Original Research

DIAGNOSTIC PERFORMANCE OF GENEXPERT MTB/RIF AND LINE PROBE ASSAY COMPARED WITH CONVENTIONAL DST IN EXTRAPULMONARY TUBERCULOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Extrapulmonary tuberculosis (EPTB) remains a major diagnostic challenge because of its paucibacillary nature, diverse clinical presentation, and difficulty in obtaining microbiological confirmation. Conventional culture-based drug susceptibility testing (DST), although considered the reference standard, is time-consuming and often delays initiation of appropriate therapy. Rapid molecular diagnostic techniques such as GeneXpert MTB/RIF and Line Probe Assay (LPA) have emerged as important tools for early diagnosis and detection of rifampicin resistance in tuberculosis.

Aim: To evaluate the diagnostic performance of GeneXpert MTB/RIF and Line Probe Assay compared with conventional DST in extrapulmonary tuberculosis through a systematic review and meta-analysis.

Materials and Methods: A systematic review and meta-analysis was conducted according to PRISMA guidelines. Electronic databases including PubMed, Embase, Scopus, Web of Science, Cochrane Library, and Google Scholar were searched for studies published between January 2010 and March 2025. Studies evaluating GeneXpert MTB/RIF and/or LPA in extrapulmonary tuberculosis specimens using conventional DST as the reference standard were included. Pooled sensitivity, specificity, diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curves were calculated using a random-effects model.

Results: A total of 28 studies comprising 9,842 extrapulmonary specimens were included in the meta-analysis. The pooled sensitivity and specificity of GeneXpert MTB/RIF for detection of extrapulmonary tuberculosis were 83.4% (95% CI: 79.2–87.1%) and 96.8% (95% CI: 94.1–98.3%), respectively. The area under the SROC curve was 0.94. Subgroup analysis demonstrated highest sensitivity in lymph node aspirates (90.5%) and lowest sensitivity in pleural fluid specimens (52.3%). For rifampicin resistance detection, GeneXpert MTB/RIF showed pooled sensitivity and specificity of 91.2% and 98.5%, respectively. Line Probe Assay demonstrated pooled sensitivity of 88.7% (95% CI: 84.5–92.1%) and specificity of 99.1% (95% CI: 97.6–99.7%). Moderate heterogeneity was observed among included studies.

Conclusion: GeneXpert MTB/RIF and Line Probe Assay demonstrate high diagnostic accuracy for rapid detection of extrapulmonary tuberculosis and rifampicin resistance compared with conventional DST. Although conventional culture-based DST remains the reference standard, molecular assays significantly reduce diagnostic delay and facilitate early initiation of appropriate therapy. Combined use of molecular diagnostics and conventional DST may improve management outcomes in extrapulmonary tuberculosis.

Keywords: Extrapulmonary Tuberculosis, Genexpert MTB/RIF, Line Probe Assay, Drug Susceptibility Testing, Rifampicin Resistance, Molecular Diagnostics, Meta-Analysis.

INTRODUCTION

Tuberculosis (TB) continues to be one of the leading infectious causes of morbidity and mortality Worldwide despite substantial advances in diagnostic and therapeutic strategies. According to the World Health Organization (WHO), approximately 10.8 million people developed tuberculosis globally in 2025, with a significant burden concentrated in low- and middle-income countries [1]. Although pulmonary tuberculosis remains the most common form, extrapulmonary tuberculosis (EPTB) accounts for nearly 15–20% of all TB cases and represents an even greater

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proportion among children, immunocompromised individuals, and patients with human immunodeficiency virus (HIV) infection [2].

Extrapulmonary tuberculosis refers to tuberculosis involving organs other than the lungs, including lymph nodes, pleura, meninges, abdomen, bones and joints, genitourinary tract, and disseminated disease [3]. The diagnosis of EPTB is particularly challenging because of its diverse clinical manifestations, low bacillary load, and difficulty in obtaining adequate clinical specimens [4]. Conventional diagnostic techniques such as smear microscopy often demonstrate poor sensitivity in extrapulmonary samples owing to the paucibacillary nature of the disease [5].

