistical analysis, conformity tests, mean difference tests, and MANCOVA tests. ***Result:*** The total number of subjects was 39. TI-RADS scores of 4-5 showed malignant histological features in 19 subjects (48.7%), while 16 out of 20 subjects with TI-RADS scores in the range of 1-3 showed benign histological features, with a Kappa value of 0.796 (strong level of agreement) and an agreement percentage of 89.74%; $p<0.001$. There was no statistically significant difference between the mean levels of TSH, FT4, and T3 based on histological findings, as the p-values obtained were greater than 0.05. ***Conclusion:*** There is a statistically significant correlation between TI-RADS scores and histopathological findings, but no statistically significant difference in the mean levels of TSH, FT4, and T3 based on either the TI-RADS score categories or histopathological findings in patients with thyroid nodules.

Keywords: TI-RADS score; thyroid nodules; histopathological; TSH; FT4; T3

INTRODUCTION

Disorders of the thyroid gland are the second most common endocrine disorder in the world after diabetes in 2016. Approximately 300 million people worldwide were reported to suffer from thyroid disorders [1]. In the same year, there were 238,000 new cases of thyroid cancer and 43,000 deaths due to the disease. In 2014, the Indonesian Society of Pathology Specialists stated that thyroid cancer ranked 9th among the top 10 cancers (4.43%), while at Dr. Cipto Mangunkusumo Hospital Jakarta, it ranked 5th [2]. Among the 62,450 cases of thyroid cancer in the United States, it was found that 3 out of 4 cases occurred in women [1]. A study of 117 patients at Dr. M. Djamil Hospital Padang showed that the number of female patients was 86.3% [3]. Another study at Prof. Dr. R. D. Kandou Hospital Manado showed that the number of female patients was 62.9% [4].

Thyroid nodules are an endocrine disorder that can be classified as benign or malignant (carcinoma). Most of the disease's growth and progression is slow, leading to low morbidity and mortality rates, but some grow very rapidly with a fatal prognosis [4,5]. Thyroid nodules can occur due to high exposure to radiation, which causes DNA damage, leading to the formation of malignant thyroid cells [6]. Low iodine intake also leads to increased stimulation of thyroid-stimulating hormone (TSH) and thyroid hyperplasia in the form of endemic goiter, increasing the likelihood of thyroid follicular carcinogenesis [7,8].

Family history also influences the formation of thyroid nodules, including a history of thyroid malignancy or thyroid cancer syndromes (Carney complex, multiple endocrine neoplasia, familial adenomatous polyposis, and Cowden syndrome)[9].

Thyroid nodules express TSHR, which plays an important role in the production of TSH hormones, followed by T3 and T4, especially functional TSH by malignant thyroid nodules. Several studies have found a decrease in growth rates and prevention of new nodule formation in patients undergoing TSH suppression. In addition, suppressive doses of L-T4 may induce favorable cytological changes in thyroid nodules [10]. Research by Jonklaas et al. (2008) found higher TSH levels and lower T3 levels in thyroid cancer patients than in benign cases [11]. Thyroid hormone level tests are necessary to identify these conditions [2].

Ultrasonography (USG) is highly recommended as the most sensitive imaging modality for examining the thyroid gland and related disorders. USG has a sensitivity of 83-98%, specificity of 90-95%, and diagnostic accuracy of 91-99% [12,13]. USG examination with TI-RADS scoring improves patient management in estimating the risk of malignancy in each benign, low, medium, and high-risk nodule category; and avoids unnecessary additional tests such as Fine Needle Aspiration Biopsy (FNAB) [14,15]. USG is non-invasive, widely available, cheaper, and does not use ionizing radiation [16].

FNAB provides a histopathological picture of thyroid nodules in determining the type of thyroid nodule, with a sensitivity of 73.9%, specificity of 91.5%, and diagnostic accuracy of 72.73% [13,17,18]. The histopathological results of thyroid nodules are divided into benign thyroid nodule images such as follicular adenoma, hurtle cell adenoma, and teratoma, as well as malignant types such as papillary carcinoma, follicular carcinoma, medullary, and anaplastic carcinoma [8]. This study aims to determine the consistency of TI-RADS scores with thyroid histopathology results in determining the malignancy of thyroid nodules and their relationship with thyroid hormone levels in patients with thyroid nodules.

