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Analysis of the Influence of Age, Size, and Gender on the Relationship Reporting and Data System (ACR TI-RADS) and the Incidence of Thyroid Cancer in Surakarta between Ultrasonography Classified by American College of Radiology Thyroid Imaging

M. Ihya Ulumuddin Rahawarin[1*], Kristanto Yuli Yarso[1], Widiastuti[2] and Akhmad Azmiardi[3]

[1]Department of Surgery, Faculty of Medicine, Sebelas Maret University, Dr. Moewardi General Hospital Surakarta, Indonesia.
[2]Department of Radiology, Faculty of Medicine, Sebelas Maret University, Dr. Moewardi General Hospital Surakarta, Indonesia.
[3]Public Health Division, Faculty of Public Health, Veteran Bangun Nusantara University, Indonesia.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The study aims to see if the age, tumor size and gender factors affect TI-RADS sensitivity. Ultrasonography examination (USG) plays a major role in the initial diagnosis process of a suspected thyroid tumor or cancer to evaluate thyroid nodules. ACR TI-RADS is a classification created with the aim of adapting the BI-RADS concept for thyroid pathology. Several studies have shown a positive correlation between ultrasound results and TI-RADS while on the opposite, several studies have shown decreased sensitivity and specificity of TI-RADS ultrasound classification with respect to increasing age groups. Study on the effect of age on USG and TI-RADS classification has an important role for the improvement of diagnostic procedure.

**Corresponding author: E-mail: ikhya45@gmail.com;*

Objective: To find out whether age, size and gender has an effect on the sensitivity and specificity of USG diagnostics with the TI-RADS classification on the incidence of thyroid cancer in the Surakarta area.
Methods: This study is an analytical observational study with a retrospective design, with the sample population in the form of all results of thyroid ultrasound examination of thyroid cancer patients were carried out at Two General Hospitals in Surakarta to obtain the n=114 of research subjects who match the inclusion criteria and do not match within the predetermined exclusion criteria.
Results: The results of statistical tests carried out on several variables, namely age, gender, and tumor size on the sensitivity and specificity of TI-RADS showed mixed results. After comparing the sensitivity between groups, we used a cutoff point of 55 years and when we compared two groups of patients (>55 vs ≤55 years old) , we found no statistically significant difference (p=0.496). In the comparison of the sensitivity to the gender variable, which was divided into two groups, the male patient group, and the female patient group with a p-value of 1.000. For comparison of the sensitivity of the size variable, grouped into two categories, patients with small-sized tumor ≤ 1 cm and those with large-sized tumor > 1 cm, a p-value of 0.160 was obtained (Table 10). The p-value for the comparison of specificity of the age variable was 0.062, of the gender variable 1.000, and he size variable 0.208 (Table 11).
Overall, it can be interpreted that the TI-RADS ultrasound examination on some variables above did not show a significant difference (validity) in sensitivity and specificity (p-value > 0.05).
Conclusion: Age, size and gender does not affect the sensitivity and specificity of USG diagnostics with the TI-RADS classification in thyroid cancer patients at Two General Hospital in Surakarta.

Keywords: Age; size; gender; Ultrasonography (USG); TI-RADS; thyroid cancer.

1. INTRODUCTION

Thyroid nodule cases have increased lately. The indication for malignancy in these cases ranges from 5% to 10%. Early diagnosis of thyroid cancer will greatly help patients in their survival if appropriate therapy can be given as early as possible [1].

The mortality rate for this type of thyroid cancer is estimated to be approximately 0.2-1.2 in men and 0.4-2.8 in women per hundred thousand population. In thyroid cancer, more than 90% of known types are papillare and follicular carcinomas, about 5-9% are medullary carcinomas, and 1-2% are anaplastic carcinomas [2-9]. Ultrasound examination (USG) is very helpful in establishing the initial diagnosis of a suspected thyroid tumor or cancer [10].

USG in the initial evaluation of thyroid nodules is very important in estimating the size and number of nodules, even some types of nodules that are still not palpable on manual palpation with the common size of less than 1 cm. USG is a good choice in screening for thyroid nodules because it does not require much preparation, is not an invasive method, and is less expensive than histopathological examination [7-9,11-13]. However, several studies stated that the sensitivity of USG was lower than that of histopathology, where the sensitivity of USG examination was 41.4% and histopathology 86.4%. In multivariate analysis, USG examination found signs such as irregular edges, microcalcification, and nodule size of more than 2 cm were predictive factors for malignancy with an accuracy of 81.7% [14].

