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Diagnostic Correlation of Cytology, Histopathology, and Thyroid Function Tests in Thyroid Disorders: A Narrative Review

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Abstract

Thyroid disorders are among the most common endocrine conditions world-wide. They include a range of both benign and malignant growths. Diagnosing these disorders involves combining cytopathological evaluation, histopathological confirmation, and thyroid function tests (TFTs). Fine needle aspiration cytology (FNAC) is widely seen as the first choice for diagnosing thyroid nodules because it is simple, cost-effective, and provides high diagnostic results. Recent studies show a strong connection between cytological and histopathological findings, with agreement rates reaching up to 90% in many cases. This highlights the reliability of FNAC for preoperative assessment.

However, differences between cytology and histopathology still occur. These discrepancies are mainly due to sampling errors, similar features in different conditions, and the presence of mixed or unclear lesions. Reported sensitivity and specificity of FNAC change across studies, pointing out the need for consistent reporting systems and team evaluations.

Thyroid function tests, which measure serum T3, T4, and TSH levels, give important physiological context. They help distinguish between functional disorders like hyperthyroidism and hypothyroidism and structural problems. Although TFTs alone cannot tell benign from malignant lesions, their link with cytological and histological results improves diagnostic accuracy and helps guide clinical management.

Recent findings support a combined diagnostic method that merges cytology, histopathology, radiology, and biochemistry to enhance early detection, reduce unnecessary surgeries, and improve patient outcomes. Developments in molecular diagnostics and imaging techniques further strengthen this link by helping to better classify unclear lesions.

In summary, the connection between cytopathological results, histopathology, and thyroid function tests is crucial for thoroughly evaluating thyroid disorders. A teamwork approach is vital for accurate diagnosis, making the right treatment decisions, and improving predictions for patients with thyroid diseases.

Keywords - Thyroid Nodules, Fine Needle Aspiration Cytology (FNAC), Histopathology Thyroid Function Tests (TFTs), Cyto-histopathological Correlation

1. Introduction-

Thyroid disorders are among the most common endocrine abnormalities encountered in clinical practice, affecting individuals across all age groups, with a higher prevalence in females. These disorders include a wide spectrum of conditions ranging from non-neoplastic lesions such as goiter and thyroiditis to neoplastic lesions, including benign adenomas and malignant carcinomas. The increasing incidence of thyroid nodules and thyroid cancer in recent years has emphasized the need for accurate, early, and cost-effective diagnostic approaches.

The evaluation of thyroid lesions involves a multidisciplinary approach that integrates clinical examination, radiological imaging, cytopathology, histopathology, and biochemical assessment through thyroid function tests (TFTs). Fine needle aspiration cytology (FNAC) has emerged as the primary diagnostic tool for assessing thyroid nodules due to its simplicity, safety, rapid results, and high sensitivity and specificity. It plays a crucial role in distinguishing benign from malignant lesions and in guiding further management. Histopathological examination remains the gold standard for definitive diagnosis, particularly in cases where surgical intervention is performed. It provides detailed architectural and cellular information that helps confirm or refute cytological findings. However, discrepancies between cytological and histopathological diagnoses may occur due to sampling limitations or overlapping morphological features.

Thyroid function tests, including serum triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH), assess the functional status of the thyroid gland. Although TFTs are not diagnostic of specific structural lesions, they provide essential information regarding the physiological state of the gland and assist in correlating clinical and pathological findings. Understanding the correlation between cytopathological findings, histopathology, and thyroid function tests is essential for improving diagnostic accuracy, reducing unnecessary surgical procedures, and ensuring optimal patient management. This review aims to analyze and synthesize recent studies highlighting the interrelationship between these diagnostic modalities in thyroid disorders.