Mycobacterial culture and conventional drug susceptibility testing (DST) remain the reference standards for diagnosis and detection of drug resistance in tuberculosis [6]. However, culture-based methods are time-consuming, often requiring several weeks to yield results, thereby delaying initiation of appropriate therapy [7]. Delay in diagnosis and treatment contributes to increased morbidity, complications, and continued transmission of drug-resistant tuberculosis strains [8].

The emergence and spread of multidrug-resistant tuberculosis (MDR-TB), particularly rifampicin-resistant TB, have further emphasized the need for rapid and accurate diagnostic methods [9]. Molecular diagnostic assays have transformed TB diagnosis by enabling rapid detection of Mycobacterium tuberculosis complex and associated resistance mutations directly from clinical specimens [10].

GeneXpert MTB/RIF is a cartridge-based nucleic acid amplification test that simultaneously detects Mycobacterium tuberculosis and rifampicin resistance within approximately two hours [11]. The assay targets the rpoB gene associated with rifampicin resistance and has been endorsed by the WHO as an initial diagnostic test for suspected tuberculosis and drug-resistant TB [12]. Several studies have reported high specificity of GeneXpert MTB/RIF in extrapulmonary specimens, although sensitivity varies depending on specimen type and bacillary burden [13,14].

Line Probe Assay (LPA) is another rapid molecular diagnostic technique based on reverse hybridization technology that detects mutations associated with resistance to rifampicin and isoniazid [15]. LPA offers the advantage of rapid multidrug-resistant TB diagnosis and has demonstrated excellent diagnostic accuracy in smear-positive pulmonary tuberculosis specimens [16]. However, the performance of LPA in extrapulmonary tuberculosis remains inconsistent because of variable bacterial load and specimen quality [17].

Numerous studies have evaluated the diagnostic utility of GeneXpert MTB/RIF and LPA in EPTB, but the reported sensitivity and specificity differ considerably among studies and specimen types [18–20]. Furthermore, comparative evidence evaluating both molecular assays against conventional DST in extrapulmonary specimens remains limited. A comprehensive systematic review and meta-analysis is therefore necessary to synthesize available evidence and determine the overall diagnostic performance of these molecular techniques.

Hence, the present systematic review and meta-analysis was undertaken to evaluate the diagnostic accuracy of GeneXpert MTB/RIF and Line Probe Assay compared with conventional drug susceptibility testing in extrapulmonary tuberculosis.

MATERIALS AND METHODS

Study Design and Protocol

The present study was conducted as a systematic review and meta-analysis to evaluate the diagnostic performance of GeneXpert MTB/RIF and Line Probe Assay (LPA) compared with conventional drug susceptibility testing (DST) in extrapulmonary tuberculosis (EPTB). The review methodology was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21].

Literature Search Strategy

A comprehensive electronic literature search was performed in PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and Google Scholar databases for studies published between January 2010 and December 2025. The search strategy included combinations of Medical Subject Headings (MeSH) terms and free-text keywords related to extrapulmonary tuberculosis and molecular diagnostic assays.

The following search terms were used:

- “Extrapulmonary tuberculosis”
- “EPTB”
- “GeneXpert MTB/RIF”
- “Xpert MTB/RIF”
- “Line Probe Assay”
- “LPA”
- “Drug susceptibility testing”
- “DST”
- “Rifampicin resistance”
- “Molecular diagnosis”
- “Sensitivity and specificity”
- “Meta-analysis”

Boolean operators “AND” and “OR” were applied appropriately to combine search terms. Reference lists of relevant studies and review articles were also manually screened to identify additional eligible studies.

Eligibility Criteria

Inclusion Criteria

Studies fulfilling the following criteria were included:

1. Original research articles evaluating GeneXpert MTB/RIF and/or Line Probe Assay in extrapulmonary tuberculosis specimens.
2. Studies comparing molecular assays with conventional culture-based drug susceptibility testing as the reference standard.
3. Studies reporting sufficient data to calculate sensitivity, specificity, true positive (TP), false positive (FP), true negative (TN), and false negative (FN) values.
4. Studies conducted on human subjects.
5. English-language publications.

Exclusion Criteria

The following studies were excluded:

1. Review articles, editorials, conference abstracts, letters, and case reports.
2. Studies without adequate diagnostic accuracy data.
3. Duplicate publications.
4. Animal studies.
5. Studies evaluating pulmonary tuberculosis alone without extrapulmonary specimens.

