`Prospective Evaluation of TIRADS Introduced At the University of Iowa Hospital and Clinics

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ABSTRACT

Objective: This study aimed to evaluate the diagnostic ability of the Zayadeen scale that has been introduced to discriminate between benign and malignant thyroid nodule disease.

Methods: A total of 238 patients who were referred for ultrasound (US)-guided fine needle aspiration (FNA) in King Hussein Medical Centre were included in the study. US and FNA were performed by one of three experienced radiologists using a 6-15 MHz linear probe. Nodule features were recorded regarding exact location, size, presence of calcification, echogenicity, consistency, margins, shape and the presence of suspicious cervical lymph nodes. According to the tested Zayadeen scoring system, the major risk factors were weighted equally and given a score of 2 for the presence of each factor; the minor risk factors were given a score of 1. Each nodule was given a total scale score by adding the scores of individual risk factors. The performance of the scale score using the Thyroid Imaging Reporting and Data System (TIRADS) scoring system was evaluated using receiver operating characteristic (ROC) analyses.

Results: This study included a total of 182 patients (150 women and 32 men). Subject age ranged from 15 to 85 years. ROC analysis showed that the area under the ROC curve was 0.801 (95% CI: 0.72, 0.88) indicating that the total scale score had good accuracy to predict malignancy. The optimum cut-off value to discriminate between benign and malignant disease was 2. At the established cut-off value, the sensitivity was 0.68 and the specificity was 0.76. Categorising the total scale score using this cut-off value was significantly associated with increased odds of malignancy. The odds of having malignancy for patients with 2 or more risk factors was 6.6 times the odds for patients with fewer than 2 risk factors (OR = 6.6; 95% CI: 3.0, 14.3).

Conclusion: Zayadeen's scale has good accuracy to discriminate between benign and malignant thyroid nodules.

Keywords: Ultrasound, thyroid nodule, thyroid cancer, TIRADS, ultrasound-guided FNA.
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Disclosure Statement

The authors declare that no competing financial interests exist.

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Introduction

Thyroid nodule is a discrete lesion that is distinct radiologically from thyroid tissue [1]. It is a very common clinical issue with no standards to differentiate between benign and malignant nodules. The prevalence of thyroid nodules is 50-60% in healthy people. Thyroid cancer is the sixth most common thyroid cancer among Jordanians in 2015, accounting for 4.1% of all cancers**.** The most common morphological type of thyroid cancer in Jordan is papillary carcinoma [2].

The majority of thyroid nodules are discovered incidentally in asymptomatic patients by imaging for reasons unrelated to the thyroid. [3] Thyroid ultrasound (US) is a key examination for the management of thyroid nodules. Thyroid US is easily accessible, non-invasive, cost-effective, and is a mandatory step in the workup of thyroid nodules. The main disadvantage of the method is that it is operator-dependent [4]. Thyroid US assessment of the risk of malignancy is crucial in patients with nodules to decide on who should undergo a fine needle aspiration (FNA) biopsy. Ultrasound features are evaluated thoroughly in many studies, classifying nodules with benign or malignant features; however malignancy cannot be reliably predicted by a single US feature alone [5-10].

FNA is very reliable and safe to discriminate malignant from benign nodules, especially when it is done under US guidance [11]. A meta-analysis by Brito et al. [12] included 31 studies assessing more than 1,800 nodules. The features with the highest diagnostic odds ratio (DOR) for predicting malignancy were a ‘taller-than-wide’ shape (DOR = 11.1; 95% CI: 6.6-18.9) and internal calcifications (DOR = 6.8; 95% CI: 4.5-10.2). A meta-analysis by Campanella et al. [13] included 41 studies with about 30,000 nodules showed that the highest risk of malignancy was associated with a ‘taller-than-wide’ shape (DOR = 10.2; 95% CI: 6.7-15.3), microcalcifications (DOR = 6.8; 95% CI: 4.7-9.7) and irregular margins (DOR = 6.1; 95% CI: 3.1-12.0). Remonti et al. [14] found the highest specificities for a ‘taller-than-wide’ shape (96.6%), stiff nodules (86.2%), microcalcifications (87.8%) and irregular margins (83.1%).