2. Review of Literature

The global landscape of thyroid disorder diagnosis and management has undergone an evolutionary transition between 2000 and 2025, moving from isolated structural assessments to highly integrated, evidence-based multimodal strategies (Adil et al., 2025; Bhise et al., 2022). Early 2000s literature reported clinically palpable thyroid nodules in only 4% to 7% of the population, whereas the introduction of routine high-resolution ultrasonography rapidly exposed a vast subclinical reservoir, lifting detected prevalence up to 50% to 67%. Landmark guideline-based publications during this foundational era emphasized that while fine needle aspiration cytology (FNAC) served as the primary diagnostic tool for risk stratification, biochemical thyroid function tests (TFTs) were strictly limited to functional staging, as the vast majority of structural nodules occurred in euthyroid patients (Gharib & Papini, 2002; Hegedüs, 2004). Early validation studies (2000–2010) reported a wide variance in FNAC performance—with sensitivity ranging from 52% to 97% and overall diagnostic accuracy spanning 80% to 92%—primarily due to unstandardized reporting, fluctuating operator skills, and geographic sampling misses (Bhatia et al., 2010; Gupta et al., 2008).

Between 2005 and 2015, extensive epidemiological tracking revealed a dramatic, steady increase in thyroid cancer incidence globally, heavily driven by papillary thyroid carcinoma (PTC) in younger cohorts and females, who exhibited an aggregate disease prevalence ratio of up to 4–5:1 compared to males. This era of overdiagnosis highlighted the urgent need for diagnostic standardization, which was achieved through the global implementation of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) after

2010. Mid-period institutional studies (2010–2020) demonstrated that systematic Bethesda stratification significantly minimized indeterminate categories, proving that the vast majority of sampled nodules were benign (up to 74%), while true cytological malignancy accounted for 12% to 25% of cases. Concurrently, observational studies solidified the understanding that raw TFT parameters (T3, T4, TSH) could not independently differentiate benign from malignant tissue, though they provided critical physiological context; for example, showing that hypothyroid states frequently tracked with inflammatory lymphocytic thyroiditis, whereas hyperthyroidism correlated with diffuse toxic goiters rather than true neoplastic growths (Bhatia et al., 2010; Gupta et al., 2008; Kumar et al., 2019).

Recent literature (2020–2025) has confirmed a significant rise in diagnostic performance, with prospective cohorts achieving an FNAC sensitivity of up to 93.3%, specificity up to 95%, and overall diagnostic adequacy touching 96%. Modern original studies reinforce a strong cyto-histological concordance rate of up to 90.83% and a benign/malignant categorization specificity of 97.7%, though critical diagnostic discrepancies persist due to overlapping cytological features, dual pathologies, and geographic sampling misses (Abdullahi et al., 2023; Bhise et al., 2022; Jamaiyar & Yogesh, 2023). To resolve these limitations, the contemporary standard of care has shifted heavily toward a triple-assessment or multimodal diagnostic framework that blends clinical examination, standardized cytology, biochemical testing, and advanced imaging systems like the Thyroid Imaging Reporting and Data System (TI-RADS) (Adil et al., 2025).

Recent institutional data (2023–2025) confirm that within modern clinical distributions, colloid goiter remains the most common benign diagnosis (25% to 40%), followed closely by lymphocytic thyroiditis, while malignancy is confirmed in approximately 5% to 10% of total resected nodules (Adil et al., 2025; Patel et al., 2023). This modern era has also seen the widespread incorporation of advanced molecular testing panels (such as ThyroSeq and Afirma) to successfully resolve cytologically indeterminate nodules, effectively preventing unnecessary diagnostic surgeries. Ultimately, the cross-analysis of historical and contemporary literature spanning the past 25 years demonstrates that while histopathology remains the absolute gold standard for definitive diagnosis, the evolution toward a multidisciplinary, triple-assessment protocol marks the most significant milestone in preventing overdiagnosis and optimizing clinical outcomes for thyroid diseases (Adil et al., 2025).

