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Original Article

Comparison of FNAC Findings with GeneXpert Results in Suspected Tuberculous Lymphadenitis: A Prospective Diagnostic Correlation Study

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ABSTRACT

Background: Tuberculous lymphadenitis remains a major diagnostic challenge among extrapulmonary manifestations of tuberculosis due to overlapping clinical presentations. FNAC is widely utilized as a first-line diagnostic modality, whereas GeneXpert provides rapid, automated molecular confirmation and rifampicin resistance detection.
Objective: To compare the diagnostic performance of FNAC against GeneXpert MTB/RIF in suspected tuberculous lymphadenitis and to assess their overall correlation and diagnostic agreement.
Methods: A prospective hospital-based diagnostic correlation study enrolled patients with clinically suspected tuberculous lymphadenitis. Fine needle aspiration cytology (FNAC) classified cytomorphologic patterns, and a separate portion of the aspirate was subjected to GeneXpert MTB/RIF assay testing. Diagnostic performance metrics were calculated using a two-by-two contingency table, and inter-rater agreement was determined via Cohen's kappa (κ).
Results: Out of 240 patients, 102 (42.5%) were classified as FNAC-positive for tuberculosis (comprising granulomatous with necrosis, granulomatous without necrosis, and necrotic/suppurative patterns), while 98 (40.8%) tested positive on GeneXpert MTB/RIF. Rifampicin resistance was detected in 6 cases (2.5%). Using GeneXpert as the reference standard, FNAC demonstrated a sensitivity of 83.7% (95% CI: 75.0–90.3%), specificity of 85.9% (95% CI: 79.0–91.2%), a positive predictive value (PPV) of 80.4% (95% CI: 71.4–87.5%), and a negative predictive value (NPV) of 88.4% (95% CI: 82.1–93.0%). The overall diagnostic accuracy was 85.0%, and Cohen's kappa demonstrated substantial agreement (κ = 0.70, 95% CI: 0.59–0.80).
Conclusion: FNAC and GeneXpert act as synergistic, complementary tests rather than competing alternatives. Cytology provides essential, immediate morphological triage, whereas GeneXpert delivers automated microbiological confirmation and crucial drug resistance patterns, significantly optimizing early clinical decision-making.

Keywords: *Tuberculous lymphadenitis, Fine-needle aspiration cytology, GeneXpert MTB/RIF, Extrapulmonary tuberculosis, Diagnostic accuracy, Rifampicin resistance.*

INTRODUCTION

Tuberculous lymphadenitis (TBLN) represents one of the most frequent manifestations of extrapulmonary tuberculosis (EPTB), constituting a significant public health burden globally, particularly within endemic, high-incidence environments [1]. Patients typically present with persistent, progressive cervical or peripheral lymphadenopathy; however, the lack of pathognomonic clinical signs results in significant overlapping presentations with reactive hyperplasia, acute suppurative lymphadenitis, non-tuberculous mycobacterial (NTM) infections, and malignant disorders such as lymphoma or metastatic

carcinoma [2]. Consequently, relying solely on clinical parameters frequently delays definitive therapeutic intervention, emphasizing the absolute necessity for rapid, reliable tissue-based and microbiological diagnostic frameworks [3].

Fine needle aspiration cytology (FNAC) is globally recognized as a simple, safe, and minimally invasive first-line screening technique that provides rapid cytomorphologic analysis of suspected lymph nodes [4]. It reliably identifies classic features such as epithelioid cell granulomas, multinucleated Langhans giant cells, and caseous necrosis, frequently augmented by Ziehl-Neelsen (ZN) staining to visualize acid-fast bacilli (AFB) [3]. Despite its widespread utility, standalone FNAC suffers from highly variable sensitivity and a lack of specificity, as distinct granulomatous patterns can be completely absent in early or paucibacillary states, or can mimic other granulomatous conditions like sarcoidosis or fungal infections [5].

