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Diagnostic accuracy of fine needle aspiration cytology in comparison with thyroid ultrasound for solitary thyroid nodule taking histopathology as gold standard

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Abstract

Background: Solitary thyroid nodules are a common clinical finding requiring accurate diagnostic differentiation between benign and malignant nodules. Ultrasound plays an important role in initial assessment, while fine needle aspiration cytology (FNAC) provides cytological confirmation. This study compared the diagnostic efficacy of the ultrasound-based Thyroid Imaging Reporting and Data System (TIRADS) and FNAC, using histopathology as the gold standard.

Methods: This prospective, cross-sectional study was conducted over 12 months from September 2023 to August 2024 on 70 patients with solitary thyroid nodules at the Department of Pathology, Lahore General Hospital, Lahore. Each participant underwent ultrasound and FNAC, with results compared with final histopathological findings. Diagnostic metrics, ROC curves, cross-tabulations, logistic regression, and concordance analysis were used for evaluation.

Results: Out of 70 patients, 19 cases were malignant and 51 were benign. ROC curve analysis revealed superior diagnostic performance of FNAC (AUC=0.856) compared to TIRADS (AUC=0.605). FNAC demonstrated higher sensitivity (78.95%), specificity (92.16%), and overall accuracy (88.57%). TIRADS showed high specificity (100%) but low sensitivity (21.05%). Chi-square tests confirmed significant associations of both methods with histopathology (TIRADS p=0.0052 and

Bethesda p<0.001), with FNAC showing a stronger correlation. Logistic regression confirmed FNAC as the only independent predictor of malignancy. There is significant concordance between TIRADS and the Bethesda classification system, with a kappa value of 0.298 and p-value <0.001.
Conclusion: FNAC via the Bethesda system is a significantly more reliable diagnostic tool than ultrasound-based TIRADS for solitary thyroid nodules.

Introduction

Solitary thyroid nodules are very common in clinical practice, with an incidence of 4-7% among populations of 10-18 million people and a prevalence estimated between 20 to 76% on ultrasonography and 8-65% in autopsy findings [1,2]. The underlying etiology of thyroid nodules is diverse and includes iodine deficiency, autoimmune diseases like Hashimoto's thyroiditis, and benign or malignant neoplasms. The majority of the thyroid nodule are non neoplastic and the incidence of thyroid malignancy is noted to be 5.4% for men and 6.5% for women, with only a small proportion of nodules being cancerous [2].

FNAC is recognized as a simple, cost-effective, and gold standard technique for diagnosing thyroid malignancies. It is considered a crucial secondary diagnostic step following initial assessment with ultrasonography [3]. The 2023 Bethesda System for Reporting Thyroid Cytopathology recommends 06 reporting categories: (i) non-diagnostic; (ii) benign; (iii) atypia of undetermined significance (AUS); (iv) follicular neoplasm; (v) suspicious for malignancy (SFM) & (vi) malignant [2].

FNAC is an economical procedure, provides a cytological diagnosis of nodules and supports decision-making in patient management, thereby reducing unnecessary surgery. [4,5]

USG is a non-invasive imaging technique using sound waves, useful for diagnosing and monitoring medical conditions, including the evaluation of thyroid nodules. It allows the detailed assessment of nodules, examining their size, shape, and internal characteristics, such as their composition (solid, cystic, or mixed), echogenicity (hypoechoic, isoechoic, hyperechoic), margins, shape, and the presence of calcifications [6]

Nodules can be benign or malignant. According to some research, less than 10% of thyroid nodules are cancerous, while nodules are found in up to 50-67% of the population [7].

Various TIRADS classifications have been developed, such as the American College of Radiology-TIRADS (ACR-TIRADS), Kwak-TIRADS, and EU-TIRADS, which categorize nodules based on suspicious ultrasound features as echogenicity, margins, shape, and calcifications [8]. TIRADS scores 1 and 2 lesions are considered benign, while TIRADS scores 3, 4, and 5 require further evaluation through fine needle aspiration cytology [9].

This study aimed to compare the diagnostic accuracy of FNAC and ultrasound for solitary thyroid nodules using histopathology as the gold standard.

Materials and Methods:

Study Design, and Setting

This prospective, cross-sectional study was conducted at the Department of Pathology, Lahore General Hospital, Lahore. The study was conducted over a period of 12 months, from September 2023 to August 2024. In this study, 70 patients with thyroid nodules had a complete history and clinical examination.

Inclusion criteria:

Patients of all ages and gender
Adults with a solitary thyroid nodule, detected either clinically or incidentally.

