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Ultrasonographic Features in Recognition of Malignant Thyroid Nodule with Fine Needle Aspiration Cytology as the Gold Standard

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ABSTRACT

A thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding tissue. The diagnosis of these nodules is a common clinical procedure globally. **Objectives:** To determine the sensitivity, specificity, and predictive values of ultrasound for identifying malignant thyroid nodules, using fine-needle aspiration cytology (FNAC) as the gold standard. **Methods:** In this cross-sectional study, 209 consecutive patients with suspected thyroid nodules were enrolled after providing written consent. Each participant underwent a cervical ultrasound performed by an experienced radiologist, which was followed by an FNAC. The Bethesda System was used for the cytological diagnosis. The diagnostic performance of ultrasound was calculated against the FNAC results, and data were analyzed using SPSS version 26.0. **Results:** The mean age of the 209 patients was 43.58 ± 9.87 years. Using FNAC as the gold standard, ultrasound demonstrated a diagnostic accuracy of 88.04%. The sensitivity was 86.3%, the specificity was 89.7%, the positive predictive value (PPV) was 88.89%, and the negative predictive value (NPV) was 87.27%. **Conclusions:** The study concludes that ultrasound characteristics are a highly sensitive and accurate method for identifying malignant thyroid nodules, with an overall diagnostic accuracy of 88.04%.

INTRODUCTION

Thyroid nodules, defined as focal lesions within the thyroid gland that are sonographically distinct from surrounding parenchyma, are diagnosed frequently throughout the world [1]. The lifetime risk of developing a palpable nodule is 5-10%; however, due to the ubiquitous high-resolution imaging, this number has had significant growth [2]. The large majority (>90%) of these nodules, however, are benign, but the main clinical challenge remains to distinguish between benign and malignant (7-15% of cases) [3]. Initial assessment of a thyroid nodule combines history and physical examination with diagnostic studies. Clinical history and the physical examination are important for risk stratification, with male sex, history of childhood neck irradiation, a family history of thyroid carcinoma, along with the presence of firm or fixed mass or lymphadenopathy, which increases such suspicion [4]. The single most valuable laboratory test to perform initially is a sensitive assay for TSH. In current diagnostic algorithms, ultrasonography represents the mainstay of the initial investigation because it is safe, cost-effective, and available in virtually all institutions [5]. It is important information regarding

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nodular characteristics and directs further management [6, 7]. Nevertheless, ultrasonography has operator dependency and its accuracy is not conclusive for cancer diagnosis [5]. A study reported the US's sensitivity (89%) and specificity (93%) in the diagnosis of malignant nodules, with a positive predictive value of 65.5% for US compared to FNAC [8]. The gold standard to diagnose these is still FNAC, which may be the most specific and sensitive method for detecting doubtful lesions that in many cases must be approached surgically [9, 10]. It is important because these benign diagnoses are going to spare many surgeries without indication [11]. However, FNAC is invasive and more time-consuming, and more costly than an ultrasound examination for the aspiration due to laboratory technicians' support cost; therefore, it was important to clearly what the role of ultrasonography is in screening and triage [12]. The most important initial laboratory test is a sensitive thyroid-stimulating hormone (TSH) assay. For a single nodule with normal TSH, no further tests are routinely needed unless autoimmune disease is suspected. Surgeon-performed ultrasound has been shown to significantly impact surgical planning, with one study finding it changed management for 17.6% of patients, for example, by identifying previously missed malignant lymph nodes [13–15]. Advanced imaging, like CT or MRI are not a first-line investigation due to cost. A study by Bakkar et al. suggests that nodules ≥3 cm diagnosed as benign on FNAC may still harbor malignancy, with a reported cancer risk of 22.8% in their cohort [16].

This study fills in a gap in the literature, given that many investigations were small samples and showed no firm conclusions. Through a comprehensive assessment, we hope to offer insight into which detected ILL features may help in the coordination of diagnosis and treatment of thyroid nodules.This study aimed to assess the diagnostic value of ultrasonography as a tool for detecting cancerous thyroid nodules in relation to FNAC, also in terms of common metabolic factors, recognizing that metabolic syndrome components such as hypertension and dyslipidemia may influence tissue vascularity and echogenicity.