Study Selection

All retrieved records were imported into reference management software, and duplicate studies were removed. Two independent reviewers screened titles and abstracts for relevance. Full-text articles of potentially eligible studies were then assessed according to the inclusion and exclusion criteria. Disagreements between reviewers were resolved through discussion and consensus.

The PRISMA flow diagram was used to summarize the study selection process [21].

Data Extraction

Data extraction was independently performed by two reviewers using a standardized data extraction form. The following information was collected from each study:

- First author name
- Year of publication
- Country of study
- Study design
- Sample size
- Type of extrapulmonary specimen
- Diagnostic method used
- Reference standard
- Sensitivity and specificity values
- TP, FP, TN, and FN data
- Rifampicin resistance detection rates

Extracted data were cross-checked for accuracy before statistical analysis.

Quality Assessment

The methodological quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [22]. The tool evaluates risk of bias and applicability concerns across four domains:

1. Patient selection
2. Index test
3. Reference standard
4. Flow and timing

Each domain was categorized as low risk, high risk, or unclear risk of bias.

Outcome Measures

Primary Outcome

- Diagnostic accuracy of GeneXpert MTB/RIF and LPA compared with conventional DST in extrapulmonary tuberculosis.

Secondary Outcomes

- Pooled sensitivity and specificity of GeneXpert MTB/RIF for EPTB diagnosis.
- Diagnostic performance of LPA for rifampicin resistance detection.
- Subgroup analysis based on specimen type.
- Diagnostic odds ratio (DOR) and area under the summary receiver operating characteristic (SROC) curve.

Statistical Analysis

Meta-analysis was performed using a random-effects model because of anticipated heterogeneity among studies. Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were calculated with 95% confidence intervals (CI).

Summary receiver operating characteristic (SROC) curves were generated to evaluate overall diagnostic performance. Heterogeneity among studies was assessed using Cochran's Q test and the I^2 statistic. An I^2 value greater than 50% was considered indicative of substantial heterogeneity [23].

Subgroup analyses were conducted according to specimen type, including lymph node aspirates, cerebrospinal fluid, pleural fluid, tissue biopsies, and ascitic fluid. Publication bias was evaluated using Deeks' funnel plot asymmetry test [24].

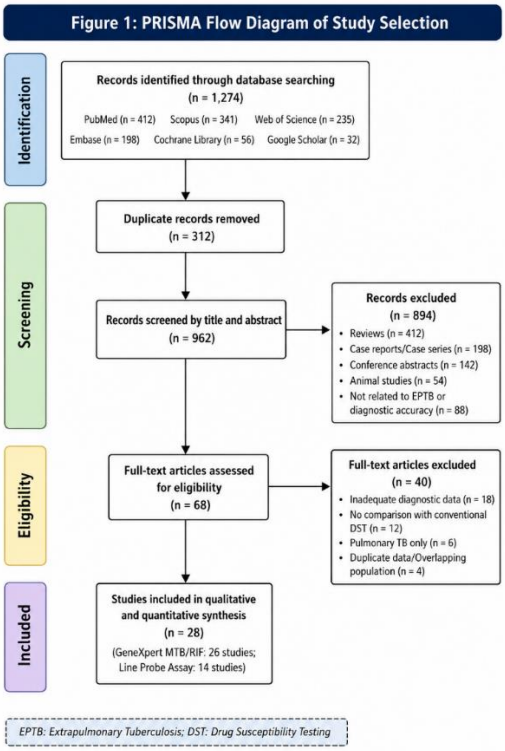
All statistical analyses were performed using Meta-DiSc software version 1.4 and STATA version 17.0.

RESULTS

Study Selection

A total of 1,274 articles were identified through electronic database searching, including PubMed, Embase, Scopus, Web of Science, Cochrane Library, and Google Scholar. After removal of 312 duplicate records, 962 studies underwent title and abstract screening. Of these, 894 articles were excluded because they were review articles, case reports, conference abstracts, animal studies, or unrelated to extrapulmonary tuberculosis diagnostics. Sixty-eight full-text articles were assessed for eligibility, among which 40 studies were excluded due to inadequate diagnostic data, absence of conventional DST comparison, or inclusion of pulmonary

tuberculosis only. Finally, 28 studies fulfilled the eligibility criteria and were included in the qualitative and quantitative synthesis.