Exclusion criteria:
Patients with Recurrent solitary thyroid
Adults with thyroidectomy diagnosed with non-thyroid follicular cells associated pathology.
Patients with metastatic thyroid disease
Patients with coagulopathy

Study Procedures:
This prospective, cross-sectional study was conducted at the Department of Pathology, Lahore General Hospital, Lahore. The study was conducted over a period of 12 months, from September 2023 to August 2024. In this study, patients were diagnosed clinically and ultrasound examination was performed. The TIRADS technique had been used to classify thyroid lesions into five different categories. Ultrasound classification was performed according to the American College of Radiology (ACR) TIRADS guidelines to stratify nodules into five risk categories based on their radiological characteristics, including composition, echogenicity, shape, borders, and the presence of echogenic foci or calcifications [8].The radiological characteristics of the thyroid nodule include its composition, echogenicity, shape in the transverse plane, borders, and the presence of echogenic foci with identified calcifications [8]. TIRADS scores of 4 and 5 were classified as indicative of malignancy, while scores of 1-3 were classified as not indicative of malignancy. All patients additionally underwent FNAC. The procedure was performed using a 23-25 gauge needle attached to a 10 mL syringe. Multiple passes were made through the nodule to ensure adequate sampling. Smears were then prepared on glass slides, fixed, and stained with Hematoxylin and Eosin (H&E) stains for cytological assessment. The thyroid lesions were classified in accordance with the six categories of the Bethesda system. The categories are as follows: Bethesda I is non diagnostic; Bethesda II is benign; Bethesda III is atypia of undetermined significance or follicular lesion of undetermined significance; Bethesda IV is follicular neoplasm or suspicious for follicular neoplasm; Bethesda V is suspicious for malignancy; and Bethesda VI is malignant. Surgical specimens obtained from total or hemi-thyroidectomy were fixed in 10% buffered formalin. Representative sections were processed through standard paraffin embedding, sectioned at 4-5 micrometers, and stained with Hematoxylin and Eosin (H&E) for microscopic examination by a certified pathologist. The results of the FNAC and ultrasound scan tests were then compared with the final histopathological diagnosis.
Ethical considerations Following approval by the research ethics committee of the Lahore General Hospital, reference number 00-144-S-2023, dated 08 May 2023. Written informed consent was obtained from all participants prior to their inclusion in the study, and the confidentiality of each participant's information was guaranteed.

DATA ANALYSIS:
The collected DATA were analyzed by the statistical package for the social sciences software program, IBM SPSS Statistics for Windows, version 27 (Armonk, IBM Corp., New York, USA). Categorical data were presented as frequency and percentage, while numerical data were initially verified for normality using the Shapiro-Wilk test and were expressed as means and standard deviation. Furthermore, receiver operating characteristics (ROC) curve analysis was applied to determine the best cutoff and the discrimination power of TIRADS and Bethesda scoring systems for diagnosing malignant thyroid nodules, considering histopathologic diagnosis after surgery as the gold standard. Then, the associations of TIRADS and Bethesda with histopathologic diagnosis of malignant thyroid nodules were performed by Pearson's $\chi 2$ test, and the diagnostic accuracy indices of each classification system were calculated. They included sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios with their 95%

confidence intervals. Finally, concordance between TIRADS and Bethesda classification systems was done by Cohen's weighted kappa statistics. A *p*-value of ≤ 0.05 was considered statistically significant

Results:

This study included 70 patients with solitary thyroid nodules. The mean age of the participants was 38.4 ± 11.2 years, with ages ranging from 16 to 65 years. The majority of patients belonged to the 30-39 year age group (30.0%), followed by the 40-49 year age group (22.9%). A detailed breakdown of the age distribution is as follows: 16-29 years (21.4%), 30-39 years (30.0%), 40-49 years (22.9%), and ≥50 years (25.7%). Histopathology confirmed 19 cases (27.1%) as malignant and 51 cases (72.9%) as benign. TIRADS scoring for all patients included TIRADS 1(4,5.6%), TIRADS 2(50,70.4%), TIRADS3(12,16.9%), TIRADS 4(4,5.6%). Bethesda classification of FNAC of nodules revealed Bethesda II in 51 cases (72.9%), Bethesda III in 1 case (1.4%), Bethesda IV in 11 cases (15.7%), Bethesda V in 4 cases (5.7%), Bethesda VI in 3 cases (4.3%) and Bethesda I in 0 cases.

ROC curve analysis revealed that the TIRADS classification system at cut of more than 3 showed low to moderate discrimination between malignant and benign nodules (AUC: 0.605). Alternatively, the diagnostic performance of Bethesda outperforms TIRADS significantly. At a cut off more than II, Bethesda showed significant power of diagnosis of malignant nodules (AUC: 0.856).

TIRADS shows low sensitivity (21.05%) compared with Bethesda (78.95%), whereas true negative and specificity were higher in TIRADS (0.79,100%) than in Bethesda (0.23, 92.16%). The overall accuracy of Bethesda (88.57%) was higher compared with TIRADS (78.57%) (Table 2).

