

Clinical and Cytological Predictors of Malignancy in Patients Presenting with Thyroid Swelling

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Abstract

Introduction: Thyroid swelling is common, but differentiating benign from malignant nodules remains challenging. Clinical predictors and fine-needle aspiration cytology (FNAC) are key in preoperative evaluation, yet indeterminate cytology often leads to unnecessary surgery. **Objective:** To associate clinical and cytological predictors of malignancy in patients with thyroid swelling and develop a risk stratification model. **Methods & Materials:** This cross-sectional study included 50 patients undergoing thyroidectomy at Rajshahi Medical College Hospital (June-December 2014). Clinical, ultrasonographic, FNAC (Bethesda classification), and histopathological data were analyzed. Malignancy rates were compared using odds ratios, 95% confidence intervals, and Fisher's exact test. **Results:** Malignancy prevalence was 14.0% (7/50). Extreme age (<20 or >50 years) had a 33.3% malignancy rate vs. 9.1% for ages 21 - 50 years ($p = 0.02$). Malignancy was higher in males (25.0%) than in females (11.9%), but this was not statistically significant ($p = 0.31$, descriptive only). Solitary nodules (26.7%) and solid nodules (20.0%) were associated with higher malignancy. FNAC demonstrated sensitivity 85.7%, specificity 100%, and NPV 97.7%; after excluding indeterminate Bethesda IV cases, accuracy was 98.0%. For Bethesda IV (follicular neoplasm, $n = 6$), overall malignancy was 16.7%; in an exploratory analysis, adding extreme age stratified risk to 50% (with extreme age) vs. 0% (age 21 - 50 years). Malignancy prevalence was 14.0% (7/50). Extreme age (<20 or >50 years) had a 33.3% malignancy rate vs. 9.1% for ages 21 - 50 years

($p = 0.02$). Malignancy was higher in males (25.0%) than in females (11.9%). Solitary nodules (26.7%) and solid nodules (20.0%) were associated with higher malignancy. FNAC demonstrated sensitivity of 85.7%, specificity of 100%, NPV of 97.7%, and accuracy of 98.0%. For Bethesda IV (follicular neoplasm, $n = 6$), overall malignancy was 16.7%; adding extreme-age stratified risk increased it to 50% (with extreme age) vs. 0% (age 21 - 50 years). **Conclusion:** Age extremes, male sex, solitary and solid nodules are associated predictors. FNAC has excellent diagnostic accuracy. An exploratory model combining Bethesda IV with age requires external validation before any clinical application.

Keywords

Thyroid Nodule, FNAC, Bethesda Classification, Malignancy Predictors, Age, Risk Stratification

1. Introduction

Thyroid swelling, or goiter, represents one of the most common clinical presentations encountered in endocrine practice. The vast majority of thyroid nodules are benign, yet thyroid cancer is the most frequent malignancy of the endocrine system, with a globally rising incidence over recent decades [1] [2]. This increasing prevalence, largely attributed to the widespread use of high-resolution ultrasonography and incidental detection, has created a critical clinical dilemma: how to accurately identify the small subset of nodules that are malignant while avoiding unnecessary invasive procedures in the majority of patients with benign disease [3]. The cornerstone of current preoperative evaluation rests on two pillars: clinical assessment and cytopathological analysis. Clinical predictors—including patient age, sex, family history of thyroid cancer, history of head and neck irradiation, rapid nodule growth, voice hoarseness, cervical lymphadenopathy, and suspicious ultrasound features such as microcalcifications, irregular margins, and taller-than-wide shape—provide essential initial risk stratification [4] [5]. However, clinical features alone lack sufficient sensitivity and specificity to guide definitive management [6]. Fine-needle aspiration cytology (FNAC), guided by ultrasound, has emerged as the gold standard diagnostic tool, boasting high sensitivity and specificity [7]. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has standardized reporting, categorizing results from nondiagnostic to malignant [8]. Despite its utility, FNAC carries inherent limitations. Up to 20% - 30% of aspirations yield indeterminate cytology (Bethesda categories III, IV, and V), a diagnostic gray zone where the risk of malignancy is variable but not negligible, often leading to diagnostic lobectomy or thyroidectomy for histopathological confirmation [9] [10]. Consequently, many patients with indeterminate nodules undergo unnecessary surgery for what ultimately proves to be benign dis-

ease [11]. Therefore, there is a pressing need to refine preoperative risk prediction beyond cytology alone. Identifying robust clinical and cytological predictors that can distinguish benign from malignant thyroid swellings would enable more personalized decision-making [12]. Such predictors could help avoid surgery in low-risk patients, guide the extent of surgery (lobectomy vs. total thyroidectomy) in intermediate-risk cases, and expedite definitive treatment in high-risk scenarios [13]. This study aims to evaluate clinical and cytological predictors of malignancy in patients presenting with thyroid swelling, with the goal of developing a practical risk-stratification model to optimize patient management and reduce unnecessary surgical interventions.