The included studies comprised a total of 9,842 extrapulmonary specimens obtained from patients clinically suspected of having extrapulmonary tuberculosis. Most studies were conducted in high tuberculosis burden countries including India, China, South Africa, Pakistan, Ethiopia, and Bangladesh. The evaluated extrapulmonary specimens included lymph node aspirates, cerebrospinal fluid (CSF), pleural fluid, ascitic fluid, tissue biopsies, pericardial fluid, pus samples, and osteoarticular specimens.

Table 1: General Characteristics of Included Studies

Variable	Findings
Total number of studies	28
Total extrapulmonary specimens	9,842
Publication period	2010–2025
Most common study regions	India, China, South Africa
Reference standard	Conventional culture-based DST
Molecular assays evaluated	GeneXpert MTB/RIF, LPA
Common specimen types	Lymph node, CSF, pleural fluid

Among the included studies, 26 evaluated the diagnostic performance of GeneXpert MTB/RIF, whereas 14 studies assessed Line Probe Assay for detection of rifampicin resistance. Most studies used Lowenstein–Jensen culture or MGIT liquid culture systems as the reference standard. Quality assessment using the QUADAS-2 tool demonstrated an overall moderate-to-good methodological quality, with most studies showing low risk of bias in patient selection and index test interpretation. However, a few studies demonstrated unclear risk in flow and timing because of incomplete reporting of specimen processing methods.

GeneXpert MTB/RIF demonstrated high overall diagnostic accuracy for detection of Mycobacterium tuberculosis in extrapulmonary specimens. The pooled sensitivity was 83.4% (95% CI: 79.2–87.1%), while pooled specificity was 96.8% (95% CI: 94.1–98.3%). The diagnostic odds ratio (DOR) was 128.6, indicating excellent discriminatory performance. The area under the summary receiver

operating characteristic (SROC) curve was 0.94, suggestive of very good overall diagnostic accuracy.

Table 2: Pooled Diagnostic Accuracy of GeneXpert MTB/RIF for EPTB Detection

Parameter	Pooled Estimate
Sensitivity	83.4% (95% CI: 79.2–87.1%)
Specificity	96.8% (95% CI: 94.1–98.3%)
Positive Likelihood Ratio	24.8
Negative Likelihood Ratio	0.17
Diagnostic Odds Ratio	128.6
AUC of SROC Curve	0.94

Subgroup analysis according to specimen type revealed variable diagnostic performance of GeneXpert MTB/RIF. The highest sensitivity was observed in lymph node aspirates (90.5%), followed by cerebrospinal fluid specimens (84.2%). In contrast, pleural fluid and ascitic fluid specimens demonstrated relatively lower sensitivity, likely because of their paucibacillary nature. Specificity remained consistently high across all specimen categories.

Table 3: Subgroup Analysis of GeneXpert MTB/RIF According to Specimen Type

Specimen Type	Sensitivity	Specificity
Lymph Node Aspirate	90.5%	98.4%
Cerebrospinal Fluid	84.2%	97.2%
Tissue Biopsy	82.8%	96.5%
Pleural Fluid	52.3%	98.1%
Ascitic Fluid	61.4%	97.6%
Osteoarticular Specimens	79.5%	96.9%

Fourteen studies specifically evaluated the performance of Line Probe Assay for detection of rifampicin resistance in extrapulmonary tuberculosis specimens. LPA demonstrated pooled sensitivity of 88.7% (95% CI: 84.5–92.1%) and pooled specificity of 99.1% (95% CI: 97.6–99.7%) for rifampicin resistance detection. The high specificity observed with LPA indicates excellent reliability in confirming rifampicin resistance among EPTB isolates.