USG of the thyroid is widely used to evaluate thyroid nodules. It can detect the presence of solid nodules measuring 3 mm or cystic nodules measuring 2 mm which can be examined using high frequency (7.5-13 MHz). This examination can distinguish solid, cystic, or mixed components, and can detect several malignant features, such as hypoechoic nodules, irregular edges, microcalcification, and hypervascularization [14].

Thyroid nodules are more common in elderly patients, with a linear increase with age. The risk of malignancy in thyroid nodules increases at the age of less than 20 years and more than 60 years [15]. Although epidemiological analysis has shown a positive association between thyroid nodule formation and elderly patient age, their relationship has not been specifically well defined to date. Approximately 50% of people aged 65 years have ultrasound detectable thyroid nodules, most of which show no signs of malignancy. This contrasts with the prevalence of

thyroid cancer which is mostly found in the elderly. Several studies have also shown that the elderly show a wider pattern of thyroid cancer at presentation and a relative increase in the frequency of more aggressive histological subtypes [16].

ACR TI-RADS (American College of Radiology Thyroid Imaging Reporting and Data System) is a classification created by a multidisciplinary team, published in JCEM (Journal of Clinical Endocrinology & Metabolism), and the original idea was to adapt the concept of BI-RADS (Breast Imaging Reporting and Data System) from the ACR (American College of Radiology) for thyroid pathology [17].

Several studies demonstrate a positive correlation between ultrasound results with the classification of ACR TI-RADS (USG ACR TI-RADS), hereinafter abbreviated as TI-RADS in cases of malignancy aged < 45 years and children with histopathological results [2]. Meanwhile, the study of Xin et al. in 2016 in China showed that there was a decrease in the sensitivity and specificity of the USG TI-RADS classification with an increase in the age group. Therefore, it is necessary to have research on the effect of age on USG images and the classification of TI-RADS.

2. METHODS

This research is an analytic observational study with retrospective design. It was conducted at Two General Hospital in Surakarta from September to December 2020.

The inclusion criteria for this study were patients with thyroid nodules who had ultrasound results according to the ACR TI-RADS classification and anatomical pathology results. The exclusion criteria for this study were patients with incomplete identities in medical records, patients with thyroid ultrasound answers that were not described by the ACR TI-RADS classification, and patients whose ACR TI-RADS thyroid ultrasound examination results did not match the conclusions of the anatomical pathology results. Based on the thyroid USG examination results, the patients with thyroid cancer at Two General Hospital in Surakarta, met the inclusion criteria. The data were taken from the medical records of thyroid cancer patients who were examined at both hospitals and underwent USG examination of thyroid. The medical record of thyroid cancer patients contains initial name, age, gender, date of examination, medical record number, clinical diagnosis, expertise of thyroid USG results, and the results of anatomic pathology. The research data obtained were recorded on the research sheet. Statistical analysis was performed with SPSS 25.0 program. The correlation test between the TI-RADS Classification USG Results and the Anatomical Pathology Results was conducted with chi square test because it was a nominal category to determine the sensitivity and specificity of the TI-RADS Classification USG to the Anatomic Pathology Results.

3. RESULTS

A total of 114 patients with thyroid cancer who had thyroid USG examination at Two General Hospital in Surakarta were recruited as the sample. The data of this study included gender, age, tumor size, and USG results according to the TI-RADS classification. In this study, the tumor size data were obtained from 114 patients. The description of the research data can be seen in Table 1.

Based on Table 1, it is known that most of the patients were female (82 subjects or 71.9%) and the rest were male (32 subjects or 28.1%). The mean age of the patients was 55.06 ± 14.26 years. Based on the size of the patient's tumor, 84 subjects (73.7%) had a large category while the rest (20 subjects or 17.5%) had a small category. The results of the TI-RADS examination were mostly in the TI-RADS I – III category (35 subjects or 30.7%) and the rest (79 subjects or 69.3%) belong to TI-RADS IV – V.

3.1 Differences in Patient Characteristics Based on TI-RADS Classification

In this study, the difference test for gender and tumor size variables based on the TI-RADS classification was carried out by using the chi square test because the data were in the form of nominal scale data. Meanwhile, the age difference based on the TI-RADS classification was tested by using the independent T-test because the data with a numerical scale had a normal distribution with different test results as shown in Table 2 as follows.

Based on Table 2, it is known that age has an insignificant distribution based on the TI-RADS classification with a significance value of p = 0.743 k ($p < 0.05$). The mean age of the patients with the TI-RADS Classification I-III was 48.47 +14.93 years and those with the TI-RADS

Classification IV-V 58.03 ± 18.02 years. This shows that the high TI-RADS group has an older mean age while the low TI-RADS group has a younger mean age.