METHODS

This descriptive cross-sectional study was conducted in the Department of Radiology, Bolan Medical College/ Hospital, Quetta, Balochistan, via a non-probability consecutive sampling technique. In this study, a total of 209 patients fulfilling the inclusion criteria were enrolled and referred from the surgical Department to the Radiology for ultrasound assessment, followed by cytology at Bolan Medical Complex Hospital, Quetta. Permission was taken from the hospital with CPSP no: CPSP/REU/RAD-2020-001-3096. The duration of this study was from November 2022 to April 2023. For the study, the sample size is calculated by using a sensitivity specificity calculator with a confidence level (1-a) was considered as 95%, with a desired precision (d) of 0.07, expected sensitivity (89% specificity (93%) with an approximate population estimation of 36.9 % taken from the parent study [3, 8]. For all the values entered, the calculated sample size was 209. The inclusion criteria included any individual aged between 25 and 60-years having evidence of a suspected thyroid nodule of either gender. All patients with multinodular goiter, any patient having a history of either hypothyroidism or hyperthyroidism, and any patient with known bleeding diathesis were excluded from the study. All the included patients underwent a detailed history and clinical examination by the surgery team before being sent to the Department of Radiology. Proformas were filled out for all those patients who had given written consent to be included in the study. The first serum TSH assessment was performed along with scintigraphy when a functional nodule was confirmed. Thereafter, all individuals with thyroid nodule undergone ultrasound assessment followed by cytology. Cervical ultrasound scanning was performed by a qualified Consultant Radiologist, who possessed at least more than 15 years' experience in ultrasound scanning of the thyroid. The criteria for the identification of ultrasound features indicative of thyroid malignancies were developed based on the findings of Lew et al parameters The Bethesda System for reporting thyroid cytopathology was used for diagnosis of the FNAC procedure [7]. FNAC was done without local Anesthesia in a few of our patient we used 23 and in a few others 24 needle in a few others. Smears were fixed using 95% alcohol solution, or staining was done using hematoxylin and eosin stain. The study used the Bethesda System for reporting thyroid cytopathology, in which there are six main diagnostic groups, in which Thy-5 and Thy-6 were considered as malignant. Above-mentioned information, such as height, age, gender, weight, BMI, nodule size, ultrasound, and cytology reports, was recorded and noted down in a pre-designed proforma. In addition to core demographic and nodule characteristics, baseline systolic/diastolic blood pressure and serum cholesterol levels were recorded. These variables were included in a secondary, exploratory analysis to assess their potential influence on the sonographic appearance and diagnostic classification of thyroid nodules. The Exclusion criteria were followed strictly to manage effect modifiers and bias in study outcomes. Data were entered and analyzed using SPSS version 26.0. Mean value and standard deviation or Median IQR for non-normal data were calculated for quantitative variables like height, age, BMI, and weight. Normality of data was assessed by using the Shapiro-Wilk test.

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RESULTS

209 patients were selected for this study. Patients' mean age was 43.58 ± 9.87 years. The mean systolic BP was 125.37 ± 8.69 mmHg. The mean diastolic BP was 77.86 ± 7.71 mmHg. The mean weight recorded was 75.49 ± 8.33 kg. The mean height recorded was 1.65 ± 0.03 meters. The mean BMI was 27.56 ± 3.34 kg/m^2, and the mean serum cholesterol level was 161.20 ± 17.27 mg (Table 1).

Table 1: Baseline Characteristics of the Study Population (n=209)

Variables	Mean ± SD
Age (Years)	43.58 ± 9.870
Systolic BP (mmHg)	125.37 ± 8.691
Diastolic BP (mmHg)	77.86 ± 7.710
Weight (kg)	75.4 ± 8.333
Height (meter)	1.6563 ± .03788
BMI	27.5676 ± 3.34202
Gender (Female)	0.551 ± 0.497
Serum Cholesterol (mg)	161.20 ± 17.274

According to age distribution, there were 55 (26.3%) patients between the age group of 25 to 35 years, 61% patients were in the age group of 36 to 45 years, and 93 (44.5%) patients were in the age group of 46 to 60 years (Figure 1).

