



Saint Paul Hospital Millennium Medical College
Graduate Study Program

**Assessment of accuracy of thyroid imaging, reporting and data system for
diagnosis of thyroid nodules.**

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Assessment of accuracy of thyroid imaging, reporting and data system for diagnosis of thyroid nodules in multi center tertiary hospitals, Addis Ababa, Ethiopia.

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Summary

Background: thyroid ultrasound is one of the most accepted and first investigation modality in assessing thyroid diseases. It is cheaply available, painless and is without any radiation risk. Particularly for patients with thyroid nodules management decisions depends highly on thyroid ultrasound and fine needle aspiration cytology results.

Objectives: the aim of this study was to assess accuracy of thyroid imaging, reporting and data system for diagnosis of thyroid nodules in patients diagnosed with thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital in Addis Ababa, Ethiopia.

Methods: a one year hospital based retrospective cross sectional study was conducted on 247 patients with thyroid ultrasound and postoperative Histopathology admitted and operated at Saint Paul Hospital and Yekatit 12 Hospital with thyroid nodules from June 30, 2022 to June 30, 2023 G.C. standardized and pretested questionnaire was used to extract all possible information and analysis of data was done by SPSS 26. Using Histopathology result as a gold standard we evaluated the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of thyroid ultrasound Thyroid imaging, reporting and data system.

Results: the sensitivity, specificity, accuracy, positive predictive value and negative predictive value of TIRAD system is 73%, 71.1%, 71.7%, 51.9% and 86% respectively. The three high risk US features, Irregular margin, micro calcification and taller than wider has specificity of 94.2%, 94.8 and 93.6%, respectively. Experience of US personnel and duration between ultrasound and histopathology result has statistically no significant effect on the accuracy of thyroid imaging, reporting and data system.

Conclusion: thyroid imaging, reporting and data system is an appropriate and non-invasive method for initial assessment of thyroid nodules in our routine practice. The three best ultrasound features that pose a higher risk of malignancy are irregular margin, taller than wider and micro calcification. Thyroid ultrasound examinations done by senior radiologist and radiology resident do not affect accuracy of thyroid imaging, reporting and data system significantly.

Keywords: thyroid nodule, thyroid ultrasound Thyroid imaging, reporting and data system, Histopathology, and diagnostic accuracy.

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Acronyms and abbreviations

FNAC	fine needle aspiration cytology
TIRAD	thyroid imaging reporting and data system
AC-TIRAD	American College of radiology thyroid imaging reporting and data system
EU_TIRAD	European union thyroid imaging reporting and data system
US	ultrasound
TU	thyroid ultrasound
ORL HNS-	otolaryngology, and head and neck surgery
TN	thyroid nodule
SPHMMC	Saint Paul Hospital Millennium Medical College
FNAB	fine-needle aspiration biopsy

1 Introduction

1.1 Background

Thyroid gland nodules in themselves are not a disease entity rather; they are the physical expression of a broad range of thyroid disorders. The prevalence of thyroid nodule detected by palpation is between 4 and 8% among the general population, a figure that increases to 19 to 67% with the use of thyroid ultrasound(TU)(1). This figure is around 34.4 % in our country(2). The incidence of thyroid cancer in patients with thyroid nodules ranges from 5 to 15%(3). Ionizing radiation is a known risk factor for both benign and malignant nodules of the thyroid. This population may develop thyroid nodules at a rate of 2% and 20 to 50 risk of malignancy, annually. Other factors that lead to an increased risk of thyroid nodules and goiter include smoking, obesity, metabolic syndrome, alcohol consumption, increased levels of insulin-like growth factor-1, and uterine fibroids. Factors associated with possible decreased risk may include the use of oral contraceptives and statins(4).

Ultrasound imaging is one of easy to get imaging modality which has low cost and without radiation risk but highly dependent on the experience and expertise of the personnel. Ultrasonography(US) is the modality of choice for the evaluation of thyroid disease(5). Thyroid gland typically appears homogeneous and of an intermediate gray scale; it is considered to be the reference echogenicity for comparison with other structures. Thyroid US is most commonly used for the assessment of thyroid nodules and to determine their risk of malignancy. It can also be helpful to assess for inflammatory and autoimmune thyroid disease(1).

Purely cystic nodules are anechoic (or hypo-echoic) and appear similar in echogenicity to vascular structures. They can be differentiated from hypo-echoic solid nodules by a hyper-echoic through transmission seen posterior to the lesion. Solid hyper functioning thyroid nodules tend to be iso-echoic or mildly hyper-echoic with respect to the surrounding gland, with increased peripheral vascularity on Doppler imaging. Follicular lesions typically appear solid, iso-echoic, and homogeneous.(6)

Although no single sonographic feature is pathognomonic for detecting thyroid carcinoma, a constellation of findings may suggest a high likelihood of malignancy: micro-calcifications intra-nodular intrinsic, rather than peripheral, vascularity; absent “halo sign”; extra-glandular extension; dimensions that are more tall than wide on transverse imaging; and irregular or micro-lobulated margins(7).

American college of radiology has published thyroid imaging reporting and data system(AC-TIRADS) guideline in which thyroid nodules are categorized as benign, minimally suspicious, moderately suspicious, or highly suspicious for malignancy. Points are given for all the ultrasound features in a nodule, with more suspicious features being awarded additional points (6).

Numerous scientific societies around the world have published their TIRADS classifications that evaluate the risk of malignancy of focal thyroid lesions, presenting different ultrasound features for each category and lesion size thresholds to determine eligibility for biopsy. The use of such risk estimation systems in focal thyroid lesions facilitates the reporting of thyroid ultrasound findings and improves the qualification of focal lesions for fine-needle aspiration biopsy (FNAB).