2. Objective

2.1. General Objective

To associate clinical and cytological predictors of malignancy in patients with thyroid swelling to improve preoperative risk stratification and reduce unnecessary surgery.

2.2. Specific Objectives

- 1) To determine the prevalence of malignancy on histopathology in operated thyroid swellings.
- 2) To associate independent clinical and ultrasound predictors of malignant thyroid nodules.
- 3) To evaluate the diagnostic accuracy of FNAC (Bethesda System) against histopathology.
- 4) To assess the malignancy rate within indeterminate cytology categories (Bethesda III, IV, V).
- 5) To explore a simple risk stratification model combining clinical and cytological predictors.

3. Methods and Materials

This hospital-based, observational, cross-sectional study was conducted in the Department of Ear, Nose, and Throat (ENT) and Head-Neck Surgery at Rajshahi Medical College Hospital (RMCH), Rajshahi, Bangladesh, over a 6-month period from June 2014 to December 2014. The study population comprised all consecutive patients admitted to the department with a clinical and ultrasonographic diagnosis of thyroid swelling who subsequently underwent thyroidectomy. Of 52 patients screened, 2 were excluded (1 declined participation, 1 had incomplete data), and 50 were enrolled. A total of fifty patients were enrolled during the study period. Although the calculated sample size using the formula $n = (Z^2 \cdot pq) / d^2$ (assuming a prevalence of malignancy of 10%, a margin of error of 5%, and a 95% confidence interval) was 136, the sample size was limited to fifty due to time constraints of the dissertation. Patients of any age, sex, or race with a clinically diag-

nosed goiter who voluntarily provided informed consent were included; those who declined to participate were excluded. All patients underwent a standardized evaluation, including detailed history-taking—covering age, sex, duration of thyroid swelling, presenting complaints, history of radiation exposure, family history of thyroid malignancy, and medication history—and a thorough physical examination. This encompassed general and systemic examinations, inspection and palpation of the thyroid gland (assessing size, consistency, nodularity, mobility, tracheal position, and fixity), assessment of cervical lymph nodes, and indirect laryngoscopy to evaluate vocal cord mobility. High-resolution ultrasonography of the thyroid was performed in all patients to characterize nodules, specifically to determine whether they were solid or cystic. Fine-needle aspiration cytology (FNAC) was conducted using a 22-gauge needle under sterile conditions; smears were air-dried and alcohol-fixed, then stained with Giemsa and Papanicolaou stains. Local cytological diagnoses were assigned to the Bethesda System as follows: colloid goiter was classified as Bethesda II (benign); follicular neoplasm as Bethesda IV (follicular neoplasm); and papillary carcinoma as Bethesda VI (malignant). For the purposes of calculating diagnostic accuracy, Bethesda II was considered negative for malignancy, Bethesda VI was positive for malignancy, and Bethesda IV was also treated as positive for malignancy—assuming the worst-case scenario for sensitivity analysis. Preoperative assessments included complete blood count, random blood sugar, blood urea, serum creatinine, urine routine and microscopy, chest X-ray (posterior-anterior view), and electrocardiography when indicated. Surgical procedures—ranging from hemithyroidectomy, subtotal thyroidectomy, to total thyroidectomy with or without neck dissection—were performed based on preoperative clinical and cytological findings, with the specific type documented. Resected thyroid specimens were sent for histopathological examination by the Department of Pathology at RMCH, serving as the gold standard for the final diagnosis (benign or malignant, including specific histological types). Data were recorded on a pre-designed data collection sheet, compiled, and analyzed using descriptive statistics (frequencies, percentages, and rates). Diagnostic accuracy measures—sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy—were calculated for FNAC against histopathology, accompanied by 95% confidence intervals. Malignancy rates were compared across age groups, sexes, types of swelling, symptom duration, and ultrasound findings using odds ratios and Fisher's exact test, with $p < 0.05$ considered statistically significant. Non-significant findings are reported as descriptive only. Additionally, an exploratory risk stratification model integrating FNAC categories and patient age was developed for indeterminate (Bethesda IV) nodules. Ethical approval was obtained from the Institutional Ethics Committee of Rajshahi Medical College Hospital. All patients provided written informed consent in Bengali after a comprehensive explanation of the study; they were assured of their right to withdraw at any stage without affecting their medical care, and all data were kept confidential and used solely for research purposes.