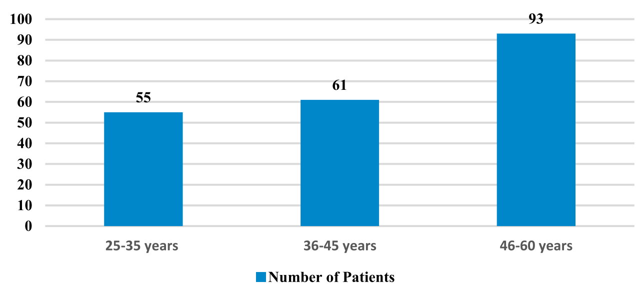

Figure 1: Age Distribution of the Patient Population

In our research, the frequency of female patients was 120 (57.4%), and the frequency of male patients was 89 (42.6%) (Figure 2).

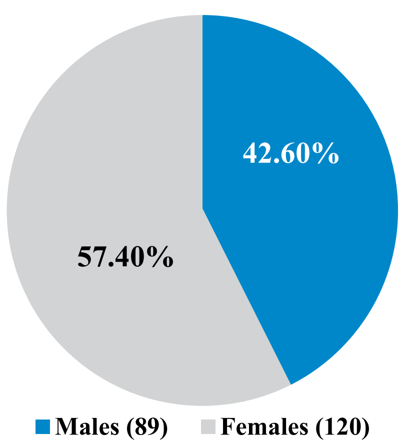

Figure 2: Distribution of Patients Based on Gender

Regarding the size of the nodule, 119 (56.9%) patients had a size of nodule <2mm while 90 (43.1%) patients had a size of nodule ≥ 2 mm (Figure 3).

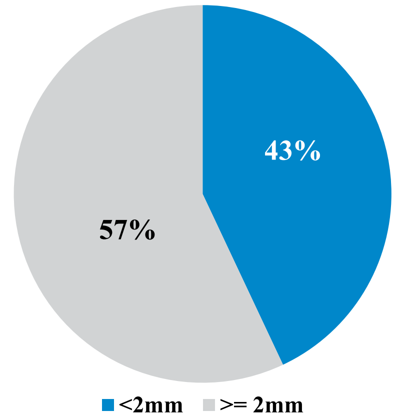

Figure 3: Distribution of Thyroid Nodules by Size

According to the BMI distribution, 54 (25.8%) patients had a BMI between 20 and 24.9 kg/m^2, 107 (51.2%) had a BMI between 25 and 29.9 kg/m^2, and 48 (23%) had a BMI ≥ 30 kg/m^2 (Figure 4).

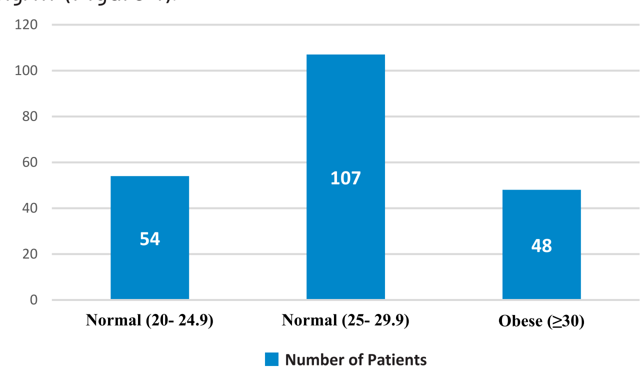

Figure 4: BMI Distribution of Patients

Among the FNAC results, 88 (86.3%) patients were True Positives (TP), 11 (10.3%) patients were False Positives (FP), and among the negative FNAC results, 14 (13.7%) were False Negatives (FN), and 96 (89.7%) were True Negatives (TN). This shows sensitivity: 86.3%, Specificity: 89.7%, PPV: 88.89%, NPV: 87.27%, and diagnostic accuracy: 88.04% (Figure 5).

