RESEARCH PAPER

MULTIMODAL CORRELATION OF ULTRASONOGRAPHIC FINDING THYROID IMAGING, REPORTING AND DATA SYSTEM (TIRADS) WITH CYTOLOGY (BETHESDA SYSTEM), HISTOLOPATHOLOGICAL AND BIOCHEMICAL PARAMETERS IN THYROID LESIONS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Thyroid nodules are common, and accurate integration of radiological, cytological, histopathological, and laboratory parameters is essential for effective preoperative risk stratification and prediction of malignancy.

Objective: To evaluate the clinical utility of integrating radiological (American College of Radiology Thyroid Imaging, Reporting and Data System (ACR TI-RADS)), cytological (Bethesda), histopathological, haematological, and biochemical parameters for risk stratification of thyroid nodules.

Methods: This single-centre hospital-based analytical cross-sectional study was conducted at Chettinad Hospital and Research Institute, Chennai, from November 2025 to February 2026 among 69 adults with thyroid nodules who underwent thyroid ultrasonography with ACR TI-RADS categorisation and Fine Needle Aspiration Cytology (FNAC) reported using the Bethesda System.

Results: Among 69 patients with thyroid nodules, the mean age was 43.1±12.4 years, and 84.1% were women. Most presented with palpable thyroid swelling (82.6%); solitary nodules predominated (65.2%), with mean size 2.3±1.1 cm. TI-RADS categories were mainly TR4 (31.9%) and TR3 (29.0%), while Bethesda II was the commonest cytology category (52.2%). On histopathology, nodular hyperplasia/colloid goiter was most frequent (37.1%), followed by papillary carcinoma (28.6%). Increasing TI-RADS category was associated with progressively higher-risk Bethesda categories and malignancy. Among operated cases, malignancy was absent in TR1–TR3, but occurred in 15.8% of TR4 and 83.3% of TR5 nodules. Bethesda outperformed TI-RADS for predicting malignancy, with higher sensitivity (84.6% vs 76.9%) and accuracy (91.4% vs 85.7%). Malignant nodules also showed higher red cell distribution width (RDW), neutrophil lymphocyte ratio (NLR), and thyroid stimulating hormone (TSH), but lower T4.

Conclusion: Integrated assessment using ACR TI-RADS, Bethesda cytology, histopathology, and selected laboratory markers improved thyroid nodule risk stratification, with Bethesda showing higher diagnostic accuracy than TI-RADS for predicting malignancy.

Keywords: Thyroid nodules, American College of Radiology Thyroid Imaging, Reporting and Data System, Bethesda system, Fine-needle aspiration cytology, Histopathology, Malignancy risk stratification

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Introduction

Thyroid nodules are a common clinical problem in endocrine and general surgical practice. The 2015 American Thyroid Association (ATA) guidelines state that palpable thyroid nodules are present in approximately 5% of women and 1% of men living in iodine-sufficient regions, whereas high-resolution ultrasonography can detect nodules in 19%–68% of randomly selected individuals, with higher frequencies in women and older adults.(1) Although most nodules are benign, the major clinical concern is exclusion of thyroid cancer, which is estimated to occur in about 7%–15% of nodules depending on demographic and clinical risk factors.(1) Differentiated thyroid carcinoma, comprising papillary and follicular carcinoma, accounts for more than 90% of all thyroid cancers, making accurate preoperative stratification of thyroid nodules a major priority.

Ultrasonography is the first-line imaging modality for thyroid nodules because it can define nodule architecture, echogenicity, margins, calcifications, and shape, all of which influence malignancy risk assessment. However, individual sonographic findings are not equally informative. In the systematic review and meta-analysis by Brito et al. (2014), benignity was more strongly associated with cystic and spongiform morphology, whereas taller-than-wide orientation emerged as the strongest malignant predictor among ultrasound features, while nodule size alone was not an accurate discriminator of malignancy.(2) These observations explain why structured sonographic scoring systems are preferred over isolated ultrasound descriptors in routine practice.(3) Fine-needle aspiration cytology remains the cornerstone of preoperative evaluation because it directly samples lesional cells and provides standardized cytomorphologic categorization. The 2017 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) recommends that every thyroid FNA report be assigned to one of six diagnostic categories and links each category to an implied malignancy risk and management pathway.(4) In the revised Bethesda framework, the expected risk of malignancy is 0%–3% for benign nodules, 10%–30% for AUS/FLUS, 25%–40% for follicular neoplasm/suspicious for follicular neoplasm, 50%–75% for suspicious for malignancy, and 97%–99% for malignant cytology, illustrating the strong gradient of risk embedded within cytology-based classification.(5)

