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Role of TIRADS and Bethesda Scoring Systems in Management of Thyroid Nodules

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ABSTRACT

Background: Fine-needle aspiration (FNA) is the first-line diagnostic procedure, with the Bethesda System used to classify cytology findings into six categories based on malignancy risk. Despite some diagnostic variability, this system enhances diagnostic accuracy and minimizes unnecessary surgeries. **Objective:** This study aimed to measure the correlation between the thyroid imaging reporting and data systems (TIRADS) and Bethesda scoring systems and the final histopathology, whether benign or malignant, in thyroid nodules (TNs). **Patients and Methods:** This cross-sectional observational study was conducted on 30 patients with single or multiple thyroid nodules measuring more than 1cm. All patients underwent FNA cytology from suspicious nodules. Patients with thyroid nodules that are smaller than 1cm, history of thyroid surgery and history of radiotherapy were excluded from the study.

Results: TIRAD can significantly predicted histopathology (P = 0.018, AUC = 0.683) at cut-off ≤ 3 with 90.00 % sensitivity, 45.00 % specificity, 71.1 % PPV and 75.0% NPV. Bethesda system significantly predicted histopathology (P = 0.032, AUC = 0.659) at cut-off ≤ 2 with 73.33 % sensitivity, 55.00% specificity, 71.0% PPV and 57.9% NPV.

Conclusions: Both TIRAD and the Bethesda system are significant predictors of the histopathology of thyroid nodules, with superiority of TIRAD in sensitivity (90%) compared to the Bethesda system (73.33 %).

Keywords: TIRADS, Bethesda Scoring System, Thyroid Nodules, FNA.

INTRODUCTION

The American Thyroid Association (ATA) establishes thyroid nodule (TN) as a distinct lesion located inside the thyroid gland. It is radiologically differentiated from the adjacent parenchyma of the thyroid. It might be single, numerous, cystic, or solid [1].

TN is an aberrant proliferation of thyroid cells that creates a mass inside the thyroid gland. A minority of thyroid nodules, despite the majority being benign, may harbor thyroid cancer [2]. Thyroid nodules are prevalent and clinically significant, with the majority being benign; only 4.5 to 6.5% are malignant. Distinguishing these instances is essential to minimize needless thyroidectomies. In Egypt, thyroid cancer is the sixth most common malignancy among females and the seventeenth in males [3]. The identification of TN with palpation is 4-7%, but ultrasonic detection ranges from 20-76% [4]. Various circumstances may lead to the formation of nodules in the thyroid gland, involving normal thyroid tissue overgrowth, thyroid cysts, and chronic thyroid inflammation. Multinodular goiter, thyroid carcinoma, iodine insufficiency [5].

The sonographic features of a TN correlated with an elevated risk of malignancies involve hypoechogenicity, augmented intranodular vascularity, uneven borders, microcalcifications, absence of a halo, and a taller-than-wide configuration in the transverse dimension. Consequently, many malignant and benign ultrasonic grayscale and Doppler characteristics were developed over the last decade that might be used in diverse manners to assign probabilities, alongside a methodology predicated on the Breast Imaging Reporting and Data System (BIRADS). Similarly, many US TIRADS have been suggested for the risk categorization of TN. In recent years, ultrasound-guided FNA has largely supplanted thyroid scintigraphy as the preferred method for evaluating euthyroid individuals with a thyroid nodule, owing to its accuracy, simplicity, and cost-effectiveness [6, 7]. FNA utilized as a primary diagnostic method reveals that 50% of excised nodules are malignant, leading to a substantial reduction in the number of patients requiring surgical intervention[8].

In euthyroid individuals with nodules, thyroid FNA has shown great sensitivity in diagnosing and differentiating benign from malignant lesions, facilitating optimal management and preventing needless procedures. Nonetheless, its clinical application remains somewhat restricted, and its practical implementation in medical practice is subject to scrutiny. TIRADS is an ultrasonic categorization that enhances the diagnostic accuracy of TN and mitigates the need for preoperative FNA. The nodules are often classified into several groups according to TIRADS and then referred for FNA. Conduct a follow-up based on the varying risk of malignancy[5, 9].

The primary objective of TIRADS is to enhance patient care and cost-efficiency by circumventing superfluous FNA. Biopsies for individuals with TN have a specificity of 49%, sensitivity of 88%, positive predictive value (PPV) of 49%, negative predictive value (NPV) of 88%, and accuracy of 94%[10].