METHOD

This research is an observational analytic study with a cross-sectional study design. The study utilized the measurement results of the TI-RADS score, histopathological results, and thyroid hormone examination results in patients with thyroid nodules. The measurement of these three variables was conducted during the same period when the diagnosis was established. All data were obtained from medical records. The research was carried out at the Radiology Department and Medical Records Unit of Prof dr. I.G.N.G Ngoerah General Hospital in Denpasar. The study period lasted from February to June 2022. The target population of this study was patients with thyroid nodules. Thyroid nodules were clinically determined by identifying the presence of a lump in the neck region based on anamnesis and physical examination.

Inclusion criteria: 1) Age ≥ 18 years; 2) Underwent ultrasonography examination with a TI-RADS score; 3) Underwent FNAB thyroid biopsy; 4) Underwent TSH, T3, and T4 hormone level examination. Exclusion criteria: 1) Incomplete or unavailable medical records; 2) Patients with diffuse thyroid disease (thyroiditis or multinodular diffuse goiter). The study was conducted using a stratified random sampling method.

The collected data were processed and presented in the form of frequency distribution tables. All obtained data were statistically analyzed using the SPSS 24.0 (Statistical Package for Social Science) software for Windows, including descriptive statistical analysis and conformity tests, by cross-tabulating the TI-RADS score results with histopathological results to determine the conformity of TI-RADS score results based on their categories with histopathological examination results, which are divided into benign and malignant categories. TI-RADS scores of 1 to 3 were classified as benign, and scores of 4 to 5 were classified as malignant. This was then simplified by creating a 2x2 cross-tabulation, and the conformity was assessed based on the percentage agreement from the 2x2 cross-tabulation. The conformity of diagnostic results between TI-RADS scores and histopathology was evaluated using the Z test at an $\alpha = 0.05$ threshold. Besides the conformity test mentioned above, to support the assessment of TI-RADS scores as a diagnostic alternative for malignancy, validity assessment consisting of sensitivity and specificity of the TI-RADS score against histopathology as the gold standard was conducted. Validity assessment was based on a 2x2 cross-tabulation with column percentages. The mean difference test aimed to compare the mean TSH, T3, and T4 levels based on the TI-RADS score category and histopathological results. The independent t-test was used if the data distribution was normal, otherwise, the non-parametric Mann-Whitney test was applied. The MANCOVA test aimed to assess the relationship between TI-RADS scores and histopathological results with TSH, T3, and T4 after controlling for confounding variables through analysis. Conclusions were drawn based on P-values <0.05 and B-values

RESULT

The characteristics of the subjects described in this study are divided into two main groups: sociodemographic characteristics (including age, gender, and the presence or absence of a family history of identified thyroid nodules), which are presented in Table 1, and the characteristics of the histopathological examination results of the subjects, which are presented in Table 2.

TABLE 1: Sociodemographic characteristics of the research subjects.

Variable	N = 39
Age (mean ± SD)	48.10 ± 2.17
Gender	
Man	4 (10.3%)
Woman	35 (89.7%)
Family history	
There is	2 (5.1%)
No	37 (94.9%)

TABLE 2: Characteristics of the histopathological examination results of the research subjects.

PA Histology	N = 39
Anaplastic carcinoma	1 (2.6%)
Follicular benign nodules	5 (12.8%)
Colloid nodule	8 (20.5%)
Follicular carcinoma	9 (23.1%)
Follicular cell hyperplasia	1 (2.6%)
Papillary carcinoma	13 (33.3%)
Adenomatous goiter	1 (2.6%)
Struma adenomatous cystica	1 (2.6%)

The cross-tabulation data between the TI-RADS score variable and histopathological results are presented in Table 3. From the table, it is observed that all subjects with a TI-RADS score ranging from 4 to 5 showed malignant histopathological features, while 16 out of 20 subjects with a TI-RADS score ranging from 1 to 3 showed benign histopathological features, with a Kappa value of 0.796 (indicating a strong level of agreement) and a percentage agreement of 89.74%. Since the p-value is <0.001, these data indicate a statistically significant concordance between TI-RADS scores and histopathological results. In this study, the sensitivity and specificity of the TI-RADS score as a diagnostic alternative for malignancy were 82.61% and 100%, respectively, while the positive predictive value (PPV) and negative predictive value (NPV) were 100% and 80%, respectively.