Despite these advances, important grey zones remain. In a recent concordance study by Huang et al. (2023), American College of Radiology Thyroid Imaging, Reporting and Data System (ACR TI-RADS) 3 nodules showed a high negative predictive value of 94.6% against Bethesda scoring, whereas surgically excised TI-RADS 5 nodules had a histopathologic malignancy rate of 71.4%, underscoring that sonographic risk escalates meaningfully across categories but also that borderline categories still need cytologic and clinical correlation.(6) The same study also found that small TI-RADS 4 and 5 nodules not meeting size criteria for FNA could still harbour malignancy, highlighting the limitations of relying on imaging thresholds alone.(6) Adjunct biochemical and haematological markers may further refine this pathway, particularly in indeterminate nodules. A 2024 meta-analysis by Fan et al. concluded that elevated serum TSH is associated with differentiated thyroid cancer and may have diagnostic value in thyroid nodules,(7) whereas the meta-analysis by Liu et al. found that preoperative neutrophil-to-lymphocyte ratio (NLR) did not consistently distinguish differentiated thyroid cancer from benign nodules.(8) This unresolved area provides the rationale for evaluating thyroid nodules through an

integrated model that combines ultrasound-based TI-RADS, Bethesda cytology, histopathology, and selected haematological and biochemical parameters rather than relying on any single modality alone.

Against this background, the objective of the present study was to evaluate the clinical utility of integrating radiological (TIRADS), cytological (Bethesda), histopathological, haematological, and biochemical parameters for risk stratification of thyroid nodules, and to determine the diagnostic performance (accuracy, sensitivity, specificity, Positive Predictive Value, and Negative Predictive Value) of TIRADS and the Bethesda system in predicting malignancy.

Materials and Methods

This was a single-centre, hospital-based, analytical cross-sectional study conducted in the Chettinad Hospital and Research Institute, Chennai, Tamil Nadu, India over a period of four months between November 2025 and February 2026. The study was approved by the Institutional Human Ethics Committee (IHEC) 2025. Participants were included if they presented with one or more thyroid nodules and underwent a diagnostic work-up comprising thyroid ultrasonography with TIRADS categorisation and fine-needle aspiration cytology reported using the Bethesda System, with subsequent histopathological examination available for correlation where surgery was performed. Both adult males and females were eligible. Patients were excluded if imaging or FNAC reports were unavailable or incomplete, if cytology samples were inadequate/non-diagnostic without repeat sampling, if histopathology confirmation was not available for cases intended for cyto-histo correlation, or if prior thyroid malignancy or previous thyroid surgery could confound index assessment.

The sample size was calculated using a single-proportion formula based on the anticipated sensitivity of ultrasound risk stratification for malignancy. A sensitivity of 94.7% (rounded to p = 94%) for ACR TI-RADS compared against histopathology was taken from Söylemez et al.(9) Using a 95% confidence level (Z = 1.96), absolute precision (d) = 6%, q = 100 − p = 6, and 10% non-response/incomplete data rate, the minimum required sample size was estimated as 69 participants; enrolled using nonprobability sampling technique – convenient/purposive sampling. Baseline demographic and clinical details were recorded using a structured proforma, including age, sex, relevant symptoms, duration of swelling, past history of thyroid disease, prior irradiation/surgery, family history of thyroid malignancy, and relevant comorbidities/medications. Each participant underwent thyroid ultrasonography using a high-frequency linear transducer. Both thyroid lobes and isthmus were evaluated and the dominant/suspicious nodule(s) were documented for location (lobe/isthmus; upper/mid/lower pole), size in three orthogonal dimensions, and sonographic characteristics. Nodules were categorized using the ACR TI-RADS lexicon by assigning points for composition, echogenicity, shape, margins, and echogenic foci, and the total score was used to classify nodules into TR1–TR5 (Benign to highly suspicious) risk categories. Where clinically indicated, and in accordance with TI-RADS size thresholds, ultrasound guidance was used to select the target nodule for aspiration.