Chi-square testing confirmed a significant association between TIRADS and histopathological diagnosis (p=0.0052) and between Bethesda classification and histopathological diagnosis (p<0.001). (Table 3). Demonstrates the binary logistic regression models were constructed to assess predictive power. TIRADS only model failed to converge meaningful (OR unstable,p=0.999, R^2 0.086) (Table 4). Bethesda only model significantly predicted

malignancy (OR=3.79, 95% CI 2.28-5.29, p<0.001, R^2=0.264). In combined model, Bethesda remains significant (OR=3.48, p<0.001). TIRADS added no value, overall model R^2=0.281. This confirms Bethesda is strong independent predictor of malignancy whereas TIRADS offered limited diagnostic value in isolation. Significant concordance between TIRADS and Bethesda classification system with kappa value 0.298 and p <0.001.

Figure 1 displays the Receiver Operating Characteristic (ROC) curve analysis comparing the diagnostic performance of the TIRADS classification and the Bethesda system for detecting malignancy. The Area Under the Curve (AUC) for the Bethesda system (blue line) is 0.856, which is substantially higher than the AUC for TIRADS (red line) at 0.605. The Bethesda curve's position closer to the top-left corner indicates a superior balance of sensitivity and specificity. This analysis demonstrates that the Bethesda system is a significantly more accurate and reliable predictor of malignancy in solitary thyroid nodules compared to the TIRADS classification. The cohort included 70 patients with a mean age of 38.4 ± 11.2 years (range 16-65 years). Histopathology identified 19 malignant (27.1%) and 51 benign (72.9%) cases. TIRADS 2 was the most frequent ultrasound category (70.4%), while Bethesda II was the most frequent FNAC category (72.9%). TIRADS and Bethesda showed significant but fair concordance (weighted kappa = 0.298, p<0.001). Most TIRADS 2 cases corresponded to Bethesda II, whereas higher TIRADS categories included more Bethesda IV-VI cases.

Participants ranged from 16 to 65 years, with a mean age of 38.4 ± 11.2 years. The largest age group was 30-39 years (30.0%), followed by >=50 years (25.7%), 40-49 years (22.9%), and 16-29 years (21.4%).

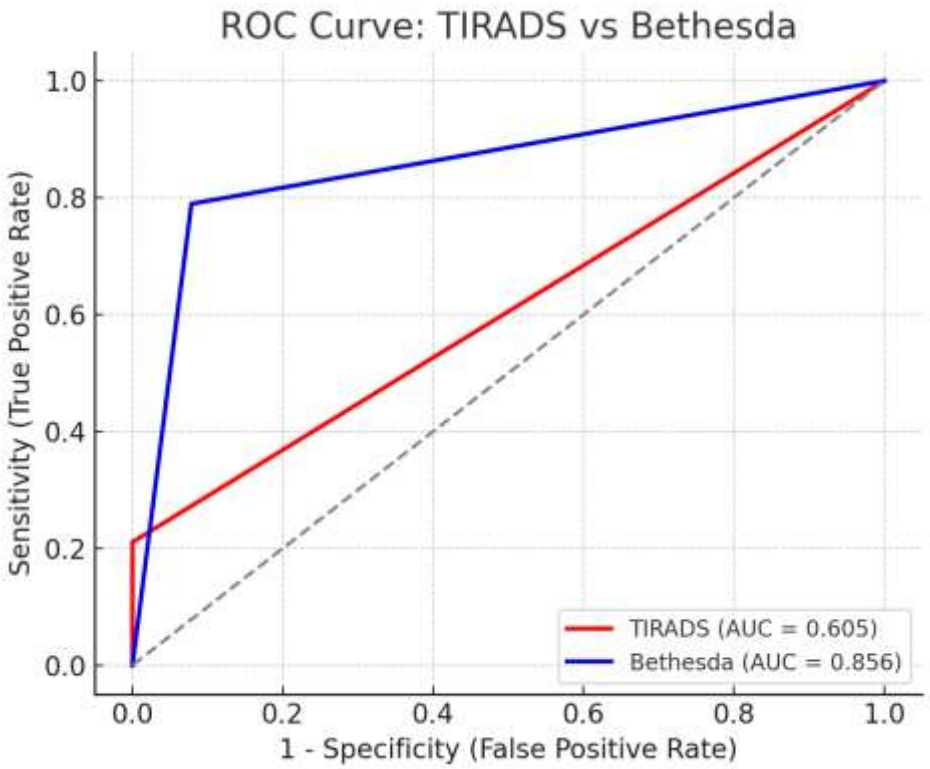

Figure 1: ROC Curve Analysis.