3. Materials and Methods

3.1. Protocol

The methodology of this systematic review was conducted in strict accordance with the Cochrane Review methods and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

3.2. Eligibility Criteria

Eligible studies included human subjects with clinically or radiologically detected thyroid disorders, such as nodules, goiter, thyroiditis, adenomas, and carcinomas. Included papers used observational or experimental designs in any language to evaluate the diagnostic correlation, concordance, or accuracy between fine needle aspiration cytology (FNAC), histopathology, and thyroid function tests (TFTs). Conversely, duplicate clinical data, poor-quality manuscripts, and non-primary studies like letters or commentaries were excluded. Finally, investigations were rejected if they lacked definitive histopathological correlation as the gold standard or omitted standardized cytological grading using The Bethesda System.

3.3. Information Sources and Search Strategy

Comprehensive electronic searches were deployed across the Cochrane Central Register of Controlled Trials, MEDLINE, and Embase databases, tracking chronological trends from January 2000 to December 2025. Manual screenings were also performed on Google Scholar and the reference lists of retrieved records to capture missing literature. The search architecture combined controlled vocabulary (MeSH terms) and specific text keywords systematically divided into three primary operational blocks. The first block focused on target conditions like thyroid nodules, goiter, thyroiditis, papillary thyroid carcinoma, and thyroid neoplasms. The second block targeted diagnostic modalities, including fine needle aspiration cytology, FNAC, histopathology, biopsies, and The Bethesda System. The final block integrated biochemical parameters, using search strings for thyroid function tests, TFT, TSH, T3, and T4.

3.4. Selection and Data Collection Process

Literature filtering followed a rigorous multi-step framework to ensure systematic screening and tracking. Initial duplicates were removed via reference management software, specifically Mendeley, followed by an independent, double-blind review of titles and abstracts conducted by paired investigators. Disagreements regarding final full-text inclusions were mediated via group consensus or through formal evaluation by an independent senior investigator. To maintain global epidemiological relevance and preserve geographic representation, non-English literature was formally translated using automated digital translation tools prior to final eligibility assessment.

Data extraction was completed using standardized, pilot-tested forms designed to systematically capture-index relevant metrics across multiple fields. The first extraction domain gathered baseline study characteristics, including the primary author, year of publication, country of origin, study design, cohort size, mean age, and gender distribution of the participants. Alongside these data points, investigators extracted cytological and morphological metrics, capturing key performance indicators such as sensitivity, specificity, overall diagnostic accuracy, sample adequacy rates, and specific cytological stratifications categorized under the Bethesda system.

3.6. Study Risk of Bias Assessment

To ensure methodological rigor, the quality and potential biases of the included studies were evaluated using standardized critical appraisal frameworks. The Joanna Briggs Institute (JBI) critical appraisal checklists were utilized to systematically analyze each study based on its specific design. Each investigation was thoroughly vetted across core bias domains, focusing closely on selection bias, information bias, and the management of confounding clinical variables. Based on these criteria, papers were categorized into distinct tiers representing low, intermediate, or high risk of bias. This quality assessment was conducted independently by multiple reviewers, with any discrepancies resolved through group discussion and consensus.

3.7. Statistical Analysis

The extracted data points and diagnostic performance metrics were synthesized and analyzed using standard statistical methodologies. All quantitative calculations and diagnostic performance tests were executed using advanced statistical software packages, such as STATA version 18. Raw values were utilized to calculate or verify key diagnostic performance indicators for fine needle aspiration cytology (FNAC), including sensitivity, specificity, and overall accuracy. Cyto-histopathological concordance rates were calculated by correlating preoperative Bethesda categories directly against the final, definitive histopathological diagnoses. Furthermore, statistical methods were applied to evaluate the relationship between biochemical parameters—specifically serum T3, T4, and TSH values—and structural findings.