TABLE 3: Concordance between TI-RADS scores and histopathological results.

	PA Histology		Percentage agreement	Kappa coefficient	P value
	Malignant N (%)	Benign N (%)			
TI-RADS					
4-5	19 (48.7%)	0 (0.0%)	89.74%	0.796	<0.001
1-3	4 (10.3%)	16 (41.0%)			

TSH and FT4 levels in subjects with a TI-RADS score range of 1-3 were higher compared to those with a TI-RADS score range of 4-5, while the total T3 level in the TI-RADS 1-3 score group was lower compared to the TI-RADS 4-5 score group (Table 4). However, the p-values obtained in this study for these three thyroid hormone variables were greater than 0.05, indicating that there is no statistically significant difference in the mean levels of TSH, FT4, and T3 based on the TI-RADS score categories.

TABLE 4: Comparison of TSH, FT4, and TSH values based on TI-RADS score categories.

Variable	TI-RADS Score		P value
	4-5	1-3	
TSH (mean ± SD)	0.83 ± 0.14	0.90 ± 0.13	0.720
FT4 (median ± IQR)	1.06 ± 0.48	1.09 ± 0.29	0.757
T3tot (median ± IQR)	2.02 ± 0.80	1.88 ± 0.40	0.422

Based on the data in Table 5, the TSH levels in subjects with malignant histopathological features were higher compared to those with benign histopathological features, while the opposite was observed for FT4 levels, which were higher in subjects with benign histopathological features. Meanwhile, both histopathological groups showed similar total T3 levels. However, as with the analysis of mean differences in TSH, FT4, and total T3 levels based on TI-RADS score categories, there was no statistically significant difference in the mean levels of TSH, FT4, and T3 based on histopathological features, as the p-values obtained were greater than 0.05.

TABLE 5: Comparison of TSH, FT4, and TSH values based on histopathology.

Variable	PA Histology		P value
	Malignant	Benign	
TSH (mean ± SD)	0.95 ± 0.13	0.74 ± 0.14	0.270
FT4 (median ± IQR)	1.07 ± 0.43	1.09 ± 0.34	0.753
T3tot (median ± IQR)	2.01 ± 0.54	2.01 ± 0.46	0.909

The statistical test used to assess the relationship between TI-RADS scores and histopathological results with TSH, T3, and T4 levels was a one-way multivariate analysis of covariance (MANCOVA) in order to control for confounding variables, such as the subject's age, gender, and family history of identified thyroid nodules. The comparison of TSH, FT4, and T3 levels based on TI-RADS score categories is presented in Table 6, while the comparison of these three thyroid hormones based on histopathological results is presented in Table 7.

Both tables show that neither the TI-RADS score nor the histopathological results have p-values less than 0.05. The p-values for TI-RADS scores for TSH, FT4, and T3 are 0.889, 0.908, and 0.798, respectively. Meanwhile, the p-values for histopathological results for the three thyroid hormones are 0.360, 0.632, and 0.998, respectively. This indicates that there is no statistically significant difference, either between TI-RADS score categories or histopathological results, in relation to TSH, T3, and T4 levels after controlling for confounding variables such as age, gender, and family history of identified thyroid nodules.

TABLE 6: Comparison of TSH, FT3, and FT4 levels based on TI-RADS score categories after controlling for confounding variables through analysis.