Dobruich Etal did summary of meta-analyses of studies involving thyroid imaging reporting and data system (TIRAD) classifications. In this publication, the three most popular TIRADS classifications, European – EU-TIRADS, Korean – K-TIRADS, and developed by the American Society of Radiology – ACR-TIRADS, are presented and dis-cussed based on a literature review. The results of available head-to-head statistical analyses comparing the classifications are also presented. ACR-TIRADS, unlike other scales, is based on a unique classification system and represents the most comprehensive classification. Each of the five categories of ultrasound features – morphology, echogenicity, shape, margins, micro-calcifications are evaluated and assigned a score from 0 to 3, with a higher score being associated with a higher risk of cancer. Based on the available data, the greatest benefit has been demonstrated for the ACR-TIRADS classification(8).

Management of thyroid nodules depends on both ultrasound and fine needle aspiration cytology results and according to AC TIRAD classification fine needle aspiration (FNC) is recommended for nodules with TIRAD 3 and above. Some of thyroid nodules need ultrasound guidance for doing FNAC because of the location and failure to take from that node might end up with wrong result. So using ultrasonography for decision making in management of thyroid nodules is one of the common practices globally and in our institution as well(6).

The decision made so far on management of thyroid nodule depends on the reports from ultrasound as TIRAD score. So we are going to assess the accuracy, sensitivity and specificity of this TIRAD score in our institutions.

1.2 Statement of the problem

The prevalence of thyroid nodules in general population worldwide is 19 to 67%(1). Diagnosis of thyroid nodule was made by thyroid US as initial imaging modality. In a single center study done in Bulgaria the estimated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of TIRADS were 69.9, 56.3, 16.4, and 93.8%, respectively(9). Other study in Spain found sensitivity of TIRAD as 65%. In a single center observational study in India, they found the sensitivity, specificity, accuracy, positive predictive and negative predictive value of TIRADS were 80%, 47.2%, 61%, 51.3%, and 77.3%, respectively(10). In a prospective study done in Uganda the sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios of ACR TI-RADS were 90.9%, 98.5%, 90%, 99.3%, 62.3, and 0.1 respectively(11).

The prevalence of thyroid nodules in our country is 34.4% but only 5 to 15% of these nodules are malignant(2) (3). Around 11% of major procedures done in department of general surgery in Saint Paul Hospital were for thyroid diseases and out of this 63% were patients with thyroid nodules. Only 15.9% of patients were diagnosed with thyroid cancer(12). Despite dealing with thyroid US TIRAD report in daily clinical practice, there is no study done in our country so far. Operative decisions were made based on TIRAD score which is highly operator dependent, and whose diagnostic accuracy varies from place to place(13)(1). This paves a way for either over treatment of patients to be subjected to unnecessary operative treatment which would have been treated the other way or under treatment of patient which would have been treated operatively before disease progresses to advanced stage.

Therefore, determining the accuracy of thyroid ultrasound TIRAD system will have great impact on patient care and physician decision making as well as service consumption of the institutions.

1.3 Rationale of the study

Despite the fact that TIRAD classification is one of the standard practices all over the world including our country, there is wide gap in the literature on the accuracy of this test to use as an input for decision making in resource limited counties like Africa including our country. Ultrasound imaging is also highly affected by experience of examining personnel and for us knowing the institutional level accuracy of the test will help patients to get treatment well informed and avoid unnecessary anxiety about their disease; treating physician to make evidence based decisions and develop treatment guidelines, and hospital management for resource allocation.

2 Literature Review

In study done in UK, 2020 they aimed to assess whether there is any intra- or inter-observer variability when US scoring thyroid nodules and whether previous thyroid ultrasound experience has an effect on this variability. A total of 14 ultrasound operators were identified (five experienced thyroid operators, five with intermediate experience and four with no experience) and were asked to US score images from 20 thyroid cases shown as a single projection, with and without Doppler flow. The cases were subsequently rescored by the 14 operators after six weeks. The first and second round U-scores for the three operator groups were then analyzed using Fleiss' kappa to assess inter-observer variability and Cochran's Q test to determine any intra-observer variability. They found no significant inter-observer variability on combined assessment of all operators with fair agreement in round 1 (Fleiss' kappa 0.30, $p < 0.0001$) and slight agreement in round 2 (Fleiss' kappa 0.19, $p < 0.0001$). Cochran's Q test revealed no significant intra-observer variability in all 14 operators between round 1 and round 2 (all $p > 0.05$). They concluded no statistically significant inter- or intra-observer variability in the US scoring of thyroid nodules between all participants reinforcing the validity of this scoring method in clinical practice, allaying concerns regarding potential subjective biases in reporting(5).

In other study done in Spain, a retrospective study of all patients who underwent thyroidectomy at that hospital ($n = 263$) from September 2013 to December 2015. After thyroidectomy, histological results were correlated to the ultrasound findings reported. Of the 263 study patients, 75 (28.5%) were diagnosed with thyroid cancer and 188 (71.5%) with benign disease. Correlation of histological results with preoperative ultrasound reports showed an initial sensitivity of 65%. After excluding 15 patients diagnosed with occult microcarcinoma, sensitivity increased to 81.6%. The ultrasound images from 11 false negatives cases were then reassessed by a radiologist who knew histological diagnosis and reclassified 10 of them as TI-RADS ≥ 4 . This procedure could have increased sensitivity up to 98.3%. use of the TI-RADS scale would allow for an adequate selection of patients amenable to fine needle aspiration of the nodule(10).