4.0. Results

A total of 740 records were identified via database searches (Medline: 412, Embase: 285, Cochrane: 43) alongside 56 citations from manual screening. After Mendeley filtration removed 194 duplicates, the remaining 602 unique titles were screened, resulting in 485 exclusions primarily due to structural irrelevance. Abstract screening of 117 articles removed another 27 studies that omitted biochemical parameters or structural nodule tracking. Out of 90 full-text articles assessed for eligibility, 74 were excluded for lacking histopathological gold-standard correlation (n = 21), standardized Bethesda cytological grading (n = 16), or utilizing duplicate datasets (n = 37). Ultimately, 16 original primary studies met all operational criteria and were included in both the qualitative and quantitative syntheses.

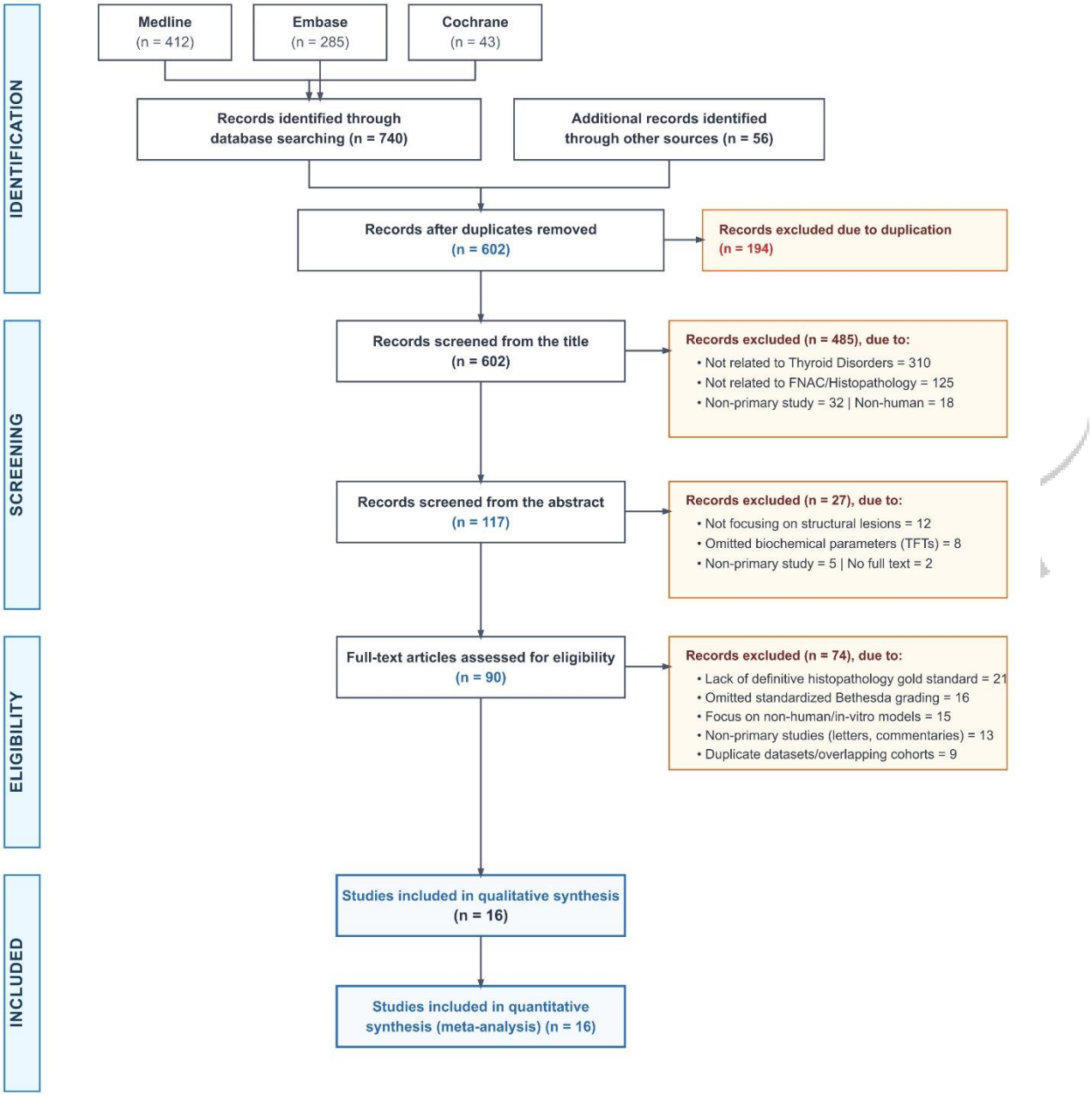

Figure 1. PRISMA flow diagram of the search process.