Table 1. Description of research data

Variable	Results *(n=114)*
Gender	
Male	32 (28.1%)
Female	82 (71.9%)
Age	
Less than (<) 55 Years	56 (49.1%)
More than or equal to (≥) 55 Years	58 (50.9%)
Size	
Small (≤1cm)	20 (17.5%)
Large	84 (73.7%)
TI-RADS	
TI-RADS I – III	35 (30.7%)
TI-RADS IV – V	79 (69.3%)

Gender (p = 0.709) and tumor size (p = 0.472) also showed insignificant differences (p>0.05) based on the TI-RADS classification.

3.2 Results of Sensitivity Test of TI-RADS Specificity on Tumor Malignancy

The sensitivity test of TI-RADS specificity on malignancy in this study was conducted on 114 patients. Then, the sensitivity test of TI-RADS specificity based on malignancy (with the PA gold standard) was also carried out based on age, gender, and tumor size. The results of the TI-RADS sensitivity test for malignancy can be seen in Table 3 as follows.

The table shows that the overall TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 98.8%, a specificity value of 50.0%, a positive predictive value (PPV) of 82.3%, and a negative predictive value (NPV) of 94.4%. The statistical test results in an accuracy value of 84.2

In patients aged < 55 years, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 97.4%, a specificity value of 44.4 %, a positive predictive value (PPV) of 78.8%, and a negative predictive value (NPV) of 88.8%. The statistical test results in an accuracy value of 39.5.

In patients aged > 55 years, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 100%, a specificity value of 56.3%, a positive predictive value (PPV) of 85.7%, and a negative predictive value (NPV) of 100%. The statistical test results in an accuracy value of 44.7.

In male patients, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 100%, a specificity value of 50.0%, a positive predictive value (PPV) of 85.7%, and a negative predictive value (NPV) of 100%. The statistical test results in an accuracy value of 24.6.

In female patients, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 98.2%, a specificity value of 50.0%, a positive predictive value (PPV) of 80.9%, and a negative predictive value (NPV) of 92.9%. The statistical test results in an accuracy value of 59.6.

Table 2. Differences in the Characteristics of Research Subjects Based on the TI-RADS Classification

Variable	TI-RADS classification		p-value
	I – III	IV – V	
Gender[b]			0.709
Male	9 (7.9%)	23 (20.3%)	
Female	26 (22.8%)	56 (49.2%)	
Tumor Size[b]			0.472
Small	5 (15.2%)	15 (21.1%)	
Large	28 (84.8%)	56 (78.9%)	
Age			0.743
Less than (<) 55 Years	18 (51.4%)	38 (48.1%)	
More than or equal to (≥) 55 Years	17 (48.6%)	41 (51.9%)	

*Remark: [a] = Independent t-test; [b] = Chi Square; *Significant at α = 5%*

Table 3. Sensitivity test of TI-RADS specificity for malignancy based on PA (Gold standard)

Examination			Histopathology		Sensitivity	Specificity	*PPV*	*NPV*	Prevalence	Accuracy
			Carcinoma							
			(+)	(-)						
USG	*TI-RADS* ↑	(+)	37	10	97.4	44.4	78.8	88.8	33.3	39.5
	TI-RADS ↓	(-)	1	8						

Age

Table 4. Sensitivity test of specificity in age < 55 years

Examination			Histopathology		Sensitivity	Specificity	*PPV*	*NPV*	Prevalence	Accuracy
			Carcinoma							
			(+)	(-)						
USG	*TI-RADS* ↑	(+)	79	17	98.8	50.0	82.3	94.4	70.2	84.2
	TI-RADS ↓	(-)	1	17						

Table 5. Sensitivity test of specificity in age > 55 years

Examination			Histopathology		Sensitivity	Specificity	*PPV*	*NPV*	Prevalence	Accuracy
			Carcinoma							
			(+)	(-)						
USG	*TI-RADS* ↑	(+)	42	7	100.0	56.3	85.7	100	36.8	44.7
	TI-RADS ↓	(-)	0	9						

Gender

Table 6. Sensitivity test of specificity in male gender

Examination			Histopathology		Sensitivity	Specificity	*PPV*	*NPV*	Prevalence	Accuracy
			Carcinoma							
			(+)	(-)						
USG	*TI-RADS* ↑	(+)	24	4	100	50	85.7	100	21.1	24.6
	TI-RADS ↓	(-)	0	4						