4. Results

Fifty patients with thyroid swelling who had thyroidectomy at Rajshahi Medical College Hospital from June to December 2014 were included. All 50 eligible patients who underwent thyroidectomy during the study period were enrolled consecutively; none were excluded. All underwent clinical assessment, ultrasonography, FNAC, and histopathology.

4.1. Histopathological Diagnosis

Figure 1 shows about 50 patients who underwent thyroidectomy; histopathology showed that 43 (86.0%) had benign disease and 7 (14.0%) had malignant disease. Nearly one in seven thyroid swellings was cancerous.

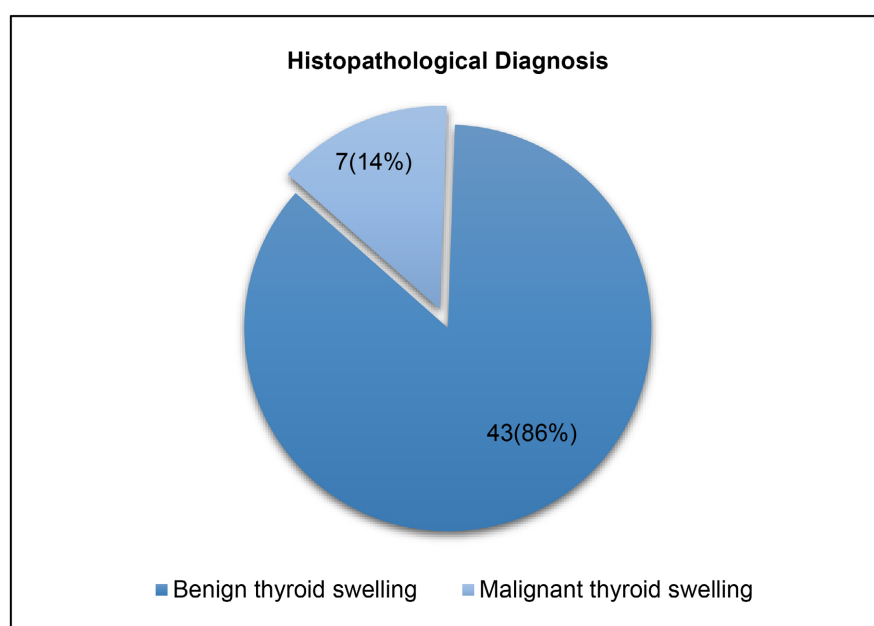


Figure 1. Histopathological diagnosis of the study patients (N = 50).

4.2. Age Distribution and Malignancy Rate

Table 1 shows that the patients ranged in age from 11 to 59 years. The largest group was aged 31 - 40 years (20 patients, 40.0%). The highest malignancy rates were observed at the extremes of age: 33.3% in both the 11 - 20 years (1/3) and 51 - 60 years (1/3) groups. Compared to the reference group aged 21 - 50 years (malignancy rate 11.4%, 5/44), patients aged ≤ 20 or > 50 years had an OR of 4.33 (95% CI: 0.67 - 27.8, $p = 0.21$ by Fisher's exact test).

4.3. Sex Distribution and Malignancy Rate

Table 2 shows that thyroid swelling was more common in females (84%, 42/50). However, the malignancy rate was higher in males (25.0%, 2/8) than in females (11.9%, 5/42). Males had an OR of 2.47 (95% CI: 0.41 - 14.8, $p = 0.31$ by Fisher's exact test). This association was not statistically significant.

Table 1. Age distribution and malignancy rate (N = 50).