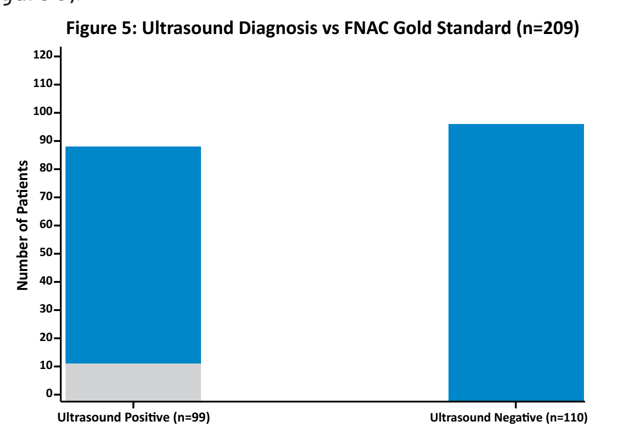

Figure 5: Ultrasound Diagnosis vs FNAC Gold Standard (n=209)

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By using FNAC, the diagnostic performance of ultrasound stratified by age group, like 25 to 35 years, 36-45 years, and 46 to 60 years, and gender, like male and female (Table 2).

Table 2: Diagnostic Performance of Ultrasound Stratified by Age Group and Gender, Using FNAC as the Gold Standard

Characteristics			FNAC		Total	p-value
			Positive	Negative		
Age						
25 to 35 years	Ultrasound Characteristics	Positive	25 (80.6%)	0 (0.0%)	25 (45.5%)	<0.001
		Negative	6 (19.4%)	24 (100.0%)	30 (54.5%)	
	Total		31 (100.0%)	24 (100.0%)	55 (100.0%)	
36 to 45 years	Ultrasound Characteristics	Positive	30 (88.2%)	1 (3.7%)	31 (50.8%)	<0.001
		Negative	4 (11.8%)	26 (96.3%)	30 (49.2%)	
	Total		34 (100.0%)	27 (100.0%)	61 (100.0%)	
46 to 60 years	Ultrasound Characteristics	Positive	33 (89.2%)	10 (17.9%)	43 (46.2%)	<0.001
		Negative	4 (10.8%)	46 (82.1%)	50 (53.8%)	
	Total		37 (100.0%)	56 (100.0%)	93 (100.0%)	
Gender						
Male	Ultrasound Characteristics	Positive	42 (91.3%)	7 (16.3%)	49 (55.1%)	<0.001
		Negative	4 (8.7%)	36 (83.7%)	40 (44.9%)	
	Total		46 (100.0%)	43 (100.0%)	89 (100.0%)	
Female	Ultrasound Characteristics	Positive	46 (82.1%)	4 (6.2%)	50 (41.7%)	<0.001
		Negative	10 (17.9%)	60 (93.8%)	70 (58.3%)	
	Total		56 (100.0%)	64 (100.0%)	120 (100.0%)	

The diagnostic accuracy of ultrasonography in identifying and characterizing the cancerous thyroid nodule, taking FNAC (fine needle aspiration cytology) as gold standard, was 88.04% with a sensitivity 86.3%, a specificity 89.7%, a PPV 88.89%, and an NPV 87.27% (Table 3).

Table 3: Diagnostic Performance of Ultrasound Stratified by Nodule Size (<2 mm vs. ≥2 mm), Using FNAC as the Gold Standard

Nodule Size			FNAC		Total	p-value
			Positive	Negative		
< 2 mm	Ultrasound Characteristics	Positive	54 (90.0%)	7 (11.9%)	61 (51.3%)	<0.001
		Negative	6 (10.0%)	52 (88.1%)	58 (48.7%)	
	Total		60 (100.0%)	59 (100.0%)	119 (100.0%)	
> = 2 mm	Ultrasound Characteristics	Positive	34 (81.0%)	4 (8.3%)	38 (42.2%)	<0.001
		Negative	8 (19.0%)	44 (91.7%)	52 (57.8%)	
	Total		42 (100.0%)	48 (100.0%)	90 (100.0%)	

The comparison of ultrasound findings with FNAC results, stratified by systolic (≤130 mmHg vs. >130 mmHg) and diastolic (≤80 mmHg vs. >80 mmHg) blood pressure groups. Ultrasound demonstrated consistently high diagnostic accuracy across all BP categories, with sensitivity ranging from 78.7% to 92.7% and specificity from 88.9% to 90.3%. The statistically significant p-values (0.0001) indicate that ultrasound performance is reliable irrespective of the patient's blood pressure (Table 4).