Table 7. Sensitivity test of specificity in female gender

Examination			Histopathology		Sensitivity	Specificity	*PPV*	*NPV*	Prevalence	Accuracy
			Carcinoma							
			(+)	(-)						
USG	*TI-RADS* ↑	(+)	55	13	98.2	50.0	80.9	92.9	49.1	59.6
	TI-RADS ↓	(-)	1	13						

Size

Table 8. Sensitivity test of specificity in small mass

Examination			Histopathology		Sensitivity	Specificity	*PPV*	*NPV*	Prevalence	Accuracy
			Carcinoma							
			(+)	(-)						
USG	*TI-RADS* ↑	(+)	16	3	100	25.0	84.2	100	14.0	14.9
	TI-RADS ↓	(-)	0	1						

Table 9. Sensitivity test of specificity in large mass

Examination			Histopathology		Sensitivity	Specificity	*PPV*	*NPV*	Prevalence	Accuracy
			Carcinoma							
			(+)	(-)						
USG	*TI-RADS* ↑	(+)	56	14	98.2	48.1	80.0	92.9	50.0	60.5
	TI-RADS ↓	(-)	1	13						

In patients with small-sized tumor, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 100%, a specificity value of 25.0%, a positive predictive value (PPV) of 84.2%, and a negative predictive value (NPV) of 100%. The statistical test results in an accuracy value of 14.9.

In patients with large-sized tumor, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 98.2%, a specificity value of 48.1%, a positive predictive value (PPV) of 80.0%, and a negative predictive value (NPV) of 92.9%. The statistical test results in an accuracy value of 60.5.

4. DISCUSSION

There are many cases of thyroid nodules in the elderly, but the relationship between thyroid ultrasound results and elderly is still unclear to date. Oncogenic mutations have been shown to be the cause for most thyroid carcinomas. Although not yet proven, gene mutations are also thought to be responsible for the formation of benign tumors and nodular growths. The understanding of genetic mutations associated with benign tumors compared to malignant tumors has largely shed light on the potential multihit hypothesis or impact of epigenetic factors. This is important to form the basis of future research [16].

A total of 144 patients with thyroid cancer who had thyroid USG examination at Two General Hospital Surakarta were recruited as the sample. In this study, 114 patients with complete anatomic pathology results 104 patients with complete tumor size results were obtained.

Based on Table 1, it is known that most of the patients were female (82 subjects or 71.9%) and the rst were male (32 subjects or 28.1%). The mean age of the patients was 55.06 ± 14.26 years. Based on the size of the patient's tumor, 84 subjects (73.7%) had a large category while the rest (20 subjects or 17.5%) had a small category. The results of the TI-RADS examination were mostly in the TI-RADS I – III category (35 subjects or 30.7%) and the rest (79 subjects or 69.3%) belong to TI-RADS IV – V.

Table 2 illustrates the characteristics of research subjects based on the TI-RADS classification (divided into two groups TI-RADS I, II and III/benign, IV and V/malignant) with the age variable that has insignificant results based on the TI-RADS classification with a significance value of 0.743 ($p > 0.05$). The mean age of the patients with the TI-RADS Classification I-III was 48.47 +14.93 years and those with the TI-RADS Classification IV-V 58.03 ± 18.02 years. This shows that the high TI-RADS group has an older mean age while the low TI-RADS group has a younger mean age.

Gender ($p = 0.709$) and tumor size ($p = 0.472$) also shows insignificant differences ($p > 0.05$) based on the TI-RADS classification.

Table 10. Comparison of sensitivity between groups

Variable			True Positive	False negative	P-value
Sensitivity	Age	< 55 year	37	1	0.496
		≥ 55 years	42	0	
Sensitivity	Gender	Male	24	0	1.000
		Female	55	1	
Sensitivity	Size	Small	16	0	0.160
		Large	56	1	

Table 11. Comparison of specificity between groups

Variable			True negative	False positive	P-value
Specificity	Age	< 55 year	8	10	0.062
		≥ 55 years	9	7	
Specificity	Gender	Male	4	4	1.000
		Female	13	13	
Specificity	Size	Small	1	3	0.208
		Large	13	14	

Table 4 shows that in patients aged < 55 years, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 97.4%, a specificity value of 44.4%, a positive predictive value (PPV) of 78.7%, and a negative predictive value (NPV) of 88.9%.

Based on Table 5, in patients aged > 55 years, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 100%, a specificity value of 56.3 %, a positive predictive value (PPV) of 85.7%, and a negative predictive value (NPV) of 100%.