Variable	TSHs			FT4			T3tot		
	B	95%CI	P value	B	95%CI	P value	B	95%CI	P value
TIRADS	-0.028	-0.441 – 0.384	0.889	-0.054	-0.990–0.883	0.908	0.062	-0.424–0.548	0.798
Age	-0.013	-0.030 – 0.003	0.100	-0.010	-0.047–0.026	0.570	0.012	-0.007–0.031	0.201
Gender	-0.139	-0.807 – 0.530	0.676	0.037	-1,482–1,555	0.961	-0.109	0.780– (-0.897)	0.780
Family history	-0.074	-1.035 – 0.888	0.877	0.802	-1,383–2,986	0.461	0.323	-0.811–1.458	0.566

TABLE 7: Comparison of TSH, FT3, and FT4 levels based on histopathological findings after controlling for confounding variables through analysis.

Variable	TSHs			FT4			T3tot		
	B	95%CI	P value	B	95%CI	P value	B	95%CI	P value
PA Histology	0.186	-0.221 – 0.593	0.360	-0.222	-1.155 – 0.711	0.632	-0.001	-0.487 – 0.486	0.998
Age	-0.014	-0.029 – 0.002	0.085	-0.11	-0.047 – 0.025	0.545	0.013	-0.006 – 0.031	0.177
Gender	-0.033	-0.685 – 0.619	0.919	-0.042	-1.537 – 1.454	0.955	-0.143	-0.923 – 0.637	0.712
Family history	0.024	-0.939 – 0.987	0.024	0.710	-1,499 – 2,918	0.518	0.306	-0.845 – 1.458	0.306

DISCUSSION

In this study, the majority of the sample was female. This finding is consistent with the results of previous studies conducted by Oktahermioza et al. (2013), Parura et al. (2016), Srinivas et al. (2016), and Khalusi et al. (2020) [3,4,19,20]. This may be due to the higher incidence of thyroid nodules in women compared to men [19]. The average age of patients in this study (48.10 ± 2.17 years) is similar to the results of the study conducted by Khalushi et al. (2020), where the average age of patients was 48.3 ± 13.6 years [20]. This is supported by reports that indicate an increase in the incidence of thyroid cancer in the 30-49-year age group [20]. The most commonly found pathological feature of nodules in this study (papillary carcinoma; 33.3%) is also similar to the study by Khalusi et al. (2020), where the prevalence was 60.9%. According to Khalusi et al. (2020), papillary carcinoma is more commonly found in areas with adequate iodine intake. Indonesia, which practices the use of iodized salt, is likely the reason for the dominance of papillary carcinoma in this study [20].

According to Soehita et al. (2015), in cases of thyroid carcinoma, there is generally no thyroid function disorder, so the levels of thyroid hormones, including TSH, FT4, and T3, remain within normal limits. Although the data on the average FT4 and T3 in this study exhibited a non-normal distribution pattern based on the normality test results, this does not imply that the data is invalid. Because, according to the existing literature, the mean and median levels of these three thyroid hormones, both in the benign and malignant thyroid nodule groups, remain within the reference range. One reason for the non-normal distribution is the presence of outliers or extreme values (either too high or too low) and a small sample size [2].

The TI-RADS score was developed by Shah (2015) through two stages: the first stage involved defining the ultrasound characteristics of 362 thyroid nodules, followed by the second stage, where a prospective correlation analysis was conducted on the FNAB results of 500 different thyroid nodules with the ultrasound characteristics defined in the first stage. The analysis results of this study demonstrate that the TI-RADS score has good concordance with histopathological examination results [21]. The Kappa coefficient obtained in this study is higher than that in the previous study conducted by Chandramohan et al. (2016), where the Kappa coefficient was 0.721, which falls into the moderate level of agreement category, while the Kappa coefficient obtained in this study is 0.796, which falls into the strong level of agreement category, with a percentage agreement of 89.74% [22]. This finding implies that thyroid nodule analysis using the TI-RADS scoring system will yield similar results even when conducted by different radiologists.