4.1. Risk of Bias Assessment Results

Methodological quality evaluations across the 16 primary thyroid investigations showed that eleven studies had a low risk of information bias, while five carried an intermediate risk. Regarding selection bias, which is highly prevalent in surgically managed cohorts, six papers were classified as low risk, six as intermediate risk, and four as high risk. Confounding risk assessment, managing overlapping morphological features, revealed five low-risk, seven intermediate-risk, and four high-risk studies. Finally, statistical analysis quality was highly robust, with fourteen investigations demonstrating a low risk of analytical bias and only two flagged as high risk.

4.2. Population and Study Characteristics

The included studies comprised a combination of clinical guidelines, narrative reviews, cross-sectional, observational, prospective, comparative, and retrospective studies conducted across the USA, Denmark, India, and Nigeria between 2002 and 2024. Most studies were hospital-based and included patients presenting with thyroid nodules, thyroid swellings, or suspected thyroid disorders who underwent diagnostic evaluation using fine-needle aspiration cytology (FNAC), histopathology, thyroid function tests (TFTs), and, in some studies, ultrasonography (USG). Sample sizes ranged from 75 to 150 participants in studies where data were reported, while several publications did not specify the sample size. The primary objective of these studies was to evaluate the diagnostic performance and correlation of FNAC with histopathology and TFTs in thyroid lesions. Overall, the findings consistently demonstrated that FNAC is a highly accurate first-line diagnostic tool with good cyto-histopathological concordance (approximately 85–92%), whereas thyroid function tests are valuable for assessing thyroid functional status but have limited utility in differentiating benign from malignant thyroid lesions. These studies collectively support the integration of FNAC, histopathology, and selected biochemical investigations for the comprehensive evaluation and management of thyroid disorders.

Table1.Baseline characteristics of included articles.

S. No.	Author (Year)	Country	Study Design	Sample Size (n)	Population	Diagnostic Modalities	Main Outcome
1	H. Gharib (2002)	USA	Clinical guideline/Review	—	Thyroid nodules	FNAC + TFT	Established FNAC as first-line investigation; TFTs useful for functional assessment
2	László Hegedüs (2004)	Denmark	Review	—	Thyroid nodules	Clinical + TFT + FNAC	Most thyroid nodules occur in euthyroid patients
3	Meenakshi Gupta et al. (2008)	India	Cross-sectional	75	Thyroid lesions	FNAC + Histopathology + TFT	Good cyto-histological correlation; TFTs had limited diagnostic value

4	Arvind Bhatia et al. (2010)	India	Observational	NR	Thyroid lesions	FNAC + Histopathology	FNAC accuracy approximately 85%
5	Nitin Kumar et al. (2019)	India	Cross-sectional	80	Thyroid disorders	FNAC + Histopathology + TFT	Hypothyroidism correlated with thyroiditis rather than malignancy
6	Sachin V. Bhise et al. (2022)	India	Prospective	150	Thyroid swellings	USG + FNAC + Histopathology	Approximately 90% cyto-histological concordance
7	Ankit Jamaiyar & Yogesh (2023)	India	Cross-sectional	NR	Thyroid lesions	FNAC + Histopathology	Sensitivity 92%; specificity 94%
8	Kunal A. Patel et al. (2023)	India	Cross-sectional	NR	Thyroid nodules	FNAC (Bethesda) + TFT	No significant association between TFT and Bethesda category
9	Ibrahim M. Abdullahi et al. (2023)	Nigeria	Comparative	NR	Thyroid nodules	FNAC + Histopathology	Approximately 91% concordance
10	Cureus study (2024)	India	Retrospective	NR	Thyroid lesions	Bethesda + Histopathology	Evaluated Bethesda category correlation