The term TIRADS had been initially introduced in 2009. TIRADS is now used for the differential diagnosis of malignant and benign TN, categorized into five levels, with the highest category indicating a strong suspicion of cancer [11].

This approach assesses ultrasonic characteristics across five areas: echogenicity, composition, form,

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margin, and echogenic foci; the cumulative points of the nodule dictate its risk level, alongside the five categories of TIRADS. The classifications were TR1:normal thyroid gland, TR2: benign lesions, TR3: presumably benign lesions, TR4:suspicious lesions, and TR5:certainly malignant lesions (with above 80% chance of cancer) [12, 13].

The Bethesda technique for recording thyroid cytopathology is a systematic framework for classifying thyroid FNA biopsy results into six diagnostic categories, each linked with unique malignancy risks and therapeutic treatment recommendations. Since its conception, the Bethesda System had been extensively used, with each category indicating a risk of malignancies and suggesting subsequent actions; nevertheless, it remains uncertain if each category also forecasts the kind and severity of malignancy [14].

The Bethesda system is a cytological categorization approach for TN, efficient in assessing malignancy risk. The Bethesda method categorizes thyroid lesions into six distinct classifications. The categories comprised Bethesda I: non-diagnostic, Bethesda II: benign, Bethesda III: atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS), Bethesda IV: follicular neoplasm/suspicious for follicular neoplasm, Bethesda V: suspicious for malignancy, and Bethesda VI: malignant[13].

This has the intrinsic limitation of intra- and inter-observer variability in cytopathological analysis. A solitary patient might have many ancillary nodules for biopsy by fine needle aspiration, attributable to their ultrasonography features, hence complicating the diagnostic-therapeutic procedure [14].

Nonetheless, the deployment of this reporting system has revealed considerable diagnostic variability, both among different pathologists and within the same pathologist, especially when classified as “atypical cells of undetermined significance, FLUS, or follicular neoplasm” (designated as Bethesda Category III, which includes a diverse array of low-risk lesions characterized by follicular cells displaying either architectural irregularities or nuclear atypia that do not conform to other established cytological categories) [14].

Recently, a meta-analysis assessed the Bethesda reporting system validity, revealing a sensitivity of 97%, specificity of 50.7%, and diagnostic accuracy of 68.8%; the NPV and PPV were 96.3% and 55.9%, respectively [15]. The objective of this study was to measure the correlation between the TIRADS and Bethesda scoring systems and the final histopathology, whether benign or malignant, in thyroid nodules (TNs).

PATIENTS AND METHODS

This cross-sectional observational study included 30 patients of both genders suffered from single or multiple thyroid nodules more than 1 cm, attending at Department of General Surgery, Sohag University Hospital, Sohag, Egypt. This study was conducted between March 2024 to August 2024.

Exclusion criteria: Patients with thyroid nodules smaller than 1 cm, a history of thyroid surgery, or a history of radiotherapy were excluded.

Each subject underwent comprehensive history taking, clinical examinations, laboratory tests including complete blood count (CBC), thyroid-stimulating hormone (TSH), free T3 (FT3), and free T4 (FT4), as well as thyroid imaging. Ultrasound findings regarding the number, size, and location of nodules were recorded, and FNA cytology was performed on suspicious nodules.

All patients were positioned supine and B-mode ultrasound scanning for thyroid nodules (TN) was performed in preparation for US-guided FNA cytology throughout the research period. Participants with TN $\geq$ 1cm identified by B mode US and who provided permission were included in the study.

An examination was conducted in the US using a SIUI Apogee 5300 US machine designated MHC-DDT-US-0012, with high-frequency linear probes operating at 7.5MHz. A 5MHz transducer was employed for enhanced penetration in obese individuals or those with large thyroid lesions. The subject was positioned supine with the neck hyper-extended, and a comprehensive examination of the whole gland was conducted. Hyperextension of the neck was achieved by positioning a cushion under the shoulders. The neck was imaged in transverse, sagittal, and oblique planes to effectively view both thyroid lobes and the isisthmus. Also, imaging employing the colour Doppler had been used. The sonographic properties of TN, including composition, form, margins, echogenicities, and echogenic foci, had been documented. A 23-gauge needle with a transparent hub had been employed to acquire samples from the nodules corresponding to each classification of TI-RADS, with a maximum. The sample had been carefully ejected onto the surface of a labeled slide of microscope from the tip of the needle utilizing a transparent syringe (5-10 mL).