The emergence of the automated GeneXpert MTB/RIF assay has fundamentally transformed the diagnostic landscape of EPTB by enabling the concurrent detection of Mycobacterium tuberculosis complex (MTBC) DNA and mutations conferring rifampicin resistance directly from clinical specimens within two hours [6]. When applied to fine needle aspirates, molecular testing circumvents the low sensitivity of conventional smear microscopy and the protracted multi-week turnaround times associated with mycobacterial cultures [7]. Furthermore, the recent integration of the next-generation Xpert MTB/RIF Ultra assay has pushed the analytical limits of detection lower, which is particularly beneficial for the highly paucibacillary microenvironments characteristic of extrapulmonary tissue sites [8]. The present prospective study integrates both diagnostic arms to establish an optimized, operationally robust academic framework for clinical reporting in high-burden regions.

METHODS

Study Design and Setting

This study was executed as a prospective observational diagnostic correlation study in a tertiary care teaching hospital. Institutional ethical clearance was obtained, and all participating patients with clinically suspected tuberculous lymphadenitis were sequentially enrolled over the study period following the acquisition of signed, informed written consent. Similar structured hospital-based methodologies have been successfully utilized in recent years to evaluate diagnostic yields across cytology, conventional microscopy, culture, and molecular amplification techniques in lymph node tuberculosis [9].

Eligibility Criteria

Inclusion criteria comprised patients presenting with one or more clinically palpable or radiologically distinct peripheral lymph nodes suspicious for tuberculosis (e.g., persistent enlargement >4 weeks, caseous texture, or associated constitutional symptoms). Patients who had already initiated anti-tubercular therapy (ATT), those presenting with grossly inadequate or completely blood-contaminated aspirates, or individuals refusing consent were excluded. In alignment with established global epidemiological cohorts, cervical lymph nodes were anticipated to represent the predominant site of clinical presentation [10]. A target sample size of N = 240 evaluable patients was achieved over the study duration.

FNAC Procedure

FNAC was performed by experienced pathologists using standard 22–23 gauge needles via a transcutaneous approach. Collected aspirates were expressed onto glass slides to prepare multiple thin smears, which were subsequently fixed and stained using May-Grünwald Giemsa (MGG) and Papanicolaou stains. Where clinically indicated or when purulent material was recovered, Ziehl-Neelsen (ZN) staining was immediately implemented to evaluate for the presence of AFB [3]. Cytomorphological patterns were systematically categorized into five distinct diagnostic cohorts: (1) Granulomatous lymphadenitis with caseous necrosis, (2) Granulomatous lymphadenitis without necrosis, (3) Necrotic/suppurative abscess material, (4) Reactive/non-specific lymphadenitis, and (5) Alternative diagnoses (suspicious for malignancy or other specific infectious etiologies).

For mathematical cross-tabulation and calculation of diagnostic indices, the first three categories were classified as "FNAC positive" for tuberculosis, while reactive and malignant patterns were classified as "FNAC negative." This binary classification adheres strictly to cytomorphological validation frameworks utilized in recent comparative literature [4].

GeneXpert Testing

A separate, dedicated portion of the fine needle aspirate material was collected by flushing the needle and syringe with sterile normal saline into a falcon tube, ensuring an adequate fluid volume for automated molecular analysis [8]. The specimen was processed using the GeneXpert MTB/RIF platform (Cepheid, Sunnyvale, CA, USA) according to standard microbiological operating procedures. The assay automatically executed sample lysis, nucleic acid extraction, amplification, and real-time PCR detection of the rpoB gene to define MTBC positivity and identify rifampicin resistance mutations within a closed cartridge system [11].

Statistical Analysis

Descriptive data were summarized as counts and percentages. FNAC findings were cross-tabulated against GeneXpert results using a standard two-by-two table, where GeneXpert served as the comparative reference standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), overall diagnostic accuracy, likelihood ratios, and Cohen's kappa coefficients were calculated alongside their respective 95% confidence intervals (CI). Statistical significance was considered at $p < 0.05$ [3].