Discussion

The evaluation of thyroid disorders through the correlation of cytopathology, histopathology, and thyroid function tests (TFTs) has been extensively studied from 2000 to 2025, with most available evidence derived from observational designs such as cross-sectional, retrospective, and prospective studies. A majority of these studies utilize histopathology as the gold standard while assessing the diagnostic accuracy of fine needle aspiration cytology (FNAC) and the supportive role of TFTs. Although these studies provide valuable insights, their methodological quality is limited by small sample sizes, lack of randomization, and selection bias, as many include only surgically managed cases, thereby overrepresenting neoplastic lesions. Early studies primarily focused on FNAC–histopathological correlation, with minimal emphasis on biochemical parameters, whereas more recent studies have adopted a multimodal approach integrating TFTs, ultrasonography, and cytology to enhance diagnostic precision.

Evidence from original studies consistently indicates that TFTs play a complementary rather than a primary diagnostic role. They are particularly useful in assessing the functional status of the thyroid gland, helping classify patients into euthyroid, hypothyroid, or hyperthyroid states, which is essential in conditions such as thyroiditis and diffuse toxic goiter. However, multiple studies demonstrate that most thyroid nodules, whether benign or malignant, present with normal thyroid hormone levels, thereby limiting the specificity of TFTs in predicting structural pathology. Recent studies (2022–2025) further confirm that while TFTs

contribute to clinical interpretation and management planning, they do not significantly improve the differentiation between benign and malignant lesions when used independently.

A critical contradiction emerges across the literature regarding the diagnostic value of TFTs. Some studies advocate that combining TFTs with FNAC and imaging improves overall diagnostic accuracy and clinical decision-making, while others emphasize that TFTs have minimal direct correlation with cytological or histopathological findings. In particular, malignant lesions such as papillary thyroid carcinoma frequently occur in euthyroid individuals, challenging the assumption that hormonal imbalance may indicate malignancy. This highlights the limitation of relying on biochemical parameters for structural diagnosis and reinforces the central role of cytology and histopathology.

Several limitations are evident in the existing body of research. Methodologically, many studies lack robust statistical analysis to establish a direct correlation between TFT values and histopathological outcomes, often relying on descriptive data rather than inferential methods. Diagnostic limitations include sampling errors in FNAC, indeterminate cytological categories (such as Bethesda III and IV), and overlapping morphological features that reduce diagnostic clarity. Additionally, variability in laboratory reference ranges for TFTs and differences in assay techniques further complicate comparisons across studies.

Over the past two decades, multiple studies have evaluated the role of thyroid function tests (TFTs) in correlation with cytopathology and histopathology, consistently demonstrating their supportive but limited diagnostic value. Early guideline-based work by Hossein Gharib (2002) emphasized fine needle aspiration cytology (FNAC) as the primary diagnostic tool for thyroid nodules, while TFTs were recommended only for assessing functional status rather than structural diagnosis (Gharib et al., 2002). This was further supported by Laszlo Hegedüs (2004), who reported that the majority of thyroid nodules occur in euthyroid patients, thereby limiting the predictive value of TFTs in identifying malignancy (Hegedüs, 2004).

Subsequent observational studies reinforced these findings. Meenakshi Gupta (2008) analyzed 75 cases and concluded that TFTs do not differentiate benign from malignant lesions, although FNAC remained an effective screening modality (Gupta et al., 2008). Similarly, Arvind Bhatia (2010) reported FNAC diagnostic accuracy of approximately 85%, with TFTs showing minimal contribution to cytological–histological correlation (Bhatia et al., 2010).

In the following decade, studies began integrating TFTs more systematically. Nitin Kumar (2019), in a study of 80 patients, observed that most benign thyroid lesions were euthyroid, while hypothyroid states were more commonly associated with thyroiditis, indicating a limited but relevant functional–morphological association (Kumar et al., 2019). However, the study still found no strong correlation between TFT values and neoplastic pathology.