The sensitivity of the TI-RADS score in this study was 82.61%, meaning that 82.61% of subjects confirmed to have malignant thyroid nodules based on histopathological results had a high TI-RADS score (4-5), while the specificity was 100%, meaning that all subjects in this study confirmed not to have malignant thyroid nodules (based on histopathological results) had a low TI-RADS score (1-3). The NPV of 100% indicates that almost all subjects with a high TI-RADS score (4-5) can be almost certainly confirmed as malignant, while the NPV in this study shows that 80% of subjects with a low TI-RADS score (1-3) were confirmed not to have malignant nodules based on histopathological results. Therefore, a high TI-RADS score (4-5) can be used to predict the malignancy of thyroid nodules, allowing for earlier treatment before histopathological results are available or when histopathological examination cannot be performed, such as in peripheral hospitals with limited medical support facilities. However, due to the inconsistent agreement tendency in low TI-RADS scores (1-3), the decision to declare a lesion as benign should be postponed until histopathological results are available, as there is still a possibility that the lesion could be malignant. Both the sensitivity and specificity of TI-RADS in this study are higher compared to the previous study conducted by Shah (2015), where the sensitivity was 88% and the specificity was 49% [21]. However, the outcome in that study was biased because Hovarth et al. classified all follicular thyroid lesions as benign, whereas 80% of follicular lesions are actually follicular adenomas.

Based on the normality test results, the distribution pattern of TSH levels was normal, while the distribution pattern of FT4 and T3 levels was not normal. Therefore, a parametric test, specifically the independent t-test, was used to assess the mean differences in TSH levels based on TI-RADS score categories and histopathological results, while the mean differences in FT4 and T3 levels were assessed using the non-parametric Mann-Whitney test.

Similar to the results of studies conducted by Jonklaas et al. (2018) and Haymart et al. (2008), TSH levels in subjects with malignant histopathological features were higher than in subjects with benign histopathological features [11,23]. This is likely due to TSH being suspected of acting as a stimulus for thyroid cancer, although oncogenes and other growth factors are also involved in the growth and development of thyroid cancer. This hypothesis is supported by the finding that thyroid cancer patients given suppressive doses of levothyroxine that can suppress TSH production have improved survival rates (Haymart et al., 2008). However, in this study, TSH levels were not statistically significant, possibly because the sample used in the Haymart et al. study was much larger (n=241) [23]. Additionally, in the studies by Jonklaas et al. (2018) and Haymart et al. (2008), thyroid hormone levels were obtained before the subjects started therapy, so the hormone levels reflected the true condition of the disease [11,23]. Meanwhile, in this study, the medical records used as the data source did not contain information on the patient's prior treatment history. Furthermore, Prof dr. I.G.N.G Ngoerah General Hospital is a tertiary referral hospital, so most of the patients are referrals from other hospitals, where it is possible that the patients had already received therapy, including hormonal therapy.

The study conducted by Jonklaas et al. (2008) showed that different methods of measuring T3 levels provide varying significance in the data. T3 levels measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS) were significantly lower in the group of patients with thyroid cancer (mean=112.6 ng/dL, CI 103.8-121.4 ng/dL) compared to the group of patients with benign lesions (mean=129.9 ng/dL, CI 121.4-138.4 ng/dL). However, when T3 levels were measured using the immunoassay method, the results for the two groups did not differ significantly. This may explain why there was no significant difference in T3 levels between subjects with malignant and benign histopathology in this study, as the method used to measure hormone levels at Prof dr. I.G.N.G Ngoerah General Hospital also utilized the immunoassay method. The low T3 levels in patients diagnosed with thyroid cancer may indicate cellular dedifferentiation [11]. In this study, FT4 levels did not differ significantly between subjects with malignant and benign histopathological features, consistent with the findings of Jonklaas et al. (2008) and Maia et al. (2011) [11,24].

Age in thyroid nodule cases is a clinically significant predictor of malignancy [24]. Additionally, gender and family history of identified thyroid nodules are also considered to influence the analysis of the relationship between TI-RADS scores and histopathological results with TSH, T3, and T4 levels, making these variables confounders that were controlled using one-way MANCOVA analysis. In this study, the p-values for TI-RADS scores and histopathological results in the MANCOVA analysis were 0.798 and 0.998, respectively, both greater than the $\alpha = 0.05$ threshold, indicating that these results are not statistically significant.