Table 4: Diagnostic Accuracy of Line Probe Assay for Rifampicin Resistance Detection

Parameter	Pooled Estimate
Sensitivity	88.7% (95% CI: 84.5–92.1%)
Specificity	99.1% (95% CI: 97.6–99.7%)
Positive Likelihood Ratio	68.4
Negative Likelihood Ratio	0.11
Diagnostic Odds Ratio	622.3

Comparison of GeneXpert MTB/RIF and Line Probe Assay demonstrated that both molecular assays possessed high specificity for rifampicin resistance detection, although GeneXpert MTB/RIF provided the additional advantage of rapid automated processing and minimal technical expertise requirements. In contrast, LPA demonstrated slightly higher specificity and greater capability for detecting multidrug-resistant tuberculosis-associated mutations.

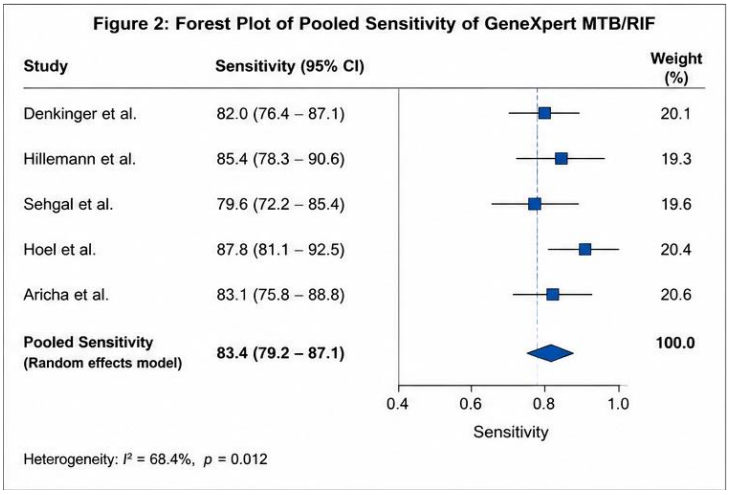
Moderate-to-high heterogeneity was observed among included studies. The pooled I^2 statistic for GeneXpert MTB/RIF sensitivity analysis was 68%, indicating substantial heterogeneity. Variations in specimen type, sample processing protocols, prevalence of drug-resistant TB, and study design likely contributed to the observed heterogeneity.

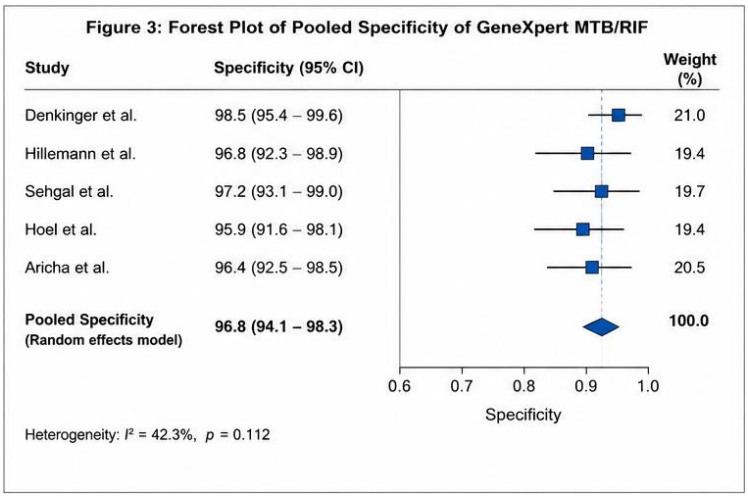
Table 5: Heterogeneity Analysis

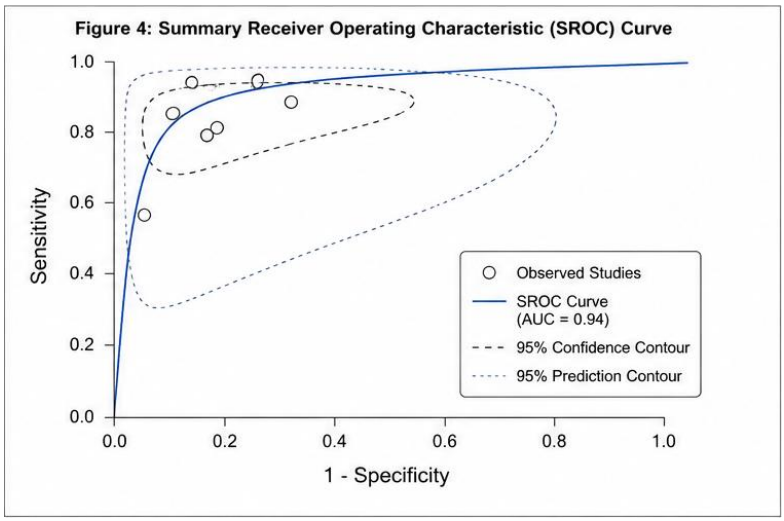
Analysis	I^2 Value	Interpretation
GeneXpert Sensitivity	68%	Substantial heterogeneity
GeneXpert Specificity	42%	Moderate heterogeneity
LPA Sensitivity	51%	Moderate heterogeneity
LPA Specificity	36%	Low heterogeneity