Table 4: Diagnostic Performance of Ultrasound Stratified by Blood Pressure Categories, Using FNAC as the Gold Standard

Characteristics			FNAC		Total	p-value
			Positive	Negative		
Systolic Distribution						
110 to 130 mmHg	Ultrasound Characteristics	Positive	62 (86.1%)	7 (10.0%)	69 (48.6%)	<0.001
		Negative	10 (13.9%)	63 (90.0%)	73 (51.4%)	
	Total		72 (100.0%)	70 (100.0%)	142 (100.0%)	
> 130 mmHg	Ultrasound Characteristics	Positive	26 (86.7%)	4 (10.8%)	30 (44.8%)	<0.001
		Negative	4 (13.3%)	33 (89.2%)	37 (55.2%)	
	Total		72 (100.0%)	70 (100.0%)	142 (100.0%)	
Diastolic Groups						
65 to 80 mmHg	Ultrasound Characteristics	Positive	0.0001 (92.7%)	6 (9.7%)	57 (48.7%)	<0.001
		Negative	4 (7.3%)	56 (90.3%)	60 (51.3%)	
	Total		55 (100.0%)	62 (100.0%)	117 (100.0%)	

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> 80 mmHg	Ultrasound Characteristics	Positive	0.0001 (78.7%)	5 (11.1%)	42 (45.7%)	<0.001
		Negative	10 (21.3%)	40 (88.9%)	50 (54.3%)	
	Total		47 (100.0%)	45 (100.0%)	92 (100.0%)	

Results evaluate ultrasound performance against FNAC when stratified by BMI categories (normal, overweight, obese) and serum cholesterol levels (≤150 mg vs. >150 mg). Ultrasound maintained high sensitivity (82.9%-93.8%) and specificity (85.2%-95.8%) across all subgroups. The consistently significant p-values (0.0001) confirm that diagnostic accuracy remains robust across varying BMI and cholesterol levels (Table 5).

Table 5: Diagnostic Performance of Ultrasound Stratified by BMI Categories and Serum Cholesterol Levels, Using FNAC as the Gold Standard

Characteristics			FNAC		Total	p-value
			Positive	Negative		
BMI Distribution						
20 to 24.9 kg/m^2	Ultrasound Characteristics	Positive	23 (85.2%)	4 (14.8%)	27 (50.0%)	<0.001
		Negative	4 (14.8%)	23 (85.2%)	27 (50.0%)	
	Total		27 (100.0%)	27 (100.0%)	54 (100.0%)	
25 to 29.9 kg/m^2	Ultrasound Characteristics	Positive	45 (88.2%)	6 (10.7%)	51 (47.7%)	<0.001
		Negative	6 (11.8%)	50 (89.3%)	56 (52.3%)	
	Total		51 (100.0%)	56 (100.0%)	107 (100.0%)	
>= 30 kg/m^2	Ultrasound Characteristics	Positive	20 (83.3%)	1 (4.2%)	21 (43.8%)	<0.001
		Negative	4 (16.7%)	23 (95.8%)	27 (56.2%)	
	Total		24 (100.0%)	24 (100.0%)	48 (100.0%)	
Serum Cholesterol						
130 to 150 mg	Ultrasound Characteristics	Positive	30 (93.8%)	4 (11.8%)	34 (51.5%)	<0.001
		Negative	2 (6.2%)	30 (88.2%)	32 (48.5%)	
	Total		32 (100.0%)	34 (100.0%)	66 (100.0%)	
> 150 mg	Ultrasound Characteristics	Positive	58 (82.9%)	7 (9.6%)	65 (45.5%)	<0.001
		Negative	12 (17.1%)	66 (90.4%)	78 (54.5%)	
	Total		70 (100.0%)	73 (100.0%)	143 (100.0%)	