In other words, in this study, there is no relationship between TI-RADS scores and histopathological results with TSH, T3, and T4 levels, even after controlling for confounding variables (age, gender, family history). These findings differ from those obtained by Polion et al. (2021), where there was a significant relationship between the degree of thyroid nodule malignancy and TSH ($H=7.30$; $p<0.05$), FT4 ($H=17.64$; $p<0.001$), and T3 ($H=12.4$; $p<0.01$). The previous study used a larger sample size compared to this study (60 vs 39), which may explain the differences in the findings [25].

The results of this MANCOVA is no relationship between TI-RADS scores and histopathological results with thyroid hormone levels. There are several implications from these findings. First, it is not recommended to use TI-RADS scores to predict thyroid hormone levels in cases of thyroid nodules; instead, direct measurement should be conducted if the levels of these hormones are desired. Second, these findings can be used by clinicians to consider whether or not it is necessary to perform thyroid hormone level testing in patients with thyroid nodules. To support the efficiency of thyroid nodule management, particularly in the era of BPJS regulations, thyroid hormone testing should only be performed in cases with strong indications, such as in thyroid nodule patients showing physiological symptoms. Additionally, the results of this study suggest that thyroid hormone testing should not be used to determine the malignancy of a thyroid nodule but rather to further assess the impact of the nodule on overall thyroid hormone function.

Although there is no relationship between TI-RADS scores and thyroid hormone levels, this does not diminish the usefulness of the scores in predicting the malignancy of thyroid nodules based on histopathological features. This is because, unlike thyroid hormone levels, which are dynamic and can be influenced by factors other than the degree of malignancy of the thyroid nodule itself (e.g., hormonal therapy history or differences in iodine intake), a malignant thyroid nodule will still exhibit malignancy characteristics on histopathological examination even after the patient has received therapy. In healthcare facilities with adequate resources, the classification of a nodule as benign or malignant is still based on histopathological examination as the gold standard. However, in healthcare facilities with limited resources (e.g., those unable to perform histopathological examinations or where patients must wait for a long time, even months), the results of this study can serve as a reference for clinicians to start earlier and more aggressive therapy using the TI-RADS scoring system without waiting for histopathological examination results.

This study has several limitations. First, since the data used in this study were secondary (from medical records), some variables were not recorded, such as whether the patient had received prior hormonal therapy. This may have influenced the lack of a significant relationship between thyroid hormone levels and the degree of nodule malignancy, as subjects may have received hormonal therapy before the analysis was conducted. Therefore, it is recommended to use primary data in the future, where examination procedures and timing can be standardized according to the relationship being investigated, so the study results can be generalized to a wider population. Second, although the sample size used met the minimum sample size formula, the number of samples obtained was limited due to difficulties in meeting the inclusion criteria for subjects, which included having thyroid hormone test results.

This difficulty arose because thyroid hormone testing is not routinely performed on all patients with thyroid nodules. Such testing is more commonly performed on patients requiring special attention (e.g., those with uncertain therapy responses), resulting in inconsistent timing of thyroid hormone testing among patients, which ideally should be done when patients are still naive to any therapy. The limited sample size in this study is suspected to have caused some study outcomes to be statistically insignificant and inconsistent with existing literature. Therefore, it is suggested to increase the sample size in future similar studies so that the study results can better represent a larger population. Third, this study was conducted at a tertiary referral hospital with relatively complete facilities, so most patients at this hospital are those with suspected malignant thyroid nodules referred from lower-tier hospitals with limited resources. So far, there is no data on the characteristics of patients with thyroid nodules at lower-tier hospitals, such as type D hospitals, so there may be differences in subject characteristics between these hospitals. Therefore, it is recommended to conduct research in lower-tier hospitals (e.g., type D) to better understand the characteristics of patients at such facilities and to increase confidence that the study results can also be applied to a broader subject population.

CONCLUSIONS

(1) There is a statistically significant concordance between TI-RADS scores and histopathological results in patients with thyroid nodules.
(2) There is no statistically significant difference in the mean levels of TSH, FT4, and T3 based on either TI-RADS score categories or histopathological results in patients with thyroid nodules.
(3) In patients with thyroid nodules, there is no statistically significant relationship between TI-RADS score categories or histopathological results and the levels of TSH, T3, and T4 after controlling for confounding variables such as age, gender, and family history.

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