The substantial interobserver variation in the reporting of some US features, especially microcalcifications, is a major challenge [15]. Some guidelines recommend FNA based on US features in correlation with nodule size, while others advise FNA based on US features alone regardless of nodule size [16-21].

This study aimed to evaluate the diagnostic ability of the scale that has been introduced by Zayadeen et al. [21] to discriminate between benign and malignant thyroid nodule disease, where the authors divided the risk factors into major and minor, and suggested performing a biopsy if the nodule harbours at least one major or two minor risk factors. The aim of this prospective study is to check the accuracy of the TIRADS introduced by Zayadeen et al. at the University of Iowa Hospital and Clinics, IA, USA.

Study design

From November 2017 to December 2018, a total of 238 patients were referred for US-guided FNA at King Hussein Medical Centre. A total of 182 patients (150 females and 32 males) were included in this prospective study. The patients were referred from different specialties, mainly surgeons and endocrinologists based on previous ultrasound reports.

Examination

Ultrasound examination was done for all patients referred for US-guided thyroid FNA at King Hussein Medical Centre on the day of FNA. US and FNA were performed by one of three experienced radiologists using a 6-15 MHz linear probe (GE Logiq E9, Rochester, MN, USA) or a 6-15 MHz linear probe (GE Logiq S8, Rochester, MN, USA). Sagittal, transverse and oblique real-time B-mode scan was performed. Doppler was utilised to guide FNA. The nodule features were recorded regarding the exact location, size, presence of calcification (microcalcification, macrocalcification and ring calcification), echogenicity (anechoic, hyperechoic, isoechoic, hypoechoic or markedly hypoechoic), consistency (solid, mixed or cystic), margins (well or ill-defined margins), shape (taller than wider or not) and the presence of suspicious cervical lymph nodes (loss of lentiform shape, loss fatty hilum with presence of calcification and cystic changes along with abnormal vascularity).

All the nodules were biopsied by an aseptic technique and direct US guidance. One to three passes were usually done with a 23 Gauge needle using minor suction, depending on the adequacy determined by the attending lab technician. No cytologist was available on site. The smears were alcohol fixed and Papanicolaou stained, or air-dried and stained with a Romanowsky-type stain. The Bethesda system was used for reporting the results of thyroid FNA. Institutional Review Board approval was obtained and signed informed consent was provided by all patients before US-guided FNA was performed.

Scoring

According to the tested TIRADS scoring system [21], the major risk factors (microcalcification, marked hypoechogenicity, taller than wider, ill-defined margins and presence of suspicious lymph nodes) were weighted equally and given a score of 2 for the presence of each factor. The minor risk factors (solid nodule, hypoechoic and presence of macrocalcification or egg shell calcification) were giving a score of one. Each nodule was given a total scale score by adding the scores of individual risk factors.

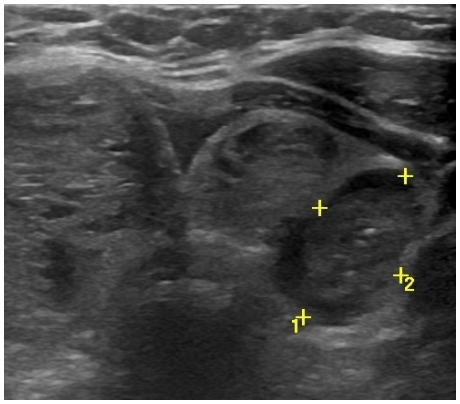

Figure 1: Solid hypoechoic, taller than wider thyroid nodule with microcalcification and partially irregular margins (Score 8). Histopathology, papillary thyroid cancer.

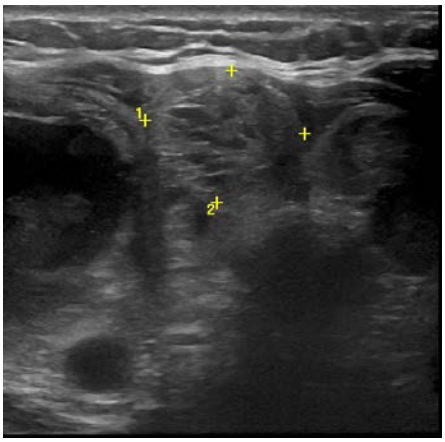

Figure 2: Mixed cystic and solid, isoechoic nodule (score 0). Cytology: Colloid cyst.