Age Group (Years)	Total	Benign	Malignant	Malignancy (%)	OR (95% CI) vs. 21 - 50 yrs	p-Value*
11 - 20	3	2	1	33.30%	4.33 (0.67 - 27.8)	0.21
21 - 30	15	12	3	20.00%	1.96 (0.42 - 9.16)	0.4
31 - 40	20	18	2	10.00%	0.96 (0.16 - 5.78)	1
41 - 50	9	9	0	0.00%	0.00 (0.00 - 7.08)	0.57
51 - 60	3	2	1	33.30%	4.33 (0.67 - 27.8)	0.21
≤20 or >50	6	4	2	33.30%	4.33 (0.67 - 27.8)	0.21
21 - 50	44	39	5	11.36%	1	—

*Fisher's exact test; non-significant ($p > 0.05$)—descriptive only.

Table 2. Sex distribution and malignancy rate (N = 50).

Sex	Total	Benign	Malignant	Malignancy (%)	OR (95% CI)	p-Value*
Female	42	37	5	11.90%	1	—
Male	8	6	2	25.00%	2.47 (0.41 - 14.8)	0.31

*Fisher's exact test; non-significant ($p > 0.05$)—descriptive only.

4.4. Clinical Predictors

Table 3 shows that solitary nodules had a 26.70% malignancy rate (4/15), versus 8.80% (3/34) for multinodular goiter. The OR was 3.78 (95% CI: 0.74 - 19.3, $p = 0.17$), not significant. Patients with symptom duration <2 years had a 16.70% malignancy rate (4/24), compared to 11.50% (3/26) for ≥ 2 years; OR was 1.53 (95% CI: 0.31 - 7.67, $p = 0.70$), also not significant.

Table 3. Clinical predictors—swelling type and symptom duration.

Clinical Predictor	Category	Total	Benign	Malignant	Malignancy (%)	OR (95% CI)	p-Value*
Type of Swelling	Solitary Nodule	15	11	4	26.70%	3.78 (0.74 - 19.3)	0.17
	Multinodular	34	31	3	8.80%	1	—
	Diffuse	1	1	0	0.00%	0.00 (0.00 - 34.8)	1
Symptom Duration	<2 Years	24	20	4	16.70%	1.53 (0.31 - 7.67)	0.7
	≥ 2 Years	26	23	3	11.50%	1	—

*Fisher's exact test; all $p > 0.05$ —descriptive only.

4.5. Ultrasound Predictor

Table 4 shows that all 7 malignant nodules (100%) appeared solid on ultrasound. Of 35 solid nodules, 20.0% (7) were malignant. None of the 15 cystic nodules were malignant (0%). The odds ratio is undefined (division by zero). Fisher's exact test yielded $p = 0.09$, which is not statistically significant at $\alpha = 0.05$.

Table 4. Ultrasound predictor—nodule consistency (N = 50).

Ultrasound Finding	Total	Benign	Malignant	Malignancy (%)	p-Value*
Solid Nodule	35	28	7	20.00%	0.09
Cystic Nodule	15	15	0	0.00%	—

*Fisher's exact test; all $p > 0.05$ —descriptive only.

4.6. Diagnostic Accuracy of FNAC

Table 5 presents that FNAC is a minimally invasive procedure for diagnosing thyroid nodules before surgery. In this study, it performed well against the gold standard, correctly identifying 6 of 7 malignancies (sensitivity 85.7%) and ruling out malignancy in all 43 benign cases (specificity 100%). Its overall accuracy was 98.0%, with only one misclassification—a follicular neoplasm that was follicular carcinoma. The high negative predictive value (97.7%) indicates that a benign FNAC result strongly suggests the nodule is not malignant.

Table 5. Diagnostic accuracy of FNAC against histopathology.

Parameter	Value (%)	95% Confidence Interval
Sensitivity	85.70%	48.7% - 97.4%
Specificity	100%	91.8% - 100%
Positive Predictive Value	100%	61.0% - 100%
Negative Predictive Value	97.70%	88.0% - 99.9%
Accuracy	98.00%	89.4% - 99.9%

4.7. FNAC vs Histopathology

Table 6 shows that FNAC accurately classified 49 of 50 cases (98% accuracy), including 38 benign and 6 malignant. One follicular neoplasm was confirmed malignant, and no benign FNAC result was missed. The data show FNAC's high specificity (100%) and solid sensitivity (85.7%), with the main diagnostic challenge in the indeterminate follicular neoplasm category.

Table 6. FNAC results vs. histopathology results of the study people (N = 50).