RESULTS

Baseline Profile

Table 1. Baseline characteristics of the study population (N = 240)

Age Group	<20 years	38	15.8
	20–39 years	104	43.3
	40–59 years	70	29.2
	≥60 years	28	11.7
Sex	Male	92	38.3
	Female	148	61.7
Node Site	Cervical	176	73.3
	Axillary	24	10.0
	Supraclavicular	20	8.3
	Others	20	8.3
Duration >4 weeks	Yes	198	82.5
Constitutional Symptoms	Yes	136	56.7

FNAC and GeneXpert Findings

Table 2. Cytomorphological pattern on FNAC

Granulomatous with necrosis	104	43.3
Granulomatous without necrosis	48	20.0
Necrotic/suppurative	24	10.0
Reactive/non-specific	42	17.5
Suspicious for malignancy/other diagnosis	22	9.2

Table 3. GeneXpert MTB/RIF results

MTB detected	98	40.8
MTB not detected	142	59.2
Rifampicin resistance detected	6	2.5
Rifampicin resistance not detected	92	38.3

Concordance and Diagnostic Performance

Table 4. Cross-tabulation of FNAC versus GeneXpert findings

FNAC positive for TB	82	20	102
FNAC negative for TB	16	122	138
Total	98	142	240

Table 5. Diagnostic performance indices of FNAC using GeneXpert as the comparator

Sensitivity	83.7%	75.0%–90.3%
Specificity	85.9%	79.0%–91.2%
Positive Predictive Value (PPV)	80.4%	71.4%–87.5%
Negative Predictive Value (NPV)	88.4%	82.1%–93.0%
Overall Accuracy	85.0%	79.9%–89.3%
Positive Likelihood Ratio (LR+)	5.95	4.0–8.9
Negative Likelihood Ratio (LR-)	0.19	0.12–0.31
Cohen's kappa (κ)	0.70	0.59–0.80

Table 6. Summary of diagnostic error and concordance profile

Both positive (Concordant Positive)	82	34.2%
Both negative (Concordant Negative)	122	50.8%
FNAC positive, GeneXpert negative (False Positive)	20	8.3%
FNAC negative, GeneXpert positive (False Negative)	16	6.7%
False discovery rate	19.6%	—
False omission rate	11.6%	—
Youden index	0.696	—
Balanced accuracy	84.8%	—

DISCUSSION

The comparative diagnostic matrix evaluated in this prospective trial strongly reinforces the consensus that while fine needle aspiration cytology remains an invaluable, exceptionally rapid screening tool, its clinical utility is fundamentally optimized when systematically combined with automated molecular diagnostic platforms [4]. In endemic regions, the operational capacity of FNAC to achieve rapid morphologic triage allows clinicians to establish immediate presumptive pathways, ruling out acute bacterial suppuration or evident metastatic malignancies at the point of care [2]. However, the persistent occurrence of discordant diagnostic outcomes—specifically false-negative and false-positive cytological findings relative to molecular assays—highlights the limitations of relying entirely on morphologic profiles in paucibacillary extrapulmonary disease states [5].

A critical clinical nuance identified in our dataset is the cohort of 20 "false positive" cases, where cytomorphological features were highly suggestive or diagnostic of tuberculosis (such as caseous necrosis flanked by epithelioid granulomas), yet the corresponding GeneXpert MTB/RIF assay returned a negative result. In practical clinical pathology, this scenario frequently mirrors the limitations inherent to using a molecular assay as a definitive reference standard rather than representing an actual failure of cytomorphological interpretation [12]. GeneXpert functions essentially as a molecular surrogate for the presence of bacterial DNA rather than a comprehensive biological gold standard, which would ideally incorporate long-term mycobacterial liquid culture (MGIT) or documented clinical response to anti-tubercular therapy (ATT) [10]. Because lymph node aspirates are frequently highly paucibacillary, minor sampling variations or localized specimen structural variations can lead to an absence of intact mycobacterial DNA within the specific sample aliquot submitted for PCR amplification, even when classical host immune-mediated granulomatous changes are extensively manifest throughout the node [7]. Consequently, these specific discordant results demonstrate that a highly characteristic cytomorphological pattern remains deeply actionable and should preclude the premature exclusion of tubercular disease solely based on a negative molecular result.