FNAC was performed under aseptic precautions, preferably under ultrasound guidance for non-palpable, deep, predominantly cystic, posteriorly located, or small nodules. Aspiration was done; aspirated material was prepared as both air-dried and alcohol-fixed smears. Air-dried smears were stained with May–Grünwald–Giemsa, and alcohol-fixed smears were stained with Papanicolaou

and/or haematoxylin and eosin. Cytology was reported according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) (Categories I–VI). Patients who proceeded to surgery had their excised thyroid specimen(s) submitted for histopathological examination, which served as the reference standard for malignancy confirmation. Surgical specimens were fixed in 10% neutral buffered formalin, with representative sampling of the nodule, capsule, suspicious areas, and resection margins as applicable, and processed for paraffin embedding. Sections were stained with haematoxylin and eosin, and the final diagnosis was rendered with tumour typing. In addition, blood samples were collected for haematological and biochemical assessment (complete blood count, thyroid function tests).

Statistical analysis: Statistical analysis was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarised as frequency and percentage, while continuous variables were expressed as mean with standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for skewed data. Cross-tabulation was used to examine the distribution of ACR TI-RADS categories against Bethesda cytology categories. Comparisons between benign and malignant nodules among operated cases were performed using the independent samples t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed variables. Associations between categorical variables were assessed using the chi-square test or Fisher's exact test, as appropriate. Histopathology was considered the reference standard for malignancy. Diagnostic performance of ACR TI-RADS and Bethesda categories in predicting malignant thyroid nodules was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy, along with 95% confidence intervals (CI). All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

Results

The study population had a mean age of 43.1 (12.4) years and was predominantly female (58/69, 84.1%). Most patients presented with a palpable thyroid swelling (82.6%). Neck pain or tenderness was reported in 15.9%, compressive symptoms such as dysphagia or dyspnea in 23.2%, and voice change or hoarseness in 2.9% (Table 1). A family history of thyroid cancer was uncommon (1.4%), whereas 24.6% were known hypothyroid patients on treatment. The median TSH was 2.23 mIU/L [IQR: 1.53–3.55], with mean T3 and T4 levels of 1.24 (0.29) ng/mL and 8.6 (1.8) µg/dL, respectively. On ultrasonography, solitary nodule was more common than multinodular goiter with a dominant nodule (65.2% vs 34.8%), and the mean maximum nodule diameter was 2.3 (1.1) cm. ACR TI-RADS were most commonly TR4 (31.9%) and TR3 (29.0%), followed by TR5 (17.4%). On FNAC, Bethesda category II (benign) predominated (52.2%), whereas Bethesda III, IV, V, and VI accounted for 14.5%, 11.6%, 7.2%, and 10.1%, respectively. Among cases with histopathological evaluation, nodular hyperplasia/colloid goiter was the most frequent diagnosis (37.1%), followed by papillary carcinoma (28.6%) and follicular adenoma (20.0%).

Table 1: Baseline demographic characteristics, clinical presentation, thyroid function profile, ultrasonography features, cytology (Bethesda) distribution, and histopathological diagnosis of participants (N=69)

	Value

Age (years), Mean (SD)		43.1 (12.4)
Gender, n (%)	Female	58 (84.1)
	Male	11 (15.9)
Presentation, n (%)	Palpable thyroid swelling	57 (82.6)
	Incidentally detected nodule	12 (17.4)
Symptoms, n (%)	Neck pain/tenderness	11 (15.9)
	Compressive symptoms (dysphagia/dyspnea)	16 (23.2)
	Voice change/hoarseness	2 (2.9)
Family history of thyroid cancer, n (%)		1 (1.4)
Known hypothyroidism on treatment, n (%)		17 (24.6)
TSH (mIU/L), Median [IQR]		2.23 [1.53–3.55]
T3 (ng/mL), Mean (SD)		1.24 (0.29)
T4 (µg/dL), Mean (SD)		8.6 (1.8)
Ultrasonography findings		
Nodule pattern, n (%)	Solitary nodule	45 (65.2)
	Multinodular goiter with dominant nodule	24 (34.8)
Maximum nodule diameter (cm), Mean (SD)		2.3 (1.1)
Composition, n (%)	Cystic/spongiform	16 (23.2)
	Mixed	22 (31.9)
	Solid	31 (44.9)
Echogenicity, n (%)	Anechoic/isoechoic	33 (47.8)
	Hyperechoic	11 (15.9)
	Hypoechoic/very hypoechoic	25 (36.2)
Taller-than-wide shape, n (%)		20 (29.0)
Margins, n (%)	Smooth	51 (73.9)
	Lobulated/irregular	17 (24.6)
	Extrathyroidal extension	1 (1.4)
Echogenic foci/calcifications, n (%)	None/large comet-tail	31 (44.9)
	Macrocalcification	20 (29.0)
	Peripheral rim	9 (13.0)
	Punctate echogenic foci	9 (13.0)
ACR TI-RADS, n (%)	TR1	5 (7.2)
	TR2	10 (14.5)
	TR3	20 (29.