Table 2: Diagnostic Accuracy Metrics

Model	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio	Accuracy
TIRADS > 3	21.05%	100.0%	100.0%	77.27%	infinity	0.79	78.57%
Bethesda > II	78.95%	92.16%	78.95%	92.16%	10.07	0.23	88.57%

Table 3: Chi-square Test Results

Comparison	Chi-square	p-value
TIRADS vs Histopathology	5.678	0.0052
Bethesda vs Histopathology	28.661	<0.001

Table 4: Logistic Regression Summary

Model	OR (Bethesda)	95% CI	p-value	Nagelkerke R^2
TIRADS only	Unstable	Wide CI	0.999	0.086
Bethesda only	3.79	[2.28, 5.29]	< 0.001	0.264
Combined	3.48	[1.94, 5.01]	< 0.001	0.281

Discussion:

Ultrasound is the most commonly used procedure for the assessment of the thyroid nodule[4]. FNAC is a simple, cost-effective, and popular procedure for the diagnosis of thyroid cancer. It is recommended as the first line of investigation for the diagnosis of thyroid lesions [3].

The objective of this study was to compare the diagnostic accuracy of FNAC and ultrasound for solitary thyroid nodules using histopathology as the gold standard.

The study included 70 patients, and the study results revealed that 19 patients were pathologically diagnosed as malignant and 51 patients were diagnosed as benign. The findings are consistent with several international studies conducted by Sikander et al where on histopathological examination diagnosis 98(61.3%) were benign and 62(38.8%) were malignant[3] and a study by Moin et al also revealed 51.5% patients as benign and 48.5% as malignant[4].

In this study, the most prevalent category was TIRADS category II. However, in a study conducted by Osama et al [1] and Gilan et al [4], the most prevalent category was TIRADS III. This discrepancy may have occurred due to a larger sample size and technical aspects. Bethesda category II was the most prevalent, with a reported percentage of 70.4%. Similarly, in the study conducted by Osama et al [1], Bethesda II was prevalent.

ROC curve analysis revealed that the Bethesda classification system exhibited notable capacity to differentiate between malignant and benign nodules, where the cut-off value was greater than II. At a cut-off value greater than 3, TIRADS classification exhibited notable capacity for accurately diagnosing malignant nodules. In the study conducted by Osama et al[1], ROC curve analysis reveals AUC for TIRADS was 0.842 and Bethesda AUC was 0.784. Another study conducted by Boudina Maria [2] revealed AUC for TIRADS was 88% and Bethesda AUC was 68.3%. our results are not in concordance with the other studies due to sample size and other technical variabilities.

The results show that FNAC is a reliable method for diagnosing malignant cases, with Bethesda showing superior performance in terms of true positive rates and sensitivity compared with the TIRADS. Conversely, true negative rates and specificity were more favorable for TIRADS. The overall accuracy of Bethesda was higher than TIRADS system. Numerous studies [1,3,7,10] have demonstrated that Bethesda has higher sensitivity and accuracy. In terms of diagnostic accuracy metrics, our study found FNAC to have a high sensitivity (78.95%), specificity (92.16%), and accuracy (88.57%). This supports the conclusion from Refaie et al. that Bethesda's overall accuracy (78.5%) is slightly higher than that of TIRADS. Our results are also in line with the high-performance metrics for FNAC reported by Elgammal et al. (sensitivity 93%, specificity 98%, accuracy 96.6%). In contrast, the study by Sikander et al. reported an outlier low sensitivity of 4.84% for FNAC, though its specificity remained high at 97.96%. [1,3,7]. Our results revealed that TIRADS has a notably low sensitivity (21%), indicating its limited ability to correctly identify malignant cases. The lower overall accuracy of TIRADS in our study (78.57%) compared to Elgammal et al. (88.2%) but similar to Refaie et al. (76.0%) further underscores this limitation. [1,3,7]

Limitations:

The limitations of this study include a relatively small sample size and a single-centre design, which may limit the generalizability of the findings. Additionally, interobserver variability in interpreting TIRADS and Bethesda categories was not assessed, which could influence diagnostic accuracy in practice.

Conclusion:
Our study highlights the diagnostic challenges associated with solitary thyroid nodules. The Bethesda system showed higher diagnostic accuracy, sensitivity and positive predictive value for malignancy when compared with TIRADS. Integration of ultrasound with FNAC may enhance diagnostic precision, but should not replace cytological confirmation. Further, multivariate studies with a large cohort are recommended to validate these findings and optimize diagnostic protocols.

Conflict-of-interest statement:
All authors declared no conflict of interest exists.

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AA: Formal analysis, abstract preparation, critical review, and data analysis.
AAS: Investigation, data curation, writing-original draft, introduction, and references
RB: Supervision, methodology, formal analysis, abstract preparation, critical review, and data analysis.
HS: Supervision, methodology, formal analysis, abstract preparation, critical review, and data analysis.
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The authors verified all scientific content, data, analysis, references, and conclusions and remain fully accountable for the integrity and accuracy of the work.

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