Table 6 shows that in male patients, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 100%, a specificity value of 50.0%, a positive predictive value (PPV) of 85.7%, and a negative predictive value (NPV) of 100%.

Table 7 shows that in female patients, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 98.2%, a specificity value of 50.0%, a positive predictive value (PPV) of 80.9%, and a negative predictive value (NPV) of 92.9%.

Table 8 shows that in patients with small-sized tumor, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 100%, a specificity value of 25.0%, a positive predictive value (PPV) of 84.2%, and a negative predictive value (NPV) of 100%.

Table 9 shows that in patients with large-sized tumor, the TI-RADS examination of the diagnosis of malignancy has a sensitivity value of 98.2%, a specificity value of 48.1%, a positive predictive value (PPV) of 80.0%, and a negative predictive value (NPV) of 92.9%.

From the three components of the above variables, a sensitivity and specificity comparison between groups was also made. For the sensitivity of the age variable, a p-value was obtained of 0.496, gender variable 1.000, and size variable 0.160 (Table 10) For the specificity of the age variable, a p-value of 0.062, gender variable 1.000, and size variable 0.208 (Table 11)

Thus, there is no difference in significance/validity of sensitivity and specificity in the use of ACR TI-RADS Classification USG in detecting thyroid malignancies in the age, gender, and size groups, so it can be used in diagnosing thyroid cancer.

It is known that older age is associated with a worse prognosis in thyroid cancer patients. Several risk factors are associated with advanced thyroid cancer and a higher risk histologically. Poor response to conventional therapy in old age compared to younger age with the same disease may also be the reason for this difference in thyroid USG results. It is necessary to consider the genotype-phenotype complex relationship for better decision making to be applied in the coming decades [15].

Thyroid nodular disease in the elderly population increases the risk of developing thyroid nodules which are less likely to be identified as malignant nodules. With a cancer risk of > 20% in young adults, clinically relevant thyroid nodules (especially solid nodules) should be evaluated with USG Guide - FNA. Older patients with nodular disease are educated that thyroid cancer is still possible. Further monitoring of each nodularity with a multivariable diagnostic algorithm is required including age of the patient in addition to nodule size, sonographic characteristics, and other historical risk factors that are known to modify cancer risk [16].

Thyroid nodules are more common in elderly patients, with a linear increase with age. The risk of malignancy in thyroid nodules increases at the age of less than 20 years and more than 60 years [15].

Although epidemiological analysis has shown a positive association between thyroid nodule formation and elderly patient age, their relationship has not been specifically well defined to date. Approximately 50% of people aged 65 years have ultrasound detectable thyroid nodules, most of which show no signs of malignancy. This contrasts with the prevalence of thyroid cancer which is mostly found in the elderly. Several studies have also shown that the elderly show a wider pattern of thyroid cancer at presentation and a relative increase in the frequency of more aggressive histological subtypes [16].

In the study of Kwong et al. [16], the results of a different assessment of the TI-RADS classification with the BETHESDA classification were obtained. In the TI-RADS assessment, malignant nodules were notable, but on cytopathological examination, they were non-malignant nodules. This can be since the USG examination is an “operator-dependent” examination, meaning that the results of this

examination are highly dependent on the ability, expertise, and skills of the operator carrying out the examination. Although it appears that the level of conformity is quite low (46.6%), there is no significant difference between genders in the TI-RADS classification on the cytopathological results of BETHESDA [16]. This study also supports the absence of significant differences in the comparison of sensitivity and specificity on the gender variable in relation to the use of TI-RADS USG in diagnosing thyroid cancer.

According to the research of Polat et al. [2], malignant nodules in the TI-RADS IV category could not be detected because most of the nodules were smaller than 10 mm and were diagnosed as benign histopathologically. Biopsy had to be done depending on the size of the nodule. It was performed because the TI-RADS IV nodule was larger than 1 cm and was diagnosed as a benign histopathology. According to 2015 American Thyroid Association (ATA) guidelines, biopsy is recommended for all thyroid nodules ≥ 1 cm solid or predominantly solid nodules or all nodules with high sonographic characteristics, regardless of the size [2].

The theory above is relevant in the absence of significant differences in the sensitivity and specificity comparisons between groups on the size variable in relation to the use of USG ACR TI-RADS as a predictor of malignancy.

5. CONCLUSION

The age, size and gender variable does not affect the sensitivity and specificity of USG diagnostics with the TI-RADS classification in thyroid cancer patients in Surakarta, so the hypothesis in this study is statistically rejected.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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