Statistical analysis

Data were entered and analysed using the IBM SPSSS, version 20. Data were described using percentages. Percentages were compared using the chi-squared test. The performance of the scale score using the TIRADS scoring system was evaluated using receiver operating characteristic (ROC) analyses. Accuracy of the scale score was assessed by calculating the area under the curve (AUC). The AUC values were classified as: 0.5-0.6 fail, 0.6-0.7 poor, 0.7-0.8 fair, 0.8-0.9 good and 0.9-1.0 excellent. Appropriate cut-off values were defined based on Youden's index (maximum [sensitivity + specificity - 1]). To further judge the ability of the scale score to predict malignancy, the sum was dichotomised based on the established cut-off value and tested for its association with malignancy using binary logistic regression. A p-value <0.05 was considered statistically significant.

Age ranged from 15-85 years and nodule size ranged from 7 mm to 55 mm. The malignancy rate was 20.3% (145 benign nodules and 37 malignant nodules).

Results

This study included a total of 182 patients (150 women and 32 men). Subject age ranged from 15 to 85 years. Nodule size ranged from 7 mm to 55 mm. Of all nodules, 83(45.6%) nodules were on the left lobe, 92 (50.55%) were on the right lobe and 7 (3.85%) on the isthmus.

Microcalcification was detected in 20 (11.0%) nodules, marked hypoechogenicity in 3 (1.6%) nodules, ill-defined margins in 19 (10.4%), taller than wider in 13 (7.1%), and nodules and suspicious lymph nodes in 2 (1.1%) patients. According to the pathology results, 145 patients had benign disease and 37 had malignancy (20.3%). (**Table I)** shows distribution of risk factor summation of each nodule according to pathology results. About one third of patients with benign disease (37.2%) and 5.4% of patients with malignancy had no risk factors (score 0). 19.3% of nodules with score of 2 and higher were benign. All patients with benign disease had five or fewer risk factors. The overall scale score for all patients ranged from 0 to 10, with a mean (SD) of 1.5 (1.9). The mean scale score was significantly much higher in the malignant group compared to the benign group (3.7 vs. 1.0; p<0.005).

Table I: Distribution of risk factor summation according to pathology results.

	Lab results			
Number of risk factors	**Benign**		**Malignant**	
	n	%	n	%
0	54	37.2%	2	5.4%
1	56	38.6%	10	27.0%
2	22	15.2%	6	16.2%
3	7	4.8%	3	8.1%
4	1	0.7%	4	10.8%
5	5	3.4%	3	8.1%
7	0	0.0%	3	8.1%
8	0	0.0%	3	8.1%
9	0	0.0%	2	5.4%
10	0	0.0%	1	2.7%
Total	145	100.0%	37	100.0%

ROC analysis was used to evaluate the predictive ability of the total scale score to predict malignancy. ROC analysis **(Figure 1)** showed that the area under the ROC curve was 0.801 (95% CI: 0.72, 0.88), indicating that the total scale score had good accuracy to predict malignancy. The optimum cut-off value to discriminate between benign and malignant disease was 2. At the established cut-off value, the sensitivity was 0.68 and the specificity was 0.76 **(Table II).** Categorizing the total scale score using this cut-off value was significantly associated with increased odds of malignancy. The odds of having malignancy for patients with 2 or more risk factors was 6.6 times the odds for patients with fewer than 2 risk factors (OR = 6.6; 95% CI: 3.0, 14.3).