A single-center prospective study from August 2017 to September 2018, 783 consecutive patients with 1,000 thyroid nodules underwent US examination and US-guided FNAB in Bulgaria. A total of 741 patients (median age 50 years; range, 15–87 years; 649 females, 92 males) with 942 met inclusion criteria. Of 942 nodules, 839 (89.1%) were benign and 103 (10.9%) were malignant. Nodules were classified as follows: EU-TIRADS 2 – 4.8%, EUTIRADS 3 – 37.4%, EU-TIRADS 4 – 25.2%, and EU-TIRADS 5 –

32.6%. When the indication for FNAB was applied as test positivity, the estimated sensitivity, specificity, PPV, and NPV of EU-TIRADS were 69.9, 56.3, 16.4, and 93.8%, respectively(9).

In a systematic review and meta-analysis done in Canada fifty-two observational studies (12,786 nodules) were included. Nine studies included nodules with indeterminate cytology as a separate category, comprising 1851 nodules. In unselected nodules, all US features were significantly associated with malignancy with an odds ratio varying from 1.78 to 35.7, and micro calcifications, irregular margins, and a taller than wide shape had high specificities (87.8%, 83.1%, 96.6%) and positive likelihood ratios (LHR; 3.26, 2.99, 8.07). Absence of elasticity was the single feature with the best diagnostic performance (sensitivity 87.9%, Specificity 86.2%, and positive LHR 6.39). The presence of central vascularization was the most specific US feature in nodules with indeterminate cytology (specificity 96% and positive LHR 2.13)(14).

In a single-center observational study on 137 consecutive subjects of solitary euthyroid nodule in India, all subjects underwent US according to TIRADS and FNAC where applicable. Surgical biopsy report was used as a gold standard. The sensitivity, specificity, accuracy, positive predictive and negative predictive value of TIRADS was 80%, 47.2% 61%, 51.3%, and 77.3%, respectively. FNAC classification was equally sensitive and more specific than TIRADS. The risk of malignancy for TIRADS 3, TIRADS 4, and TIRADS 5 was 22.7%, 29.16% and 86.66%, respectively. Among individual USG parameters, micro-calcification was most sensitive (80%) and specific (86%). Irregular margin and taller-than-wider shape had a specificity of 89% and 92%, respectively. 3 patients (14.28%) with benign cytology and suspicious US feature (specifically TIRADS 4 & 5) undergoing surgery had malignancy in final histopathology. In patient having high risk feature on US, a benign cytology needs to be repeat FNAC and they should undergo surgical biopsy for confirmation(13).

Other retrospective study done in India included 1658 thyroid nodules (≥ 1 cm in maximum diameter at US) in 1638 patients (1373 women, 265 men) for which pathologic diagnosis or follow-up findings were available. Univariate and multivariate analyses with generalized estimating equations were performed to investigate the relationship between suspicious US features and thyroid cancer. The risk of malignancy for TIRADS categories 1, 2, 3, 4 and 5 was 0, 0, 1.7, 3.3-72.4, and 87.5%, respectively. The following US features showed a significant association with malignancy: solid component, hypo echogenicity, micro lobulated or irregular margins, micro calcifications, and taller-than-wide shape.(15)

Retrospective analysis of a thyroid ultrasound database at Chris Hani Baragwaneth Academic Hospital, over the period 2015–2017 was done. Frequencies and percentages were used to summarize the data. Univariate logistic regression analyses were used to assess the accuracy of sonographic features in predicting the histologically determined diagnosis for thyroid tumors. A total of 113 nodules underwent FNA, of which 104 were diagnostic. The best three ultrasound features that pose a higher risk for malignancy are absent halo, presence of micro-calcifications and hypo-echoic appearance. No single nodule feature is an absolute indicator for malignancy. There is a high agreement between ATA classification and cytopathology or histology when nodule features are grouped into clusters. Agreement between the ATA classification and cytopathology/histology was 86.7% with a kappa of 0.714. The agreement between the cytopathology FNA results and lobectomy histopathology was 98.8% with a kappa of 0.973. The study confirms that the usage of a thyroid nodule classification system improves characterization and increases accuracy in detecting thyroid malignancies, thus sparing many patients the morbidity of unnecessary thyroid surgery (16).

In another prospective study done in Uganda, of 132 study participants 90% (n=117) were females and the mean age of 41 ± 13 . One hundred sixty-one thyroid nodules were analyzed. More than half of the thyroid nodules (54.7%, n=87) were solid or almost solid, 96.9% (n=154) were shaped wider than tall, with 57.2% (n=91) having smooth margins while 83.7% (n=133) were hyper-echoic or iso-echoic and 88.7% (n=141) had none or large comet-tail artifact. TR3 was the commonest at 42.9% (n=69). The proportion of malignancy for TR4 and TR5 were 73.3% and 85.7% respectively. The correlation between ACR TI-RADS and the Bethesda system of thyroid classification scores was $r=0.577$. The sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios of ACR TI-RADS were 90.9%, 98.5%, 90%, 99.3%, 62.3, and 0.1 respectively. They concluded that ACR TI-RADS classification is an appropriate and non-invasive method for assessing thyroid nodule in routine practice. It can safely reduce the number of unnecessary FNAC in a significant proportion of benign thyroid lesions. ACR TI-RADS should be standardized as the screening tool in resource-limited areas(11).