The evaluation of TN was conducted with the TIRAD method. The TRIADS approach was utilized to categorize single thyroid lesions into 6 classifications [13]: TI-RADS 1: normal thyroid gland. No discernible focal lesion. TI-RADS 2: nonmalignant TN. Clearly benign pattern, TI-RADS 3: likely benign TNs; TI-RADS 4:4a–indeterminate TNs, 4b–suspicious TNs, 4c–highly suspicious TNs. TI-RADS 5: Likely malignant TNs and TI-RADS 6: biopsy-confirmed malignancies.

After that, a smearing slide was added to the material, and every effort was made to ensure that both slides were sufficiently smeared. After being treated to wet fixation with alcohol and then stained via the Papanicolaou technique, one slide underwent staining employing the Diff-Quik method, while another slide was kept at ambient temperature and allowed to air-dry before being stained using the Papanicolaou procedure. A consultant pathologist then assessed all samples in accordance with the Bethesda protocol. **Figure 1**

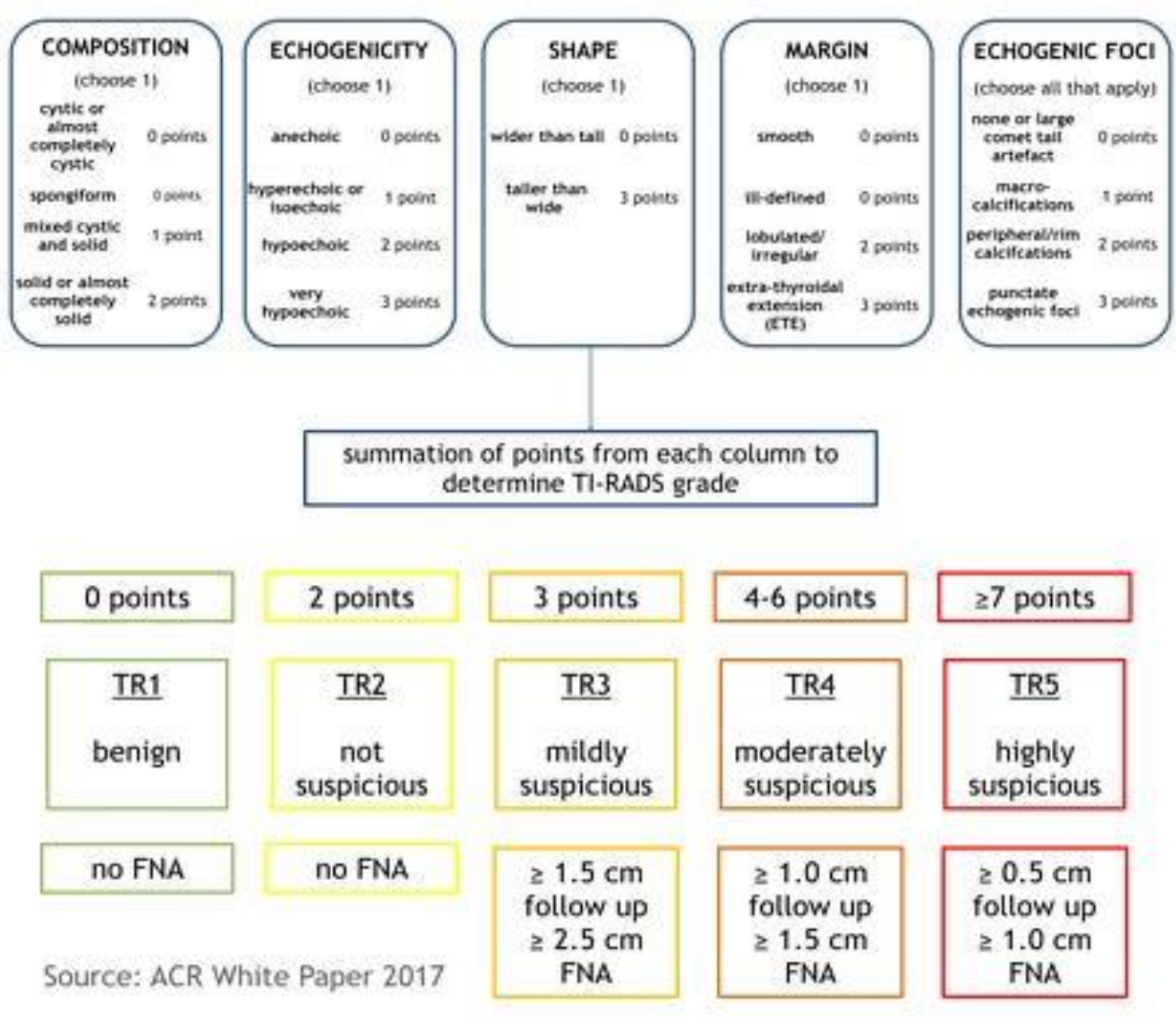


Figure (1): TI-RADS grade.

Cytological and histopathological assessment

Slides were stained with haematoxylin and eosin, after which the remaining haemorrhagic aspiration in the needle and syringe was fixed in 10% formalin and embedded in paraffin to create cell blocks. The histological sections were analyzed as an adjunctive diagnostic instrument.

Cytologic-histologic association was a reliable approach for assessing the results of FNAC diagnosis, and it was shown to reduce the incidence of unsatisfactory samples and enhance diagnostic accuracy. All FNAC and cell block slides were reviewed.

The Bethesda method classifies thyroid lesions into six groups, including [13]:

- Bethesda I: non-diagnostic
- Bethesda II: benign
- Bethesda III: atypia of undetermined significance (AUS) / FLUS
- Bethesda IV: follicular neoplasm/suspicious for follicular neoplasm
- Bethesda V: suspicious for malignancy
- Bethesda VI: malignant