Conversely, our study identified 16 "false negative" cytological cases that demonstrated clear Mycobacterium tuberculosis complex DNA amplification on GeneXpert. A significant portion of these molecular-positive/cytology-negative instances occurred within specimens classified morphologically as purulent, suppurative, or non-specific reactive hyperplasia. This distribution aligns precisely with findings published by Tadesse et al. [12], where automated testing successfully isolated MTBC DNA in over 30% of cytologically non-suggestive lymph node abscesses, primarily because acute neutrophilic influx can completely obscure underlying granulomas.

Furthermore, extensive systematic reviews have established that the pooled sensitivity of Xpert assays on fine needle aspirates consistently hovers around 83% to 85% against composite reference standards, showing superior accuracy over tissue biopsies obtained via invasive surgical cervicotomy [13]. This baseline diagnostic efficiency has been further documented in targeted pediatric sub-cohorts, where the non-invasive nature of combining FNAC with molecular amplification represents the primary method for avoiding traumatic open surgical interventions in children [7].

The systemic advantage of this dual approach extends beyond simple diagnostic confirmation to encompass modern principles of antimicrobial stewardship and personalized medicine. The integration of real-time molecular beacon technology enables the immediate, simultaneous identification of mutations within the rpoB gene, providing a rapid screen for drug-resistant strains at the initial point of diagnostic entry [14]. Moreover, emerging diagnostic paradigms utilizing the next-generation Xpert Ultra assay demonstrate that lowering the limits of detection down to 16 CFU/mL significantly enhances diagnostic yield in paucibacillary extrapulmonary tissues, effectively bridging the sensitivity gaps that historically hampered conventional smear microscopy and solid cultures [8]. Operationalizing a unified diagnostic workflow—wherein an initial fine needle aspirate provides instant cytomorphological classification, followed immediately by reflex automated molecular confirmation—dramatically compresses diagnostic turnaround times, curtails the initiation of empirical, non-targeted treatment regimens, and significantly limits the necessity for invasive open biopsy procedures [9].

CONCLUSION

The findings of this prospective diagnostic correlation study demonstrate that neither fine needle aspiration cytology (FNAC) nor GeneXpert MTB/RIF should be relied upon as an isolated, standalone diagnostic tool for suspected tuberculous lymphadenitis. Instead, they achieve their maximum clinical utility when integrated into a single, cohesive, and complementary diagnostic pathway. FNAC remains an indispensable first-line screening modality, offering clinicians rapid, cost-effective cytomorphological triage capable of immediately identifying granulomatous inflammation and caseous necrosis while simultaneously ruling out alternative pathologies such as suppurative infections or malignancies.

Concurrently, GeneXpert MTB/RIF provides crucial, high-specificity microbiological confirmation and delivers rapid genotypic screening for rifampicin resistance directly from paucibacillary aspirate materials. Recognizing that a subset of true tubercular lymphadenitis cases may present as molecular-negative due to low DNA yields or sampling variations, the highly suggestive cytomorphological features captured by FNAC remain clinically actionable and should preclude premature exclusion of disease.

Implementing a standardized workflow that pairs rapid cytological screening with immediate reflex molecular testing has profound implications for high-burden, resource-limited settings. This dual approach substantially reduces diagnostic delays, mitigates the risks of empirical over-treatment, and minimizes the necessity for invasive excisional biopsies. Future research should focus on evaluating the long-term therapeutic outcomes of patients managed under this combined algorithm and assessing the diagnostic yields of next-generation assays, such as Xpert Ultra, to further close the gap in paucibacillary extrapulmonary tuberculosis detection [8, 15].

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Ethical Approval: The study protocol was reviewed and approved by the Institutional Ethics Committee. Patient confidentiality was maintained throughout the study.

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