		0)
	TR4	22 (31.9)
	TR5	12 (17.4)
FNAC findings		
Bethesda, n (%)	I: Non-diagnostic/Unsatisfactory	3 (4.3)
	II: Benign	36 (52.2)
	III: Atypia/Follicular lesion of undetermined significance (AUS/FLUS)	10 (14.5)
	IV: Follicular neoplasm/Suspicious for follicular neoplasm	8 (11.6)
	V: Suspicious for malignancy	5 (7.2)
	VI: Malignant	7 (10.1)
Histopathology		
Histopathological diagnosis, n (%)	Nodular hyperplasia/colloid goiter	13 (37.1)
	Papillary carcinoma	10 (28.6)
	Follicular adenoma	7 (20.0)
	Follicular carcinoma	2 (5.7)
	Hashimoto thyroiditis	2 (5.7)
	Medullary carcinoma	1 (2.9)

Table 2: Cross-tabulation of ACR TI-RADS categories (TR1–TR5) with Bethesda System cytology categories (I–VI) among thyroid nodules (N=69)

	Bethesda system					
TI-RADS	I	II	III	IV	V	VI
TR1	0	4	0	0	0	1
TR2	0	10	0	0	0	0
TR3	3	16	1	0	0	0
TR4	0	6	8	5	2	1
TR5	0	0	1	3	3	5

TR1 and TR2 nodules were predominantly benign on FNAC, with TR2 entirely confined to Bethesda II (10/10), while TR1 included 4 Bethesda II nodules and 1 Bethesda VI nodule. TR3 nodules were also largely benign or non-diagnostic, comprising 16 Bethesda II, 3 Bethesda I, and 1 Bethesda III case (Table 2). In contrast, TR4 nodules demonstrated greater cytological heterogeneity, with 8 Bethesda III, 5 Bethesda IV, 2 Bethesda V, and 1 Bethesda VI case, although 6 remained Bethesda II. TR5 nodules showed the strongest association with high-risk cytology, including 5 Bethesda VI, 3 Bethesda V, and 3 Bethesda IV cases, with only 1 Bethesda III lesion. Overall, these findings indicate a progressive increase in cytological atypia and suspicion for malignancy with rising TI-RADS category. Among the 35 operated cases, the risk of malignancy increased markedly with higher TI-RADS and Bethesda categories. By TI-RADS, no malignancies were identified in TR1, TR2, or TR3 categories, whereas malignancy was seen in 3 of 19 TR4 nodules (15.8%) and 10 of 12 TR5 nodules (83.3%). Using histopathology as the gold standard, TI-RADS showed a sensitivity of 76.9%, specificity of 90.9%, PPV of 83.3%, NPV of 87.0%, and overall accuracy of 85.7% ($p<0.001$)(Table 3). By Bethesda category,

no malignancies were seen in categories I, II, or III, (Figure – 1 – Benign lesion – Hashimoto thyroiditis, TI- RADS:TR2 and Bethesda category 2) while the risk of malignancy was 25.0% in Bethesda IV, 100.0% in Bethesda V, and 85.7% in Bethesda VI. Bethesda cytology demonstrated sensitivity of 84.6%, specificity of 95.5%, PPV of 91.7%, NPV of 91.3%, and diagnostic accuracy of 91.4% (p<0.001), indicating better overall performance than TI-RADS for predicting malignant thyroid nodules