To deem a thyroid FNA specimen appropriate for examination, a minimum of 6 clusters of benign follicular cells **was required,** with each cluster including at least 10 cells. Smears exhibiting atypical cells **were consistently considered** sufficient, irrespective of cellularity. The H&E slides of the TNs **were subsequently reviewed** post-surgery.

***Ethical Consideration*:**

This study was ethically approved by local Ethical Committee at Sohag University. Written informed consent was obtained from all participants. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human subjects.

Statistical analysis

Statistical analysis had been performed employing SPSS version 26.0. The Shapiro-Wilk test and histograms have been employed to assess the data distribution normality. Quantitative parametric data had

been expressed as mean ± SD. Quantitative non-parametric data had been displayed as median and interquartile range (IQR). Qualitative factors had been displayed as frequencies and percentages (%). Sensitivity, specificity, PPV, and NPV will be utilised to evaluate sonographic and cytohistological features. The area under the curve (AUC) assesses the overall efficacy of a test, with an AUC >50% revealing acceptable performance and an AUC approaching 100% signifies optimal performance. A value below 0.5 indicates a very poor model.

RESULTS

The mean age of the patients was 41.2 ± 9.92 years. There were 4 (8%) males and 46 (92%) females. The operative time ranged from 85 to 165 minutes with a mean value (± SD) of 108.6 (±19.22) minutes. Regarding complaint, 42 (84%) patients had neck swelling, 3 (6%) had neck compression, 4 (8%) had hyperthyroidism, and 1 (2%) had hypothyroidism (Table 1).

Table 1: Demographic data and time of operation, complaint of the studied patients

		(n=50)
Age (years)		41.2 ± 9.92
Sex	**Male**	4 (8.0%)
	Female	46 (92.0%)
Time of operation(min)		108.6 ± 19.22
Neck swelling		42 (84.0%)
Neck compression		3 (6.0%)
Hyperthroidism		4 (8.0%)
Hypothroidism		1 (2.0%)