FNAC Result	Benign on Histo	Malignant on Histo	Total
Benign (Colloid-Bethesda II)	38	0	38
Follicular Neoplasm (Bethesda IV)	5	1	6
Malignant (Papillary-Bethesda VI)	0	6	6
Total	43	7	50

4.8. Histopathological Subtypes

Table 7 presents that among 7 malignant cases, papillary carcinoma was most common (6 cases, 85.7%), followed by follicular carcinoma (1 case, 14.3%). Among benign cases, multinodular goiter was most common (34 cases, 79.1%), followed by follicular adenoma (5 cases, 11.6%) and colloid goiter (4 cases, 9.3%).

Table 7. Histopathological subtype distribution (N = 50).

Diagnosis	Subtype	Number	Percentage
Malignant (n = 7)	Papillary Carcinoma	6	85.70%
	Follicular Carcinoma	1	14.30%
Benign (n = 43)	Multinodular Goiter	34	79.10%
	Follicular Adenoma	5	11.60%
	Colloid Goiter	4	9.30%

4.9. Risk Stratification Model

Table 8 shows that managing patients with indeterminate FNAC results (Bethesda IV) in thyroid surgery is challenging due to uncertain cancer risk. In this study, 6 patients with follicular neoplasms on FNAC had a malignancy rate of 16.7% (1 of 6). Adding the predictor “extreme age” (<20 or >50 years), they divided into two risk groups: follicular neoplasm + extreme age (2 patients), 50% malignancy—recommend total thyroidectomy; and follicular neoplasm + age 21 - 50 years (4 patients), 0% malignancy—recommend diagnostic lobectomy.

Table 8. Risk stratification model for follicular neoplasm (Bethesda IV) using age.

Risk subgroup (Bethesda IV)	Number of Patients	Malignant Patients	Malignancy Rate (%)
With Extreme Age (<20 or >50 Years)	2	1	50%
Without Extreme Age (21 - 50 Years)	4	0	0%
Overall Bethesda IV	6	1	16.70%

5. Discussion

The study evaluated 50 patients with thyroid swelling undergoing thyroidectomy to identify clinical and cytological predictors of malignancy and assess FNAC accuracy. The malignancy rate was 14.0%, similar to previous reports: Htwe *et al.* reported 10% in goitrous thyroids [14], Tarrar *et al.* reported 13.33% [15], Islam *et al.* reported 18.65% in solitary nodules [16], and Huque *et al.* reported 21.11% [17]. The lower rate may be due to the inclusion of multinodular goitres (68%),

which have a lower malignancy risk than solitary nodules [18]. Despite this, a 14% malignancy rate highlights the importance of preoperative risk assessment.

Age was a descriptively strong predictor of malignancy in this study. Patients at the extremes of age (<20 years and >50 years) had a malignancy rate of 33.3% each, compared to only 9.1% in those aged 21 - 50 years. This finding is consistent with the well-known bimodal distribution of thyroid cancer risk [4] [19]. Cady *et al.* demonstrated that younger age (<20 years) and older age (>60 years) are independent risk factors for aggressive thyroid cancer [20]. Similarly, the American Thyroid Association guidelines note that age <20 years and >70 years increases the suspicion of malignancy [4]. In our series, the youngest patient (11 years) had papillary carcinoma, and the oldest (59 years) had follicular carcinoma, reinforcing the importance of age in clinical decision-making.

Although thyroid swelling was more common in females (84%), the malignancy rate was higher in males (25.0% vs. 11.9%). This male predominance of malignancy, despite lower overall nodule prevalence, is well documented [5]. Tarrar *et al.* reported a 25% malignancy rate in males compared to 10.5% in females [15]. The odds ratio of 2.47 in our study (though not statistically significant, 95% CI: 0.41 - 14.8, $p = 0.31$ by Fisher's exact test due to small sample size) aligns with the literature, indicating that on gender basis male confers high risk of thyroid cancer than female. Therefore, male patients with thyroid swelling warrant more aggressive evaluation.

Solitary thyroid nodules had a 26.7% malignancy rate, over three times higher than multinodular goiter (8.8%), aligning with studies showing higher cancer risk in solitary nodules [18] [21]. Notably, 3 of 7 malignant cases also arose in multinodular goiters, indicating cancer can occur there. Short symptom duration (<2 years) correlated with higher malignancy (16.7%) than longer duration (≥ 2 years) (11.5%), likely because rapidly growing or recent nodules are more suspicious, as clinical guidelines emphasize [4] [5].