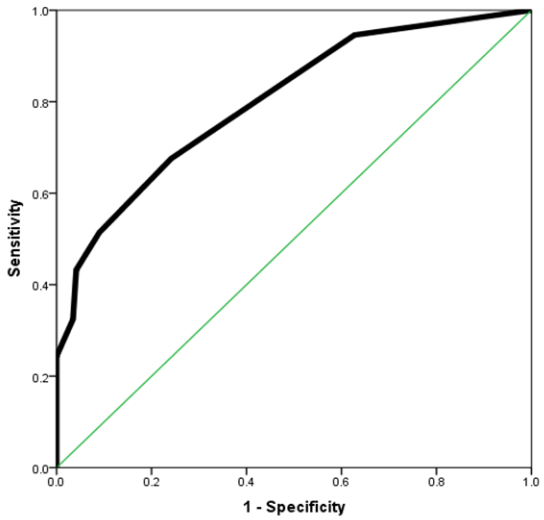

Figure 1: Area under the curve

Table II: The sensitivity and specificity of the sum of risk factors at different cut-off values to predict malignancy

Positive if greater than or equal to	Sensitivity	Specificity
1	0.946	0.372
2	0.676	0.759
3	0.514	0.910
4	0.432	0.959
5	0.324	0.966
6	0.243	1.000
8	0.162	1.000
9	0.081	1.000
10	0.027	1.000

Discussion

As a gold standard to diagnose malignancy, tissue diagnosis and FNA can differentiate most malignant and benign nodules. However, taking a biopsy for every thyroid nodule will impose a huge burden on the health system, as only 5-15% of thyroid nodules are malignant [22]. Ultrasound is cheap, safe, and widely available to evaluate thyroid nodules. There have been many features studied thoroughly in the literature that were shown to be statistically significant in predicting malignancy, such as microcalcification, hypoechogenicity, and markedly hypoechoic nodules, a taller than wider shape, ill-defined margins and extrathyroid extension with the presence of suspicious cervical lymph nodes [1,3,6-10,12-25].

No single feature alone is sensitive and specific enough to predict malignancy because of the complex imaging features of thyroid nodules. Thus, researchers have suggested different combinations and models of these features to predict malignancy accurately or at least to select nodules for FNA without putting a burden on the health system. The first TIRADS system was proposed by Horvath [23], and then Kwak [17] proposed TIRADS based on five ultrasound features. Although it is a simple classification, the features were not weighted, which means that the solid component has the same risk as microcalcification, and the presence of a suspicious lymph node which indicates extrathyroid extension was not included. The revised ATA guidelines in 2015 [25] identified microcalcification, taller than wider and irregular edges as the three most indicative features of malignancy and correlated the size of the nodule with the need to biopsy it.

The American College of Radiology TIRADS (ACR TI-RADS) was published in 2017 [26]. Uniquely, it did not recommend FNA for nodules with benign ultrasound features regardless of their size. The European Thyroid Association presented the EU-TIRADS classification [20] that divides thyroid nodules into five categories depending on the presence or absence of suspicious features (high-risk features: non-oval shape, irregular margins, marked hypoechogenicity, solid nodule and microcalcifications). If a nodule has one of these high-risk features and is 10 mm or more in size, they recommend performing an FNA biopsy. Other features may modulate the risk of malignancy in some category, such as the echogenicity of the solid part in the case of partially cystic nodules.

Zayadeen et al. [21] proposed their TIRADS in 2016 as they compared their classification system with Kwak's in a retrospective study and found that the AUC from fitting the standard binormal model was 0.878 for the Kwak model and 0.906 for the Zayadeen scoring. The difference of -0.028 (standard error = 0.015) was marginally significant using the single reader option of the OR-DBM software ($z = -1.92$; $p > |z| = 0.055$; 95% CI, -0.0572 to 0.0006). This apparent accuracy advantage of the Zayadeen scoring relative to the Kwak scoring may simply reflect that we used a preliminary analysis to develop our scoring method and so overestimated its relative accuracy. However, our scoring still offers an important advantage, i.e. a finer grain to judge malignancy. We applied the Zayadeen TIRADS method in a prospective study to our Jordan population, and it had a good accuracy to discriminate between benign and malignant thyroid nodules.

Conclusion:

The TIRADS classification proposed by Zayadeen et al. has good accuracy to diagnose malignant thyroid nodules warranting FNA, and is expected to improve patient management in a cost-effective way and reduce the number of unnecessary FNA biopsies. In addition, it will improve communication between radiologists and referring physicians, keeping in mind that the decision for FNA biopsy should be based on clinical risk factors and patient agreement in conjunction with the US features of the nodules.

Limitations

Small sample volume in a single institute.

Histopathological confirmation not available for all cytology results

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