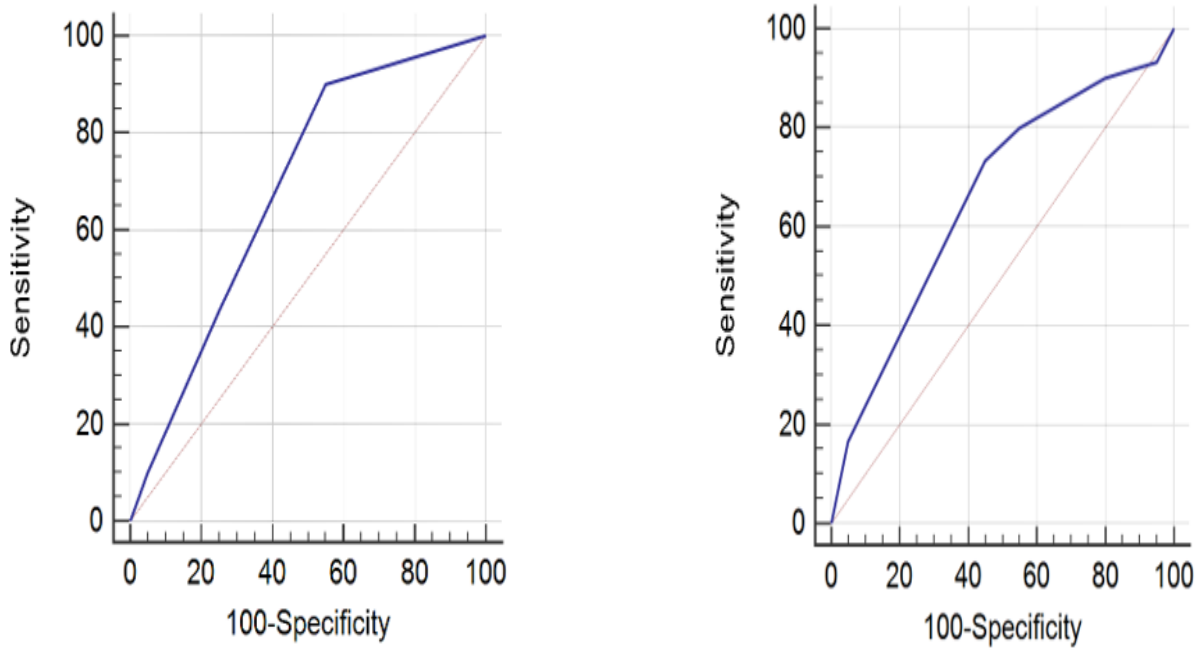
Laboratory investigations, TIRAD, Bethesda system, FNA and histopathology y (Data is presented as mean ± SD, median (IQR) or frequency (%)) of the studied patients were enumerated in **Table 2**.

Table 2: Laboratory investigations, TIRAD, Bethesda system, FNA and histopathology of the studied patients

		N=50
TSH (mlU/L)		1.9 ± 1.49
Free T3 (pg/dL)		369.6 ± 61.61
Free T4 (pg/dL)		1.3 ± 0.29
TIRAD	**IQR**	3(2-3)
	TIRAD 1	4 (8.0%)
	TIRAD 2	14 (28.0%)
	TIRAD 3	21 (42.0%)
	TIRAD 4a	10 (20.0%)
	TIRAD 4b	1 (2.0%)
Bethesda system	**Median**	2
	IQR	2 - 4
	I	6 (12.0%)
	II	25 (50.0%)
	III	4 (8.0%)
	IV	8 (16.0%)
	V	4 (8.0%)
	VI	3 (6.0%)
FNA	**Benin**	27 (54.0%)
	Malignant	23 (46.0%)
Nodular colloid goite		30 (60.0%)
Follicular throid neoplasms		2 (4.0%)
Adenoma		10 (20.0%)
Thyroiditis		7 (14.0%)
Papillary thyroid neoplasms		1 (2.0%)

Data is presented as mean ± SD, median (IQR) or frequency (%).

TIRADS can significantly predict histopathology (P = 0.018 and area under the curve = 0.683) at cut-off ≤ 3 with 90.00 % sensitivity, 45.00 % specificity, 71.1 % positive predictive value and 75.0% negative predictive value. Bethesda system can significantly predict histopathology (P = 0.032 and area under the curve = 0.659) at cut-off ≤ 2 with 73.33 % sensitivity, 55.00% specificity, 71.0 % positive predictive value and 57.9% negative predictive value. **Figure 2**



(A) **(B)**

Figure (2): ROC curve of (A) Rrole of TIRAD and (B) Bethesda system in prediction of histopathology in prediction of histopathology.

DISCUSSION

The prevalence rates of thyroid nodules vary depending on the mode of discovery; for example, they range from 8 to 65% when discovered by autopsy, 19 to 35% when discovered by ultrasonography, and 2-6% when discovered by palpation [16].