Table 3: Distribution of operated cases and malignancy risk by ACR TI-RADS and Bethesda categories, with diagnostic performance for predicting malignant thyroid nodules (gold standard: histopathology)

		Operated, n	Malignant, n	Risk of malignancy (%)
TI-RADS	TR1	1	0	0.0
	TR2	1	0	0.0
	TR3	2	0	0.0
	TR4	19	3	15.8
	TR5	12	10	83.3
Bethesda	I	1	0	0.0
	II	5	0	0.0
	III	9	0	0.0
	IV	8	2	25.0
	V	5	5	100.0
	VI	7	6	85.7

*Statistically significant at p<0.05

Comparison of laboratory parameters between benign (n=22) and malignant (n=13) operated thyroid nodules revealed no statistically significant differences in routine hematological indices. The mean hemoglobin levels were similar in benign and malignant groups (12.5 ± 1.6 g/dL vs 12.3 ± 1.7 g/dL; p=0.735). Likewise, total leukocyte count (7.4 ± 1.8 vs 7.5 ± 1.6 ×10⁹/L; p=0.814) and platelet count (280.6 ± 38.4 vs 275.1 ± 75.0 ×10⁹/L; p=0.807) did not differ significantly. Thyroid hormone T3 levels were also comparable between the two groups (1.3 ± 0.3 ng/mL in both; p=0.864), suggesting that these conventional hematological and biochemical parameters have limited utility in differentiating benign from malignant thyroid nodules.

Table 4: Comparison of haematological and thyroid biochemical parameters between benign and malignant thyroid nodules among operated cases (n=35)

Parameters	Benign (n=22)
Hemoglobin (g/dL), Mean (SD)	12.5 (1.6)
Total leukocyte count (×10⁹/L), Mean (SD)	7.4 (1.8)
Platelet count (×10⁹/L), Mean (SD)	280.6 (38.4)
RDW (%), Mean (SD)	13.4 (1.0)
Neutrophil-to-lymphocyte ratio (NLR), Median [IQR]	2.10 [1.71–2.4
TSH (mIU/L), Median [IQR]	2.20 [1.57–3.1
T3 (ng/mL), Mean (SD)	1.3 (0.3)
T4 (µg/dL), Mean (SD)	9.3 (1.9)

*Statistically significant at p<0.05

of % (95% CI)

Sensitivity, 76.9 (49.7–91.8)

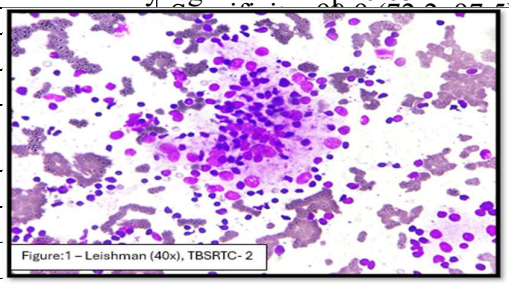
Figure:1 – Leishman (40x), TBSRTC- 2

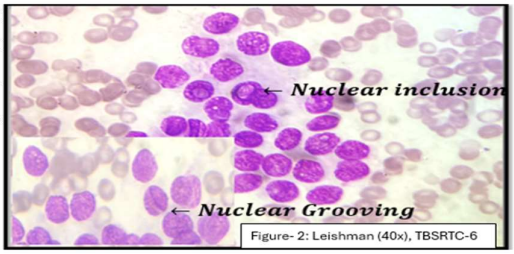

Figure- 2: Leishman (40x), TBSRTC-6

In contrast, parameters reflecting inflammatory status and thyroid function showed significant differences. Malignant nodules demonstrated a significantly higher red cell distribution width (RDW) compared to benign nodules (14.3 ± 1.2% vs 13.4 ± 1.0%; p=0.033). The neutrophil-to-lymphocyte ratio (NLR) was also markedly elevated in malignant cases, with a median of 3.70 (IQR: 2.72–4.05) versus

2.10 (IQR: 1.71–2.45) in benign nodules ($p<0.001$). Furthermore, median TSH levels were significantly higher in malignant nodules [4.42 (3.48–5.68) mIU/L] compared to benign nodules [2.20 (1.57–3.17) mIU/L] ($p=0.007$), while mean T4 levels were significantly lower in malignant cases (7.7 ± 1.3 µg/dL vs 9.3 ± 1.9 µg/dL; $p=0.006$). These findings suggest that inflammatory markers such as RDW and NLR, along with alterations in thyroid function, may aid in distinguishing malignant from benign thyroid nodules.(Table 4).