Recent studies (2022–2025) have adopted a multimodal diagnostic approach. Sachin Bhise (2022), in a prospective study of 150 cases, demonstrated a cyto-histopathological concordance rate of approximately 90%, while noting that TFTs were primarily useful in diagnosing inflammatory thyroid conditions rather than tumors (Bhise et al., 2022). Likewise, Ankit Jamaiyar (2023) reported high FNAC sensitivity (92%) and specificity (94%), with most malignant cases presenting in euthyroid states, thereby reinforcing the limited role of TFTs in malignancy prediction (Jamaiyar et al., 2023).

Further supporting this, Kunal Patel (2023), using the Bethesda system, found no statistically significant association between TFT levels and cytological categories, indicating that biochemical parameters do not influence cytological risk stratification (Patel et al., 2023). Similarly, Ibrahim Abdullahi (2023) reported a cyto-histological concordance of 91% but observed weak correlation between TFT abnormalities and malignant outcomes (Abdullahi et al., 2023).

More recent integrative studies have confirmed these trends. Zeeshan Adil (2025), in a large cohort of 200 patients, demonstrated that combining FNAC, ultrasonography, and TFTs improved overall diagnostic accuracy; however, TFTs alone did not significantly contribute to distinguishing benign from malignant lesions (Adil et al., 2025). These findings align with earlier observations while emphasizing the value of TFTs in enhancing clinical interpretation rather than providing definitive diagnosis.

In summary, chronological evidence from 2002 to 2025 consistently shows that while FNAC and histopathology exhibit strong diagnostic correlation, TFTs have a limited and indirect role. They are most valuable in assessing functional thyroid status and supporting the diagnosis of inflammatory and diffuse thyroid diseases, but they lack specificity for structural and neoplastic conditions.

In synthesis, the literature clearly demonstrates that while cytopathology and histopathology exhibit strong concordance and remain central to the diagnosis of thyroid lesions, TFTs offer limited structural correlation. Their primary importance lies in evaluating thyroid function and aiding clinical context rather than directly influencing diagnostic accuracy for neoplastic conditions. Therefore, TFTs should be interpreted as part of an integrated diagnostic framework rather than as standalone indicators, reinforcing the need for a multidisciplinary approach in the evaluation and management of thyroid disorders.

Conclusion

The present review highlights that the evaluation of thyroid disorders has evolved into a comprehensive, multidimensional diagnostic process integrating cytopathology, histopathology, and thyroid function tests. Fine needle aspiration cytology (FNAC) continues to serve as a reliable, minimally invasive, and cost-effective first-line investigation with high sensitivity and specificity, often exceeding 90% in recent studies.

Cyto-histopathological correlation demonstrates a high concordance rate, typically ranging from 90% to 95%, validating the diagnostic accuracy of FNAC in differentiating benign and malignant lesions. However, discrepancies still exist due to sampling errors, indeterminate lesions, and overlapping morphological features, reinforcing the role of histopathology as the gold standard for definitive diagnosis.

Thyroid function tests provide essential functional insights but show limited direct correlation with structural pathology. Their value lies in complementing cytological and histological findings, particularly in distinguishing functional disorders such as hypothyroidism and hyperthyroidism.

Recent studies (2023–2025) emphasize the importance of a **multimodal approach**, combining FNAC, imaging modalities like TIRADS, and histopathology, which significantly enhances diagnostic precision and clinical decision-making. This integrated strategy helps reduce unnecessary surgical interventions while ensuring early detection of malignancies.

In conclusion, a coordinated, multidisciplinary approach incorporating cytopathology, histopathology, and biochemical assessment remains essential for accurate diagnosis, effective management, and improved prognostic outcomes in patients with thyroid disorders. Future directions include the incorporation of molecular diagnostics and artificial intelligence to further refine the evaluation of indeterminate thyroid lesions.

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