A TN is a common object that is frequently discovered by accident during imaging tests carried out in accordance with non-thyroidal indications. About 4-6.5% of all palpable nodules have been discovered to be malignant [17], indicating that the great majority of these lesions are benign. Therefore, the first patient evaluation attempts to rule out those instances that do not require additional diagnostic or therapeutic work-up. In this regard, ultrasonography (US) is acknowledged as the most precise imaging technique for determining the TNs risk of malignancy (RoM) [18].

In recent years, radiologists and endocrinologists have learned about the great dependability of US-based risk stratification methods, commonly referred to as TIRADS and suggested by worldwide groups [18]. TIRADSs essentially seek to standardize the identification of TNs that need FNAC and the evaluation of TNs' RoM. ACR-, EU-, and K-TIRADS are the most widely used TIRADSs [19].

On the one hand, TIRADSs have been shown in the literature to be accurate in stratifying the RoM of TNs without observable system-to-system variations [20]. However, there were notable differences among TIRADSs in avoiding "unnecessary" FNAC, including biopsies that weren't recommended [22]. Internal composition, echogenicity, borders, echogenic foci, and nodule form were among the sonographic characteristics considered [22]. All these factors are considered while determining TIRADS scoring. The probability of a TN being cancerous increases with the cumulative TIRADS score [3].

Due to its safety, affordability, and ability to distinguish between benign and malignant lesions, fine needle aspiration cytology is a crucial technique for TN diagnosis. In order to provide a consistent reporting system for thyroid FNAC and facilitate efficient communication between radiologists, pathologists, and doctors, the Bethesda system was created [2].

The Bethesda system is divided into 6 categories, each of which is associated with a particular risk of malignancy and requires specific therapeutic care. Clinical care of the Bethesda system spans from clinical and sonographic follow-up in category II to near-complete thyroidectomy or lobectomy in categories V & VI [23].

Therefore, this observational cross-sectional study was conducted on 50 patients with TNs and aimed to evaluate the correlation between the TIRADS and Bethesda scoring systems and the final histopathology, whether benign or malignant.

In the current study, the age of participants ranged from 23 to 60 years, with a mean value (± SD) of 41.2 (± 9.92) years. There were 4 (8%) males and 46 (92%) females.

Supporting our results, **Zhang *et al.*** [23] conducted a study of 585 adult patients' data who were admitted to the hospital after having TNs identified by

ultrasonography and graded using K-TIRADS. There were two groups, 326 malignant nodules and 259 benign nodules. They showed that mean age was 48.22±12.31 and there was female predominance (69.74%).

This came in line with, **Fawzy *et al.*** [24] performed a study on individuals with TNs. They noted that mean age was 45.67±12.73 and there was female predominance (83.2%).

However, other studies **Mora-Guzmán *et al.*** [25] which conducted on patients who underwent thyroid surgery, found older age (51.8years). This disparity may be attributed to differing sample sizes and the ages of the patients who presented to the health care units.

In the current study, regarding complaint, there were 42 (84%) patients with neck swelling, 3 (6%) patients with neck compression, 4 (8%) patients with hyperthyroidism and 1 (2%) patient with hypothyroidism.

Supporting this finding, **Hossen *et al.*** [26] illustrated that incidence of thyroid malignancy in thyroid swellings is high.

Also, **Ramadan *et al.*** [27] carried out a study of 81 individuals who were candidates for complete thyroidectomy or hemithyroidectomy. They discovered that the most common complaints were neck lumps (46.9%) and pressure feelings (45.7%), with hyperthyroidism in 7.4% and hypothyroidism in 0%.

In the present study, the median (IQR) of TIRAD was 3 (2-3). TIRAD 1 existed in 4 (8%) patients, TIRAD 2 existed in 14 (28%) patients, TIRAD 3 existed in 21 (42%) patients, TIRAD 4a existed in 10 (20%) patients and TIRAD 4b was present in 1 (2%) patient. The median (IQR) of Bethesda system was 2 (2-4). Bethesda system was grade I in 6 (12%) patients, grade II in 25 (50%) patients, grade III in 4 (8%) patients, grade IV in 8 (16%) patients, grade V in 4 (8%) patients and grade VI in 3 (6%) patients. Regarding FNA, benign finding was present in 27 (54%) patients and malignant finding was present in 23 (46%) patients.

However, **Zhang *et al.*** [23] reported that TR1 was present in 10.61% of patients, TR2 in 5.89%, TR3 in 12.97%, TR4 in 22.79% and TR5 in 47.74%. The different study area and population could explain this difference from our results.