Discussion

The demographic profile of the present study is in keeping with the established epidemiology of thyroid nodular disease. The mean age of 43.1 years and the marked female predominance (84.1%) are biologically plausible, as thyroid nodules become more frequent with advancing age and are consistently reported more often in women than in men; in corroboration with Kwong et al. (2015) and Yuan et al. (2025).(10, 11) Dean & Gharib (2008) noted that nodule incidence rises with age and is increased in women, while a large multicentre ultrasonography study by Moon et al. (2018) similarly found thyroid nodules to be more prevalent in women and older individuals.(12, 13) This background helps explain why a middle-aged, female-predominant cohort is commonly encountered in hospital-based thyroid nodule practice. At the same time, the overall clinical challenge remains substantial because thyroid nodules are very common, yet only a minority—roughly 5%–15%—harbour malignancy, making accurate preoperative risk stratification essential, as emphasized by Patel et al. (2023).(14)

The predominance of palpable thyroid swelling in our cohort, with fewer incidentally detected nodules, likely reflects the symptomatic referral pattern of a tertiary-care hospital rather than a screening population. Lyuman & McArthur (2025) noted a steady increase in incidental thyroid nodule detection because ultrasonography and cross-sectional imaging are used far more widely than before, and this has shifted emphasis toward structured risk assessment to avoid unnecessary intervention in low-risk lesions.(15) In our study, solitary nodule most common than multinodular goitre with a dominant nodule, and this is clinically relevant because solitary nodules have been associated with higher malignancy risk in Alzahrani (2024) and Jena et al. (2015).(16, 17) Golbert et al. identified solitary nodules, microcalcifications, family history of thyroid cancer, and higher TSH as independent predictors of malignancy,(18) while Boelaert et al. also showed that serum TSH, age, sex, and solitary nodule status provide adjunctive predictive information beyond cytology alone.(19) Family history was rare in our cohort, but familial clustering of non-medullary thyroid cancer is well documented in Lin et al. (2020).(20)

The sonographic pattern observed in our study also aligns well with the logic of the ACR TI-RADS framework. ACR TI-RADS was designed to standardize ultrasound terminology and correlate suspicious morphological features with clear management recommendations.(21) The predominance of TR3 and TR4 nodules in our cohort suggests that many lesions occupied the intermediate-risk zone where ultrasound alone raises concern but does not settle diagnosis. This is consistent with the known weighting of suspicious features within TI-RADS: in a meta-analysis by Campanella et al. (2014), taller-than-wide shape had an odds ratio of 10.15 for malignancy, microcalcifications 6.76, irregular margins 6.12, hypoechogenicity 5.07, and solid composition 4.69.(22) Therefore, the substantial proportions of solid nodules, hypoechoic/very hypoechoic nodules, taller-than-wide lesions, irregular margins,

and punctate echogenic foci in our cohort provide a mechanistic explanation for why many cases clustered into TR4 and TR5 rather than the clearly benign TR1–TR2 groups. The cross-tabulation between TI-RADS for radiology and Bethesda categories for cytology is discussed in the present study demonstrates a biologically coherent stepwise escalation in cytological atypia with increasing ultrasound suspicion (Table -2). TR1–TR3 nodules were largely benign or non-diagnostic on cytology, whereas TR4 showed a broad spread across Bethesda II to VI, and TR5 was heavily enriched for Bethesda IV, V, and VI lesions. This pattern supports the complementary relationship between imaging and cytology envisaged by both the ACR TI-RADS white paper and the Bethesda framework. (5, 21) The heterogeneity seen in TR4 nodules is especially important because this category often contains lesions with overlapping benign and malignant sonographic features. A similar problem exists for Bethesda III and IV nodules, in which follicular-patterned lesions remain diagnostically challenging because neither ultrasound nor cytology can reliably distinguish follicular adenoma from follicular carcinoma without histologic assessment of capsular and/or vascular invasion.(23) This explains why TR4/Bethesda III–IV combinations commonly form the principal indeterminate zone in thyroid nodule practice.(24)