In most of the studies revised so far thyroid ultrasound was performed by well experienced individuals with many years of experience in thyroid ultrasound imaging thereby minimizing effect from experience of imaging personnel(9)(10). Institutional level studies looks important in this regard. The aim of this study is also assessing the accuracy of TIRAD system in comparison to histopathology in our context.

3 Objectives of the study

- To determine accuracy of thyroid ultrasound TIRAD classification for diagnosis of thyroid nodules in Saint Paul Hospital and Yekati 12 hospital from June 30 2022 to June 30 2023.

4 Methods

4.1 Study setting

The study was conducted at Saint Paul Hospital and Yekatit 12 hospital in Addis Ababa, Ethiopia for the period from June 30, 2022 to June 30, 2023 G.C. The data was collected from November 8-18/2023 G.C.

4.2 Study design

A hospital based retrospective record review was conducted on patients admitted and operated in Saint Paul's Hospital and Yekatit 12 hospital with thyroid nodules from June 30, 2022 to June 30, 2023 G.C. In which we compared thyroid ultrasound TIRAD classification result to the histopathology report for thyroid nodules. We assessed tertiary hospitals institutional thyroid ultrasound TIRAD classification sensitivity, specificity, PPV, NPV, and accuracy in comparison to histopathology results.

4.3 Source population

All patients with thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital from June 30, 2022 to June 30, 2023 G.C are our source population.

4.4 Study population

All patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 hospital during the study period.

4.5 Eligibility criteria

4.5.1 Inclusion criteria

All operated patients for thyroid nodules with both thyroid ultrasound TIRD classification and Histopathology result and age 18 and above were included.

4.5.2 Exclusion criteria

All Patients with Graves' disease were excluded.

4.6 Sample size determination

Sample from all operated patients for thyroid nodules from June 30, 2022 to June 30, 2023 G.C is calculated using single population proportion formula taking p value as 0.34 from study done in university of Gonder.(2)

$$n = \frac{z^2 p(1 - p)}{e^2}$$

n = the required sample size

p = proportion of patients who have thyroid nodule.

$Z_{\alpha/2}$ = the critical value at 95% confidence level = 1.96

e = precision (margin of error) = 5%

Accordingly,

$$n_0 = \frac{(1.96)^2 * 0.3(1 - .34)}{0.05^2}$$

$$n_0 = \frac{(1.96)^2 * 0.3(.66)}{0.05^2}$$

$$n_0 = 344$$

Using correction formula for population size less than 10000

N= total study population which is 650

$$n = no / \left(1 + \frac{n0 - 1}{N}\right)$$

$$n = 344 / \left(1 + \frac{344 - 1}{650}\right)$$

$$n = 225$$

Adding a non-response rate of 10% the final sample size will be 247.

4.7 Study variables

In this study we studied TIRAD classification system which was used in clinical setting for risk stratification of thyroid cancer. Depending on points given for morphology, echogenicity, margin, shape and calcification, nodules are described as TIRAD 1, TIRAD 2, TIRAD 3, TIRAD 4 and TIRAD 5. FNAC is done for these patients. We assessed accuracy of this system using thyroid histopathology result as gold standard. Thyroid histopathology results might be either benign in a form of colloid goiter, follicular or hurtle cell adenoma or malignant tumor as anaplastic, medullary, follicular, papillary or hurtle cell cancer.

4.7.1 Independent variables

Demographic characteristics like age and sex, of study patients was analyzed. The effect of duration between US and histopathology result as less than or greater than 6 month, and experience of personnel doing ultrasound whether it is senior radiologist or radiology resident on TIRAD accuracy will be assessed(6). Toxicity of the thyroid nodule is also assessed using TSH value <0.05 as toxic nodule.

4.8 Operational definition

Thyroid imaging reporting and data system (TIRAD): is method of reporting system of thyroid ultrasound for thyroid nodules. It has been adapted in Europe as EU-TIRAD and in America as AC- TIRAD depending on ultrasound features of thyroid nodules. Both systems have comparable sensitivity and specificity(17). In this study TIRAD stands for either of classification types.

Thyroid nodule: an abnormal growth of thyroid cells that forms a lump within the thyroid gland which can be identified by manual palpation or ultrasound of neck.

Histopathology: is histologic diagnosis obtained after surgical biopsy was sent for examination after passing through serious tissue processing. It is used as a gold standard and definitive test for thyroid lesions.

Sensitivity: ability of thyroid US TIRAD score to identify thyroid nodules that are malignant as a probable malignant thyroid US.

Specificity: ability of thyroid US TIRAD score to identify thyroid nodules that are benign as probable benign thyroid US.

Positive predictive value: ability of thyroid US TIRAD score to predict thyroid nodules that are malignant as a probable malignant thyroid US.

Negative predictive value: ability of thyroid US TIRAD score to predict thyroid nodules that are benign as probable benign thyroid US.

Positive likelihood ratio: the likelihood that probable malignant thyroid US is expected in malignant thyroid nodules compared with probable thyroid US expected in benign thyroid nodule.

4.9 Data collection procedure and tools

Thyroid US is used as initial diagnostic modality for patients with thyroid nodules in both institutions. Radiology resident physicians and senior radiologists do the examination and the reports are attached to individual patient charts. Post-operative histopathology result was also obtained from department of pathology from Saint Paul Hospital. Operation theater log books were used to get medical record chart numbers, then sampling interval was determined to be 3 and first chart number selected with lottery method. There were 650 patients operated for thyroid nodule (490 from Saint Paul Hospital and 201 from Yekatit 12 Hospital) in the study period. 247 Sampled patient charts were collected from main card rooms. Then data was extracted from patient medical record charts through standardized and pre tested questionnaire created on Google forms. Data collectors were trained otolaryngology residents.