Fawzy *et al.*[24] showed that Bethesda was I in 13.7%, II in 51.1%, III in 8.4%, IV in 15.3%, V in 6.3% and VI 5.3% and histopathology was malignant in 27.4% and benign in 72.6%.

In the current study, regarding histopathology, 30 (60%) patients had nodular colloid goites, 2 (4%) patients had follicular thyroid neoplasms, 10 (20%) patients had adenoma, 7 (14%) patients had thyroiditis, and 1 (2%) patient had papillary thyroid neoplasms.

Follicular thyroid adenomas are prevalent TN, but follicular thyroid carcinomas (FTCs) account for 10–22% of thyroid malignancies, ranking second behind papillary thyroid carcinomas (PTCs), which comprise 80–90% [28].

In the same line, **Mohammed *et al.*** [29] carried out a prospective cross-sectional study on 76 patients with thyroid lesions. They showed that follicular carcinoma was resent in 3.94 % of patients, Papillary carcinoma in 15.78 %.

Supporting our findings, **Fawzy *et al.*** [24] revealed that Colloid nodular goiter was in 52.1%, Follicular adenoma in 8.9%, carcinoma in 1.6%, thyroiditis in 1.1% and papillary thyroid in 17.9%.

In the same context,

In the same context, **Ruan *et al.*** [30] conducted retrospective research that comprised 1001 consecutive TNs from 918 individuals. They discovered that out of the 1001 TNs, 609(60.8%) were benign and 392(39.2%) were malignant. There were 342 papillary thyroid cancers (PTCs) among the 359 malignant nodules, including eight follicular variant PTCs, seven follicular carcinomas, two medullar carcinomas, two undifferentiated carcinomas, and six other malignant tumors (three lymphomas, one carcinoma with thymus-like differentiation, one metastasis, and one squamous cell carcinoma). Of the 222 benign nodules, there were 124 nodular goiters, 87 follicular adenomas, and 11 instances of thyroiditis.

Our results revealed that TIRAD can significantly predict histopathology (P = 0.018 and AUC = 0.683) at cut-off ≤ 3 with 90 % sensitivity, 45% specificity, 71.1 % PPV and 75% NPV.

This agreed with George *et al.* [31] who found that The US TIRADS exhibited a sensitivity of 72.3% and a specificity of 66.7% in the assessment of TN. The PPV had been elevated at 97.14, while the NPV was low at 13.33%.

The research conducted by **Singaporewalla *et al.*** [32] indicates that the specificity and sensitivity of US TIRADS are 90.4% and 70.6%, correspondingly.

Also, in the study by **Mathew and Mathew** [33] the concordance rates of ultrasound TIRADS with final histopathology in predicting malignancy was 75.4%.

In the same line, **Zhang and Lin** [34] carried out a study on data of 565 patients diagnosed with medullary thyroid carcinoma (MTC) and PTC or benign TNs. They were classified into the benign TNs group (n=264), the PTC group (n=189) and the MTC group (n=56) also, there were two groups benign and malignant nodules groups. They showed that ACR-TIRADS can significantly predict malignant pathology at cut-off >TR4 with 81 % sensitivity, 83% specificity 82 % PPV and .83% NPV.

This work revealed that the Bethesda system could significantly predict histopathology (P = 0.032, AUC = 0.659) at a cut-off ≤ 2, with 73.33% sensitivity, 55% specificity, 71.0% PPV, and 57.9% NPV, which showed lower sensitivity compared to TIRADS.

Alyusuf *et al.* [35] reported that calcifications and hypoechogenicity in Bethesda III and IV TNs are

significant indicators of thyroid malignancies, being associated with a two-fold higher risk of malignancy. The sensitivity, specificity, PPV, NPV, and accuracy for hypoechogenicity were 31.5%, 83%, 55.6%, 64.7%, and 62.6%, respectively, whereas for calcification, they were 32.4%, 82%, 54.5%, 67.8%, and 62%, respectively.

The limitations of this work included its single-center design, which may have led to findings that differ from those in other settings, and the small sample size, which may have resulted in statistically insignificant outcomes. In addition, we did not compare different types of TIRADS.

CONCLUSION

Both TIRAD and Bethesda system are significant predictors of histopathology of thyroid nodules with superiority of TIRAD in sensitivity (90%) over Bethesda system (73.33 %).

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