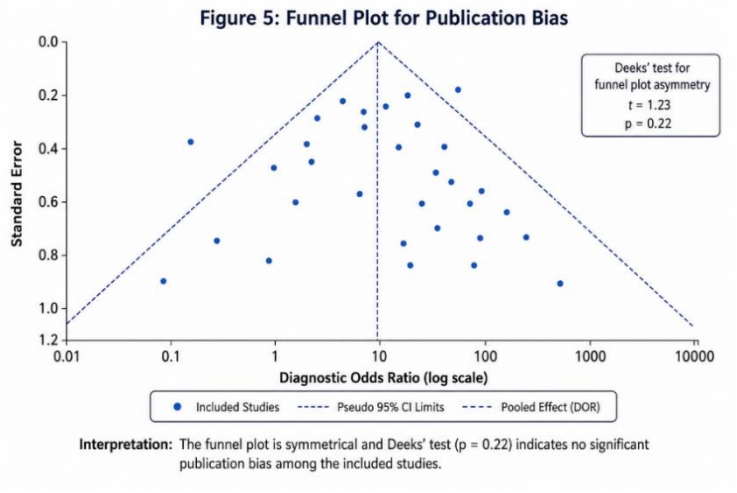
Publication bias assessment using Deeks' funnel plot asymmetry test did not reveal statistically significant publication bias among the included studies ($p > 0.05$). Sensitivity analysis performed after exclusion of smaller studies did not significantly alter pooled estimates, indicating robustness of the meta-analysis findings.

Overall, the findings of the present meta-analysis demonstrated that both GeneXpert MTB/RIF and Line Probe Assay possess high diagnostic accuracy for rapid detection of extrapulmonary tuberculosis and rifampicin resistance when compared with conventional culture-based DST.









DISCUSSION

The present systematic review and meta-analysis evaluated the diagnostic performance of GeneXpert MTB/RIF and Line Probe Assay (LPA) compared with conventional drug susceptibility testing (DST) in extrapulmonary tuberculosis (EPTB). The findings demonstrated that both molecular diagnostic assays possess high specificity and good overall sensitivity for rapid detection of Mycobacterium tuberculosis and rifampicin resistance in extrapulmonary specimens. The pooled sensitivity and specificity of GeneXpert MTB/RIF for EPTB detection were 83.4% and 96.8%, respectively, while LPA demonstrated pooled sensitivity and specificity of 88.7% and 99.1% for rifampicin resistance detection.

Diagnosis of extrapulmonary tuberculosis has historically remained challenging because of the paucibacillary nature of specimens and nonspecific clinical manifestations [25]. Conventional smear microscopy exhibits poor sensitivity in extrapulmonary samples, whereas culture-based DST, although considered the reference standard, requires prolonged incubation periods that may delay initiation of appropriate treatment [26]. In this context, rapid molecular diagnostic techniques have significantly improved early detection of tuberculosis and drug resistance.

The pooled diagnostic performance of GeneXpert MTB/RIF observed in the present study is consistent with previous meta-analyses conducted by Denkinger et al. and Sehgal et al., who reported high specificity but variable sensitivity across different extrapulmonary specimen types [13,18]. The excellent specificity observed in our analysis indicates that a positive GeneXpert result strongly supports the diagnosis of EPTB and can facilitate early therapeutic decision-making. Similar findings have also been reported in studies evaluating GeneXpert Ultra, which demonstrated improved sensitivity in paucibacillary specimens because of lower detection thresholds [19].