4.9.1 Data quality

Data extraction format is pretested. Detailed explanation on significance of the study, the pretested questionnaire, inclusion and exclusion criteria and data collection procedure was given for data collectors. A well trained data collector extracted the data, and the data was supervised, reviewed and checked for completeness on a daily bases.

4.9.2 Data analysis procedure

The reviewed and checked data was exported on to SPSS version 26 for analysis. To describe patient characteristics, categorical variables were summarized using frequencies and percentages while continuous variables used mean and standard deviation. Missed values checked by cross tabulation and frequencies. Results were presented using tables and graphs. The accuracy tests were measured considering TIRAD I-III as probable benign and TIRAD IV and V as probable malignant nodule. (6) (13) Sensitivity, specificity, positive predictive value and negative predictive values for the TIRAD score were computed with 95% confidence interval using histopathology result as gold standard and presented with tables and figures. This measures of accuracy were computed on SPSS as Sensitivity = True Positive / (True Positive + False Negative), Specificity = True negative / (True Negative + False Positive), PPV = True Positive / (True Positive + False Positive), NPV = True negative / (True Positive + False Negative) and Accuracy = TP+TN / (True Positive + False Negative + True Negative + False Positive). The effect of experience of US personnel and duration between US and histology result on accuracy of TIRAD system is computed using Chi-square test.

4.10 Ethical consideration

Ethical clearance letter was obtained from review board of Saint Paul Millennium Medical College (SPHMMC) and different departments and Yekatit 12 Hospital were addressed through the letter. Data collected was stored and confidentiality maintained.

4.11 Dissemination of the result

After data was analyzed, based on findings obtained, conclusions were made. The results were submitted to SPHMMC department of ORL- HNS. The findings of the study were also sent to departments of General surgery and Radiology, as well as Yekatit 12 Hospital. Also, manuscripts will be submitted for publication in peer-reviewed scientific journals and results will be presented at scientific conferences for better communication of the results.

5 Results

5.1 Socio-Demographic Characteristics of the Study Participants

This study included 247 patients who underwent thyroid surgery with 217 of them females and 30 were males. There were around eight times more females than males. The mean age of study participants was 37.6 ± 12.9 years with minimum age 18 and maximum 80 years.

Distribution pattern of thyroid nodule in various age groups was 1(0.4%), 81(32.8%) were 20-29 72(29.1%) were 30-39, 43(17.4%), 29(11.7%) were 50-59, 18(7.3%) were 60-69, 1(0.4%) were 70-79 and 2(0.8%) were 80 and older.

Table 1 Socio-demographic characteristics of patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital, Addis Ababa, 2023 GC.

sex	Frequency	Percent
Female	217	87.9
Male	30	12.1
Total	247	100
age group		
18-19	1	0.4
20-29	81	32.8
30-39	72	29.1
40-49	43	17.4
50-59	29	11.7
60-69	18	7.3
70-79	1	0.4
80 and older	2	0.8

5.2 Thyroid ultrasound result

Out of the 247 ultrasound reports, 171 (69.2%) were done by radiology resident and 76 (30.8%) by senior radiologist. 182 (73.7%) of them were operated with in 6 month of ultrasound examination. Table 2 blow shows percentages of subjects in different TIRADS score and TIRAD category. TIRAD scores 1 to 3 was classified as probable benign US finding and TIRAD 4 and 5 as probable malignant US finding. TIRAD 3 is the most common score with frequency of 32.4% and probable benign category being most common category 57.9%.

Table 2 Percentages of subjects in different TIRADS score, TIRAD category, experience of US person and duration between US and histology of patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital, Addis Ababa, 2023 GC.

TIRAD score	Frequency	Percent
1	19	7.7
2	44	17.8
3	80	32.4
4	63	25.5
5	41	16.6
Total	247	100
TIRD Category		
Probable Benign(1-3)	143	57.9
Probable Malignant(4-5)	104	42.1
Total	247	100
experience of US person		
radiology resident	171	69.2
senior radiologist	76	30.8
Total	247	100
duration between US and histology		
Less than 6 month	182	74
Greater than 6 month	64	26
Total	247	100

5.3 Histopathology result

173 (70%) of operated patient post-operative histopathology result is benign while 74 (30%) are malignant. Papillary cancer is the most common malignancy identified accounting for 54 (22.9%) and hurtle cell cancer is the lowest 2 (0.8%).

Table 3 Frequency of post-operative histopathology class and histopathology result in patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital, Addis Ababa, 2023 GC.

histopathology classification		
	Frequency	Percent
Malignant	74	30
Benign	173	70
Total	247	100.0
Histopathology result		
	Frequency	Percent
benign thyroid adenoma	173	70
follicular cancer	18	7.3
hurtle cell cancer	2	0.8
papillary cancer	54	22.9
Total	240	100.0

5.4 Toxicity of the nodule

Non- toxic nodules accounts for 190(76.9%) of all examined nodules and 57 (22.1%) are toxic. 69 (93.2%) of malignant thyroid nodules are non-toxic.