The FNAC distribution, with Bethesda II as the most frequent category, and our histopathology profile, with nodular hyperplasia/colloid goitre as the most common final diagnosis, reflect the known predominance of benign disease among thyroid nodules.(4) At the malignant end of the spectrum, papillary carcinoma was the leading cancer, which is consistent with Al-Brahim & Asa (2006) that identifies papillary thyroid carcinoma as the most common malignant thyroid neoplasm.(25) The operative subset in our study also showed no malignancies in Bethesda I–III (Figure – 1), whereas malignancy rose sharply in Bethesda IV–VI(Figure – 2, TI- RADS – 5; Bethesda category -6; Positive for malignancy). That trend closely mirrors the Bethesda concept of progressively increasing risk of malignancy across its six categories. Still, the absence of malignancy in Bethesda II in our operated subset should not be overinterpreted as absolute benignity, because the Bethesda system assigns a low but non-zero malignancy risk to benign cytology, and incidental carcinoma after surgery for Bethesda II nodules has been documented, including a 1.53% rate in the study by Mulita et al. (2022).(26)

The diagnostic performance of ACR TI-RADS was good, with 76.9% sensitivity, 90.9% specificity, and 85.7% overall accuracy, and the risk of malignancy rose from 0% in TR1–TR3 to 15.8% in TR4 and 83.3% in TR5. These findings support the intended purpose of TI-RADS as an effective pre-cytology triage tool. Published performance metrics for ACR TI-RADS vary considerably across study design, nodule size mix, threshold definitions, and whether all nodules or only operated nodules are analysed. Atar et al. (2024) reported 80.3% sensitivity, 60.8% specificity, and 75% accuracy,(27) whereas Eissa et al. (2024) found sensitivity and specificity of 63.5% and 76.0%, respectively.(3) In contrast, Söylemez et al. (2022) reported that ACR TI-RADS had the highest sensitivity among five classification systems, reaching 94.5% overall and 91.3% for 1–3 cm nodules.(9) Against this background, the higher specificity seen in our study may reflect the surgically enriched subset and the strong concentration of malignancy within TR5 nodules.

Bethesda cytology performed even better than TI-RADS in our dataset, with 84.6% sensitivity, 95.5% specificity, and 91.4% accuracy, and with malignancy risks of

25.0% for Bethesda IV, 100.0% for Bethesda V, and 85.7% for Bethesda VI. This superior performance is not unexpected because cytology samples cellular morphology directly, whereas ultrasound only estimates structural probability. Our findings parallel those of George et al. (2022), who reported a larger area under the ROC curve for Bethesda than for ultrasound TI-RADS (0.91 vs 0.70), with 100% of Bethesda VI lesions being malignant on final histopathology.(28) Eissa et al. (2024) also found substantially higher specificity for Bethesda than for TI-RADS (98.1% vs 76.0%).(3) However, the relationship between the two systems should be viewed as complementary rather than competitive, because ultrasound determines which nodules warrant aspiration, while Bethesda refines the post-aspiration estimate of malignancy. This layered workflow is exactly how current thyroid nodule algorithms are structured in routine practice.(21, 29)

The laboratory analysis adds an interesting adjunctive dimension to risk stratification. Malignant nodules were associated with significantly higher RDW and NLR, whereas haemoglobin, total leukocyte count, platelet count, and T3 did not differ significantly as shown in the table 4. This pattern is biologically plausible because NLR reflects systemic inflammatory activation, and thyroid carcinogenesis has increasingly been linked to tumour-associated inflammatory signalling. Sit et al. (2019) reported a significantly higher mean NLR in malignant thyroid nodules than in benign nodules (2.1±0.9 vs 1.7±0.9),(30) and a 2025 meta-analysis found pooled NLR sensitivity of 75%, specificity of 62%, and an HSROC AUC of 0.75, indicating moderate standalone diagnostic value.(31) RDW showed a similar direction of effect in prior studies: Aktas et al. (2017) found median RDW to be significantly higher in malignant than benign nodules,(32) and Kayilioglu et al. (2014) also reported higher RDW in malignant lesions within the cytologically indeterminate group.(33) These data support interpreting NLR and RDW as inexpensive adjunct markers rather than replacements for imaging or cytology. The thyroid biochemical profile in our study is also noteworthy. Malignant nodules had significantly higher TSH and lower T4, while T3 was similar between benign and malignant groups. Among biochemical markers, the association between higher TSH and malignancy is the most consistently supported in the literature. Boelaert et al. (2006) showed that the risk of malignancy increases with serum TSH concentrations even within the normal range,(19) and Golbert et al. (2017) reported higher median TSH values in malignant than benign nodules, with an approximately threefold higher malignancy risk above a threshold of 2.26 μU/mL.(18) Fiore et al. (2012) likewise concluded that higher TSH, even within reference ranges, is associated with increased frequency and more advanced papillary thyroid cancer.(34)