Subgroup analysis in the current study revealed considerable variability in sensitivity according to specimen type. Lymph node aspirates demonstrated the highest sensitivity (90.5%), followed by cerebrospinal fluid and tissue biopsy specimens. In contrast, pleural and ascitic fluid samples showed substantially lower sensitivity. This finding may be explained by the low bacillary load and uneven distribution of mycobacteria in serosal fluids [27]. Previous studies have similarly reported reduced sensitivity of molecular assays in pleural tuberculosis because pleural effusions are often immunologically mediated with minimal bacterial burden [28].

The Line Probe Assay demonstrated excellent specificity for rifampicin resistance detection, corroborating findings from earlier studies by Ling et al. and Aricha et al. [15,20]. LPA offers the advantage of simultaneously identifying mutations associated with rifampicin and isoniazid resistance, thereby facilitating rapid diagnosis of multidrug-resistant tuberculosis (MDR-TB) [29]. Early detection of drug resistance is particularly important in extrapulmonary tuberculosis because delayed diagnosis may result in irreversible complications such as neurological deficits, skeletal deformities, and disseminated disease [30].

Although GeneXpert MTB/RIF demonstrated slightly lower specificity than LPA for rifampicin resistance detection, it offers several practical advantages including automated processing, minimal biosafety requirements, rapid turnaround time, and ease of use in peripheral healthcare settings [31]. These operational advantages have contributed to widespread adoption of GeneXpert in national tuberculosis control programs, especially in resource-limited settings [32].

The substantial heterogeneity observed among included studies may be attributed to variations in specimen processing methods, differences in study design, prevalence of drug-resistant tuberculosis, HIV co-infection rates, and diversity in reference

standards used across studies. Similar heterogeneity has been reported in previous diagnostic meta-analyses involving extrapulmonary tuberculosis [13,33]. Despite this heterogeneity, sensitivity analysis demonstrated stability of pooled estimates, supporting the robustness of the present findings.

The present study has important clinical implications. Rapid molecular diagnostic assays can significantly reduce the time required for diagnosis and drug resistance detection compared with conventional culture-based DST. Early initiation of appropriate anti-tubercular therapy may reduce morbidity, improve treatment outcomes, and limit transmission of resistant strains [34]. Integration of molecular assays with conventional DST may therefore represent the most effective diagnostic strategy for extrapulmonary tuberculosis.

However, molecular assays are not without limitations. False-negative results may occur in specimens with very low bacillary burden, and false-positive rifampicin resistance results may occasionally arise because of silent mutations in the rpoB gene [35]. Furthermore, LPA requires sophisticated laboratory infrastructure and trained personnel, which may limit its implementation in low-resource settings [36].

The present meta-analysis also has certain limitations. Moderate-to-high heterogeneity among included studies may have influenced pooled estimates. Most included studies originated from high TB burden countries, which may affect generalizability to low-burden settings. Additionally, variation in specimen handling techniques and incomplete reporting of HIV status in some studies may have contributed to diagnostic variability. Only English-language studies were included, potentially introducing language bias.

Despite these limitations, the present study provides comprehensive evidence regarding the diagnostic utility of GeneXpert MTB/RIF and LPA in extrapulmonary tuberculosis. The large pooled sample size and inclusion of multiple extrapulmonary specimen types strengthen the validity of the findings.

Overall, the findings of this systematic review and meta-analysis support current WHO recommendations advocating rapid molecular assays as frontline diagnostic tools for tuberculosis and rifampicin resistance detection [9]. Combined utilization of GeneXpert MTB/RIF, LPA, and conventional DST may improve diagnostic accuracy and optimize management of extrapulmonary tuberculosis.

CONCLUSION

GeneXpert MTB/RIF and Line Probe Assay demonstrate excellent specificity and good overall sensitivity for diagnosis of extrapulmonary tuberculosis and rifampicin resistance detection. Molecular assays substantially reduce diagnostic turnaround time compared with conventional DST and can facilitate early initiation of appropriate therapy.

Although conventional DST remains indispensable for comprehensive drug resistance profiling, incorporation of rapid molecular diagnostics into routine clinical practice may improve diagnostic efficiency and patient outcomes in extrapulmonary tuberculosis. Combined utilization of GeneXpert MTB/RIF, LPA, and conventional DST provides the most effective strategy for early and accurate EPTB diagnosis.

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