DISCUSSION

The usage of ultrasonography is increasing in identifying thyroid nodules, which are a common finding in most of the general population (US). About 50% of people over 40 have thyroid nodularity, which can range in prevalence from 19% to 67% and worsens with age [17]. The need to rule out thyroid cancer, which is found in 5–15% of cases based on sex, age, and history of other risk factors for exposure, is the clinical importance of thyroid nodules [18]. Small papillary thyroid tumors, the most indolent type of thyroid cancer, are primarily responsible for the almost fivefold increase in thyroid cancer incidence during the last 50 years [19]. Hypoechogenicity, Microcalcifications, enhanced intranodular vascularity, absence of a halo, nodular form, and uneven edges are some ultrasonography indicators that have historically been connected with an increased risk of cancer. To diagnose cancer, none of these traits, taken alone, appears to be sufficiently trustworthy. Elastography, an Ultrasound technique, has lately been proposed as a method to identify thyroid nodules that are malignant [20]. This method had a 92% sensitivity and 90% specificity according to a meta-analysis. But only a few studies were included, and only three used histology of the surgical specimens for definite diagnosis. The method for identifying malignant nodules that is thought to be the most accurate is a fine-needle aspiration (FNA) biopsy [21]. It would be very laborious to do biopsies on every patient with a thyroid nodule, and FNA findings do bear some limitations. The suspicious signs are vague and ambiguous and usually encompass individuals with thyroid cancer in their families, those with significant radiation exposure, or those who have several worrisome ultrasound characteristics. The likelihood of the ultrasound characteristics linked to cancer and which combination would be more clinically effective are unknown, though. For patients with inadequate FNA specimens for diagnosis (10%) or if the specimens are inconclusive (15–30%), the latter of which carries a 20–30% malignancy risk, ultrasound characteristics may also be helpful in clinical decision making [22]. Sensitivity ranges from 26% to 87%, and specificities range from 40% to 93%, according to a recent meta-analysis examining the accuracy of ultrasound to predict malignancy in thyroid nodules. The highest diagnostic odds ratio (OR) for cancer was observed in this investigation for shapes that were taller than wide [23]. The studies included in that meta-analysis, however, used cytology rather than histology to determine the final diagnosis for benign nodules.

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Additionally, it did not assess how well elastography predicts cancer. Furthermore, the likelihood ratio of ultrasound features linked to malignancy was not described. Besides sensitivity and specificity, the probability ratio would provide further information and data that could be utilized in thyroid nodules in the clinical decision-making process [24]. Despite the advantages of ultrasonic imaging that have been highlighted, there is inconclusive information about its ability to predict thyroid cancer. Therefore, it is necessary to compare the ultrasound scanning's diagnostic accuracy to the outcomes of a gold standard test. The best, most trustworthy, and low-cost method for determining the identity of thyroid nodules is fine needle aspiration cytology (FNAC) [25]. Thyroid nodules are a frequent clinical presentation to surgical clinics; as a result, a patient's treatment will be greatly impacted by an accurate identification of any probable malignancy. In light of this, it's critical to make the best use of ultrasound imaging tools, particularly when determining which instances call for urgent surgical procedures[26]. The diagnostic accuracy of ultrasonography in identifying and characterizing the cancerous thyroid nodule, taking gold standard FNAC (fine needle aspiration cytology) as reference in our study, was 88.04% with a sensitivity 86.3%, specificity of 89.7%, PPV being 88.89%, and NPV being 87.27%. Our results are very much in line with studies [3, 8], which showed that the expected sensitivity in the identification of malignant thyroid was 89% and the specificity was 93%. Furthermore, our finding of superior sensitivity for smaller nodules (<2mm) at 90.0% is clinically significant. This supports the utility of high-resolution ultrasound in detecting small malignancies, a capability that is crucial for adhering to modern management systems like ACR TI-RADS [15], which emphasize feature-based risk stratification over size alone. This finding also contextualizes the concern by Bakkar *et al.* [16] regarding malignancy in larger nodules by demonstrating that ultrasound remains a sensitive tool for smaller, potentially early-stage cancers.

This study is limited by reliance on FNAC as the reference standard, which may miss some malignancies compared to histology, and by a lack of evaluation of ultrasound elastography and likelihood ratios for malignancy. Additionally, the optimal combination of ultrasound features for clinical decision-making remains unclear. Future research should assess the combined use of high-resolution ultrasound, elastography, and standardized risk stratification systems to improve diagnostic accuracy for thyroid malignancy.

CONCLUSIONS

This study confirms that cervical ultrasonography is a highly accurate and reliable tool for detecting malignant thyroid nodules. Using FNAC as the gold standard, ultrasound demonstrated high sensitivity and specificity, making it an excellent first-line investigation for effectively triaging patients for further diagnostic procedures.

Authors' Contribution

Conceptualization: AS
Methodology: AS, NKK, ASM, SS
Formal analysis: SS
Writing and Drafting: AS
Review and Editing: AS, NKK, ASM, SS

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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