The present study had certain limitations. Being a single-centre, hospital-based analytical cross-sectional study, the results may not be fully generalisable to the wider community or other practice settings. The sample size was modest, and histopathological confirmation was available only in the operated subset, which may have introduced selection bias in the estimation of malignancy risk and diagnostic performance, as patients proceeding to surgery are more likely to have clinically or cytologically suspicious nodules. The cross-sectional design also limited assessment of longitudinal outcomes, interval growth, and progression of nodules that were managed conservatively. In addition, the study relied on routine clinical and pathological reporting, and interobserver variability in ultrasonographic TI-RADS categorisation, cytological interpretation using the

Bethesda system, and histopathological assessment could not be separately evaluated. Molecular testing was not incorporated, which may have further refined risk stratification, particularly in indeterminate cytology.

Conclusion

In conclusion, the present study showed that integrated evaluation of thyroid nodules using ACR TI-RADS, Bethesda cytology, histopathology, and selected haematological and biochemical parameters provides clinically useful risk stratification. Higher TI-RADS was associated with progressively more suspicious Bethesda categories and a markedly higher risk of malignancy on histopathology, while Bethesda cytology demonstrated better overall diagnostic performance than TI-RADS in predicting malignant nodules. Among the laboratory markers studied, higher RDW, elevated NLR, higher TSH, and lower T4 were significantly associated with malignant nodules, suggesting that these parameters may serve as supportive adjuncts in preoperative assessment. Overall, a combined radiological, cytological, pathological, and laboratory approach appears to improve identification of high-risk thyroid nodules and may aid more accurate clinical decision-making regarding surveillance, repeat evaluation, and surgical management.

List of abbreviations:

ACR – American College of Radiology; ATA – American Thyroid Association; AUS/FLUS – Atypia of Undetermined Significance / Follicular Lesion of Undetermined Significance; CBC – Complete Blood Count; CI – Confidence Interval; FNAC – Fine Needle Aspiration Cytology; FNA – Fine Needle Aspiration; IHEC – Institutional Human Ethics Committee; IQR – Interquartile Range; NLR – Neutrophil-to-Lymphocyte Ratio; NPV – Negative Predictive Value; PPV – Positive Predictive Value; RDW – Red Cell Distribution Width; ROC – Receiver Operating Characteristic; SD – Standard Deviation; SPSS – Statistical Package for the Social Sciences; TSH – Thyroid Stimulating Hormone; T3 – Triiodothyronine; T4 – Thyroxine; TBSRTC – The Bethesda System for Reporting Thyroid Cytopathology; TI-RADS/TIRADS – Thyroid Imaging Reporting and Data System; TR – Thyroid Imaging Reporting and Data system Category; USG – Ultrasonography; WHO – World Health Organization.

TI-RADS classification:

TR1 indicates benign lesions, TR2 indicates not suspicious lesions, TR3 indicates mildly suspicious lesions, TR4 indicates moderately suspicious lesions, and TR5 indicates highly suspicious lesions.

Bethesda system categories:

Bethesda Category I indicates non-diagnostic or unsatisfactory smears; Category II indicates benign lesions; Category III indicates atypia of undetermined significance / follicular lesion of undetermined significance (AUS/FLUS); Category IV indicates follicular neoplasm or suspicious for follicular neoplasm; Category V indicates suspicious for malignancy; and Category VI indicates malignant lesions.

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