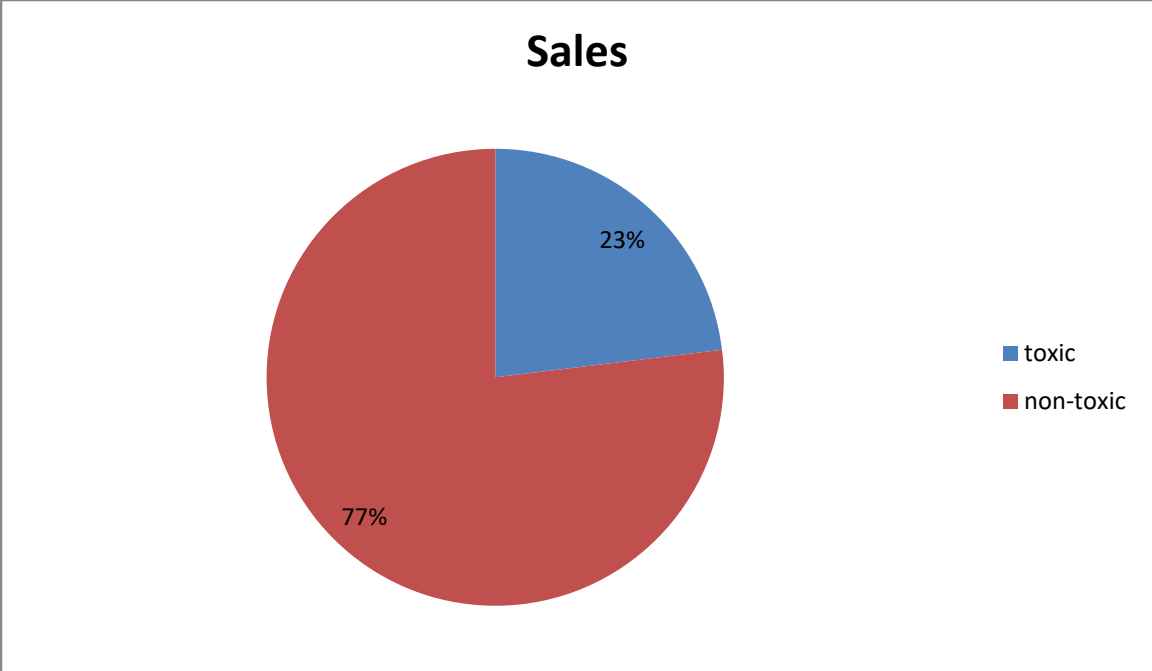


Figure 1 Frequency of toxicity of thyroid nodule of patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital, Addis Ababa, 2023 GC.

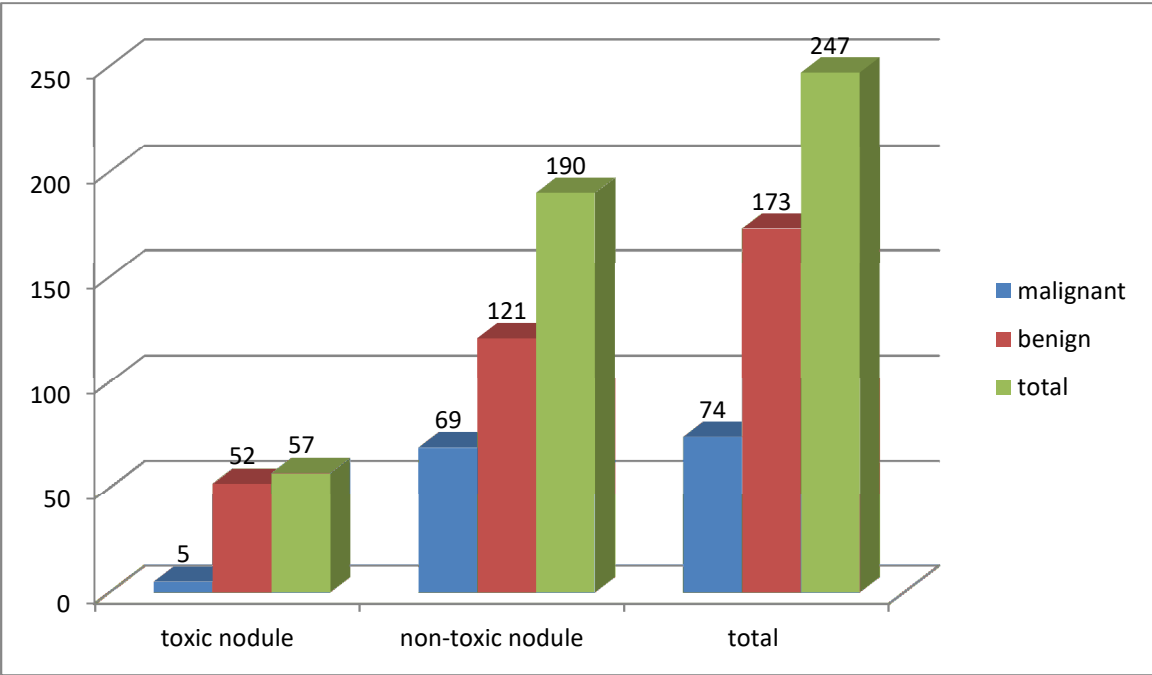


Figure 2 Toxicity of thyroid nodules in relation with histopathology result of patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital, Addis Ababa, 2023 GC.

5.5 Risk of malignancy

Risk of malignancy for individual TIRAD score was determined and presented in the table below. TIRAD 5 has risk of 82.9%. The risk is 4.5%, 22.5% and 31.8% for TIRAD 2, TIRAD 3 and TIRAD 4 respectively. Risk of malignancy is determined by dividing malignant lesion with respective TIRAD score.