Ultrasonography was valuable: all 7 malignant nodules were solid, and no malignancy was found in purely cystic lesions. The malignancy rate among solid nodules was 20.0%, aligning with a meta-analysis showing a sensitivity of 69% and specificity of 56% for solid composition [6] [22]. Cystic nodules are almost always benign, but complex cystic nodules with solid parts can still be cancerous. Our finding that all malignant nodules were solid highlights ultrasound's role in triaging for FNAC.

FNAC showed excellent diagnostic performance with a sensitivity 85.7%, a specificity 100%, and an accuracy 98.0%. These results are comparable to published data, such as Chandanwale *et al.* (sensitivity 90%, specificity 100%) [23] and Basharat *et al.* (sensitivity 80%, specificity 97.7%) [24]. The high specificity and positive predictive value (100%) suggest that a cytological diagnosis of malignancy is reliable. The negative predictive value (97.7%) indicates that benign FNAC effectively excludes malignancy, reducing unnecessary surgery. One case was misclassified—a follicular neoplasm later identified as follicular carcinoma—highlighting FNAC's limitation in differentiating follicular adenoma from carcinoma [10] [25].

The histopathological subtype distribution in this study showed that, among malignant cases, papillary carcinoma was the most common (6; 85.7%), followed by follicular carcinoma (1; 14.3%). This predominance of papillary carcinoma is consistent with global epidemiological data, which reports that papillary thyroid cancer accounts for 80 - 85% of all thyroid malignancies [1] [2]. Similarly, a large Bangladeshi series reported papillary carcinoma in 76.9% of malignant thyroid specimens [26]. Among benign cases, multinodular goiter was the most frequent diagnosis (79.1%), followed by follicular adenoma (11.6%) and colloid goiter (9.3%). This distribution mirrors findings from other South Asian studies, where multinodular goiter remains the predominant benign lesion in patients undergoing thyroidectomy [14] [17].

Six patients (12%) had a cytological diagnosis of follicular neoplasm (Bethesda IV), an indeterminate category. The overall malignancy rate was 16.7% (1/6), within the reported 15% - 30% range for Bethesda IV nodules [8] [10]. In an exploratory analysis, adding the clinical predictor of extreme age (<20 or >50 years), we further stratified risk: patients with follicular neoplasm plus extreme age had a 50% malignancy rate, while those aged 21 - 50 had 0%. However, given that there are only six Bethesda IV cases and two patients in the extreme-age subgroup, this finding remains purely hypothesis-generating and does not substantiate direct operative recommendations. External validation involving larger cohorts is imperative prior to clinical implementation. If this approach is validated, it could potentially decrease the number of unnecessary total thyroidectomies performed for benign conditions, thereby reducing the risk of complications such as hypocalcemia and nerve injury [13]. The Bethesda System estimates malignancy risks of 0% - 3% for Bethesda II, 10% - 30% for Bethesda IV, and 97% - 99% for Bethesda VI [8]. Our observed rates (0%, 16.7%, and 100%) fall within these ranges, validating the applicability of the categories. The absence of Bethesda III and V cases reflects our small sample size and cytological practice.

6. Limitations of This Study

Several limitations must be acknowledged: small sample size (n=50) limiting statistical power; single-center design with potential selection bias; short study period (6 months); absence of full Bethesda categories (III, V) and molecular markers (BRAF, TERT); limited ultrasound data (only solid/cystic consistency, lacking detailed features like microcalcifications). The proposed risk model requires external validation in larger, prospective cohorts. The proposed exploratory risk model requires external validation in larger, prospective cohorts.

7. Conclusion

This study confirms malignancy in 14% of patients undergoing thyroidectomy for thyroid swelling. Key associated predictors include age (<20 or >50), male sex, solitary nodule, short symptom duration, and solid ultrasound. FNAC has high accuracy, with a negative predictive value of 97.7%. For Bethesda IV nodules, an

exploratory analysis suggests that extreme age enhances risk assessment, showing a 50% malignancy risk in a very small subgroup. A combined FNAC and age algorithm requires external validation before clinical use. Larger studies are needed to validate this model and add ultrasound and molecular predictors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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