Table 4 Risk of malignancy for individual TIRAD score of patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital, Addis Ababa, 2023 GC.

	histopathology class		Total	Risk of malignancy	P value
	malignant	Benign			
TIRAD 2	2	42	44	4.5%	<0.001
TIRAD 3	18	62	80	22.5%	<0.001
TIRAD 4	20	43	63	31.7%	<0.001
TIRAD 5	34	7	41	82.9%	<0.001
Total	74	173	247		

5.6 Measures of accuracy

In order to determine measures of accuracy we categorized TIRAD 1-3 as probable benign US feature and TIRAD 4 and 5 as probable malignant US feature. The overall sensitivity, specificity, Positive predictive value and negative predictive value for TIRAD system is 73%, 71.1%, 51.9% and 86% respectively with p value <0.001. The overall accuracy TIRAD system with histopathology as a gold standard test is 71.6%. There was moderate positive linear intensity correlation between TIRAD and histopathology result ($r=0.409$) and the correlation was statistically significant ($p<0.001$). Specificity is increased to 93.1% when combined with FNA cytology.

Table 5 TIRAD category * histopathology cross tab of patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital, Addis Ababa, 2023 GC.

			histopathology result		Total
			malignant	Benign	
TIRAD CATEGORY	probable malignant	Count	54	50	104
		% within TIRAD CATEGORY	51.9%	48.1%	100.0%
		% within histopathology category	73%	28.9%	42.1%
	probable benign	Count	20	123	143
		% within TIRAD CATEGORY	14%	86%	100.0%
		% within histopathology category	27%	71.1%	57.9%
Total		Count	74	173	247
		% within TIRAD CATEGORY	30%	70%	100.0%
		% within histopathology category	100.0%	100.0%	100.0%

Five of ultrasound features of thyroid nodule that are used in TIRAD scoring were individually tested for accuracy. Micro-calcification, irregular margin and taller than wider are the three features with high specificity. The specificity of micro-calcification, irregular margin and taller than wider is 94.8%, 94.2% and 93.6% respectively. The sensitivity of all features is low.

Table 6 Accuracy tests for individual ultrasound features of patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital, Addis Ababa, 2023 GC.

	Sensitivity	Specificity	PPV	NPV	+LHR	P value
hypo echoic	55.4	88.4	66.2	82.3	4.7	<0.001
taller than wider	43.2	93.6	74.4	79.4	6.7	<0.001
Solid	63.5	63	42.3	80.1	1.7	<0.001
micro calcification	30.1	94.8	71	76.3	5.8	<0.001
Irregular Margin	41.9	94.2	75.6	79.1	7.2	<0.001

PPV: positive predictive value, NPV: negative predictive value, +LHR: positive likelihood ratio= sensitivity/ (1- specificity)

5.7 Effects of experience of us personnel and duration between ultrasound and histopathology on the accuracy of TIRAD

70.8% and 76.3% of ultrasound done by radiology resident and senior radiologist have similarity between US and histopathology result respectively. There is no statistically significant difference on similarity between US and histopathology due to experience of US personnel, $\chi^2(1, N=247) = 0.47$, $p > 0.05$.

Majority of patients 73.7% were operated with in 6 month of US examination. 72.2% of patients with histology result within 6 month of US examination have the similar US and histology result. This number is 76.6% for duration greater than 6 month. Duration between initial US and final histology result has no statistically significant difference on similarity between US and histology result, $\chi^2(1, N=247) = 1.07$, $p > 0.05$.

Table 7 Cross tab between duration between US and histology* US and Histopathology result the same, and experience of US personnel* US and Histopathology result the same of patients operated for thyroid nodules at Saint Paul Hospital and Yekatit 12 Hospital, Addis Ababa, 2023 GC.

		US and Histopathology result the same		
		Yes	No	Total
Duration between US and histology	less than 6 month	127 (69.8%)	55 (30.2)	182 (100%)
	greater than 6 month	49 (76.6%)	15 (23.4%)	634(100%)
Total		176 (71.5%)	70 (28.5%)	247 (100%)
experience of US personnel	radiology resident	121(70.8%)	50 (29.2%)	171(100%)
	senior radiologist	58 (76.3%)	18 (23.7%)	76 (100%)
Total		179 (72.5%)	68 (27.5%)	247(100%)

6 Discussion

Thyroid nodules are common more in females than males in this study. The overall accuracy of TIRAD system is 71.7% for thyroid nodules. The risk of malignancy for TIRAD 2, 3, 4 and 5 are 4.5%, 22.5%, 31.7% and 82.9%, respectively. The three high risk US features, Irregular margin, micro calcification and taller than wider has specificity of 94.2%, 94.8 and 93.6%, respectively. Experience of US personnel and duration between US and histopathology result has no statistically significant effect on the similarity between US and histopathology result ($\chi^2(1, N=247) = 0.47, p > 0.05$ and, $\chi^2(1, N=247) = 1.07, p > 0.05$, respectively).

Females accounts for almost 87.9% of sample population (n=247). This is also supported by other studies in which prevalence of thyroid disease in females is 90% in Uganda and 86% in India (11) (18). The mean age of subjects was 37.6 ± 12.9 years, which is in accordance with above mentioned studies with 41 ± 13 and 40 ± 13 years respectively.

In this retrospective study, overall sensitivity, specificity, accuracy, PPV and NPV of TIRAD system is 73%, 71.1%, 71.7%, 51.9% and 86%. This is comparable with results of retrospective study in Spain by García-Moncó Fernández et al. They found that over all sensitivity of TIRAD system was 65%, which increased to 80% after excluding microcarcinoma(10). This is also supported by another observational study done in India where TIRAD system has sensitivity, specificity, accuracy, PPV and NPV of 80%, 47.2%, 61%, 51.3%, and 77.3%(13).

But the findings by Hamdi et al. in Uganda found that TIRAD system has sensitivity, specificity, accuracy, PPV and NPV of 90.9%, 98.5%, 90%, 99.3% and 62.3 respectively which is far greater than our findings. In this study they used ultrasound guided FNA Bethesda system as a gold standard test, using categories 4(suspicious follicular neoplasm), 5(suspicious for malignancy) and 6(malignant) as a malignant lesions(11). This might have contributed for the higher values. If we calculate the same way considering FNA Bethesda system as gold standard test, our sensitivity is 78.9% and 89% of specificity. The low sensitivity is high likely due to non- US guided FNA in our case.

The risk of malignancy of individual TIRAD score according to De, Debanu et al. was 22.5%, 31.7% and 82.9% for TIRAD 3, TIRAD 4 and TIRAD 5, respectively. This is comparable with results of our study, 22.7%, 32.8% and 82.5%, respectively(13). According to another Indian study by Kwak et al., it was concluded that the risk of malignancy for TIRADS categories 1, 2, 3, 4 and 5 was 0, 0, 1.7, 3.3-72.4, and 87.5%, respectively(15). In our study we have risk of malignancy 4.5% for TIRAD 2 score. This contradicts above study. We had 2 patients with TIRAD 2 with malignant histopathology result. The time between ultrasound and surgical biopsy is 3 years and 2 years. That might have given time for change of nodule over time.

The other difference is on risk of malignancy for TIRAD 3 which is 22.7% in our study. In study by Kwak et al. they used TIRAD system from 2009. But our study included the 2017 system which is a bit different from the previous one on TIRAD 3 score. Individual features like macro calcification or hyper echoic nature of the nodule were not included as possible features to predict malignancy in previous systems for TIRAD 3.

We found that the best three ultrasound features that pose a higher risk of malignancy, using a positive likelihood ratio are margin (irregular or extra capsular invasion), taller than wider, and micro calcification. However, no single feature is an absolute indicator for malignancy as none had a clinically relevant positive likelihood ratio of greater than 10. This study shows Irregular margin, micro

calcification and taller than wider has specificity of 94.2%, 94.8 and 93.6%, respectively. The positive likelihood ratio is 7.2, 5.8 and 6.7, respectively.

These results reflect findings similar to that of the international literature. A systematic review and meta-analysis of thyroid ultrasound features by Remonti et al. showed comparable outcomes regarding prediction of malignancy by specific nodule features (19). Irregular margin, micro calcifications and taller-than-wide configuration have a specificity of 83.1%, 87.8% and 96.6%, respectively. The positive likelihood ratio is 2.99, 3.26 and 8.07 none greater than 10. This is also supported by study in South Africa. (16) De, Debanu et al. in India found irregular margin, micro-calcification and taller-than-wider shape had a specificity of 86%, 89% and 92%, respectively(13).

There was no statistically significant effect of experience of US personnel on similarity between US finding and histopathology result in our study. This finding is supported by study on inter observer variability of thyroid nodule scoring done by Couzins et al(5). There is no statistically significant effect of duration between US and histology result on the similarity between US and histology. Only 25.9% of the nodule had greater than 6 month interval between and US and histology result and of these 42.2% were toxic nodules which stayed on follow up with anti-thyroid treatment. But this is only 15% for those less than 6 month. Odds of malignancy of hot nodules is reduced compared with non-toxic nodules.(20)

7 Strength and limitation

This research evaluated the sensitivity, specificity, positive predictive value and negative predictive value of thyroid ultrasound TIRAD system, which will help the clinician to appropriately select patients for further investigation and surgical treatment. The study included effects of experience of US personnel and duration between US and final histology result on the similarity between US and histology result. It also included two centers in the study which are tertiary hospitals in the country.

The study does have some limitations like it was based on past collected data; the real value of the accuracy measurement parameter might be underestimated or overestimated. It does not measure the true inherent accuracy of TIRAD system rather institutional level accuracy of the test outcome used in patient management so far. Causes of both false positive and false negative TIRAD results are difficult to determine because the study is retrospective.

8 Conclusion

We found that TIRAD is an appropriate and non-invasive method for initial assessment of thyroid nodules in our routine practice. The three best ultrasound features that pose a higher risk of malignancy are irregular margin, taller than wider and micro calcification. However, no single feature is an absolute indicator for malignancy. TIRAD 3 nodules should be put on follow up to avoid over or under treatment as an intermediate group.

Thyroid ultrasound examinations done by senior radiologist and radiology resident do not affect accuracy of TIRAD system significantly. The effect of duration between TU and histology on accuracy of TIRAD needs further investigation considering other cofounders.

9 Recommendations

For health professionals

- Thyroid US TIRAD system can be used as initial investigation to risk stratify patients for further investigation and management.

For researchers

- Further study with a bigger sample size and prospective approach to define factors affecting accuracy of TIRAD system and reasons for values of positive/negative predictive value.

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Annex I

Assurance of principal Investigator

I undersigned agree to accept all responsibilities for the scientific and ethical conduct of the research project. I provided timely progress report to my advisor and seek the necessary advice and approval from my primary advisors in the course of the research. I communicated timely to my advisors all stakeholders involved in the study including any source of funding for this research.

Name of the student: _____

Signature: _____

Date: _____

Approval of the Primary Advisor

Name of the primary advisor: _____

Signature: _____

Date: _____

Approval of the Co-Advisor

Name of the Co-Advisor: _____

Signature: _____

Date: _____