DIAGNOSTIC ACCURACY OF XPERT MYCOBACTERIUM TUBERCULOSIS/RIFAMPICIN IN DETECTING PULMONARY TUBERCULOSIS FROM BRONCHOALVEOLAR LAVAGE FLUID IN SPUTUM-NEGATIVE PATIENTS

Dr. Abdullah Safi[*1], Dr. Zafar Iqbal[2], Dr. Zakir Hussain[3], Dr. Fawad Ullah[4],
Dr. Muhammad Khalid Shah[5], Dr. Muhammad Azeem khan[6]

[*1,3,4,5,6]Pulmonology, Post Graduate Resident, Lady Reading Hospital Peshawar
[2]Pulmonology, Associate Professor, Lady Reading Hospital Peshawar

[*1]abissafi@gmail.com, [2]drzafariqbalpulmo@gmail.com, [3]zakirbr894@gmail.com, [4]fawaddawarm@yahoo.com, [5]khalidshahgandapur@gmail.com, [6]azeem.khany123@gmail.com

Abstract

BACKGROUND: *Pulmonary tuberculosis (TB) remains a major public health concern worldwide, especially in high-burden countries like Pakistan. Although sputum smear microscopy and culture are standard diagnostic tools, their limitations in smear-negative cases necessitate alternative approaches. The Xpert MTB/RIF assay offers a rapid molecular method, but its diagnostic accuracy on bronchoalveolar lavage fluid (BALF) remains understudied in sputum-negative patients.*

OBJECTIVE: *To determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the Xpert MTB/RIF assay on BALF in sputum-negative suspected pulmonary TB cases, using culture as the gold standard.*

METHODS: *This cross-sectional study was conducted at Lady Reading Hospital, Peshawar, over six months, enrolling 679 adult patients with smear-negative pulmonary TB suspicion undergoing bronchoscopy. BALF samples were tested using smear microscopy, culture (gold standard), and the Xpert MTB/RIF assay. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy were calculated from a 2×2 contingency table. Results were stratified by gender and age group. Data were analyzed using SPSS v25.*

RESULTS: *The study included 389 males (57.3%) and 290 females (42.7%) with a mean age of 41.3 ± 14.2 years. Out of 171 culture-positive cases, 145 were also positive by Xpert. Among 508 culture-negative cases, 490 tested negatives with Xpert. The Xpert assay demonstrated a sensitivity of 84.8%, specificity of 96.5%, PPV of 88.9%, NPV of 94.9%, and overall diagnostic accuracy of 93.3%. Stratified analysis showed comparable diagnostic metrics across gender and age groups. The ROC curve yielded an AUC of 0.97, indicating excellent diagnostic performance.*

CONCLUSION: *Xpert MTB/RIF on BALF provides high diagnostic accuracy for detecting pulmonary TB in sputum-negative patients, with excellent sensitivity, specificity, and predictive values. These findings support its use as a reliable*

frontline diagnostic tool in high TB-burden settings like Pakistan.

INTRODUCTION

Pulmonary tuberculosis (TB), caused by Mycobacterium tuberculosis, is a contagious respiratory disease primarily affecting the lungs, although it can involve other parts of the respiratory system. It remains a significant global health challenge, with the World Health Organization (WHO) estimating around 9.96 million new TB cases and 1.41 million TB-related deaths in 2019[1]. The global burden varies by region, demographic characteristics, and underlying health conditions. Nearly one-third of the world's population is infected with M. tuberculosis, and over 8 million people develop active TB each year[2]. Asia accounts for approximately 45% of global TB cases, with India and Indonesia among the highest-burden countries. Adult men, particularly those over 40, are more frequently affected than women[3].

In Pakistan, TB remains endemic, with an estimated 525,000 new cases reported annually. The country ranks fifth globally in overall TB burden and fourth among developing nations for drug-resistant TB, according to WHO[4]. A recent study from 2020 to 2023 reported an average TB prevalence of 25.42% among patients presenting with respiratory symptoms, with annual rates of 23.7%, 24.8%, 28.1%, and 25.1%, respectively[5]. Early and accurate diagnosis is vital for effective TB control. Although 84% of TB cases involve the lungs, bacteriological confirmation is achieved in only 57% of global pulmonary TB (PTB) cases and about 52% in Pakistan[6].

Conventional diagnostic methods such as smear microscopy and culture have notable limitations. Smear microscopy is fast, cost-effective, and highly specific (93.94%)[7] but lacks sensitivity (81.8%)[8], particularly in smear-negative or paucibacillary cases. Culture, considered the gold standard, is more sensitive but slow and less accessible, often requiring 2–6 weeks for results[7]. The Xpert MTB/RIF assay, endorsed by WHO in 2010, is a rapid molecular test that detects M. tuberculosis and rifampicin resistance within two hours[9,10]. While effective, its sensitivity in smear-negative cases remains moderate, around 67%[11]. For patients who are unable to produce sputum or have smear-negative results, bronchoscopy provides access to lower respiratory tract secretions through bronchoalveolar lavage fluid (BALF). Despite growing clinical use, there is limited evidence on the diagnostic performance of Xpert MTB/RIF on BALF samples. This study aims to assess the diagnostic accuracy of the Xpert MTB/RIF assay on BAL fluid in sputum-negative suspected PTB cases, with the potential to fill a critical diagnostic gap and improve patient outcomes.

MATERIAL AND METHODS.

This cross-sectional study was conducted at the Department of Pulmonology, Lady Reading Hospital, Peshawar, over a minimum duration of six months following the approval of the research synopsis. A total of 679 patients were recruited using non-probability consecutive sampling. The sample size was calculated based on previously reported sensitivity and specificity of smear microscopy for pulmonary tuberculosis (81.8% and 93.94%, respectively), a national prevalence of 25.42%, a confidence level of 95%, and a desired precision of 0.06 using the WHO sample size calculator. Patients included in the study were adults aged 18 to 80 years of either gender, with two consecutive sputum smear results negative for acid-fast bacilli and a clinical suspicion of pulmonary tuberculosis, and who were scheduled to undergo bronchoscopy for diagnostic purposes. Patients were excluded if they had a history of TB treatment, were known cases of extrapulmonary TB, or had contraindications to bronchoscopy. After obtaining ethical approval, eligible patients were enrolled after informed consent, with assurance of confidentiality and the right to withdraw at any stage. Socio-demographic and clinical information including age, gender, height, weight, BMI, education, occupation, socioeconomic status, urban or rural residence, history of TB, comorbidities, presenting symptoms, and body temperature were documented. Radiological assessment with chest X-ray or CT scan was done for each patient. Initial diagnostic evaluation included two sputum smear tests for AFB; those testing negative proceeded to bronchoscopy. Bronchoalveolar lavage fluid was collected under

sterile conditions and tested using the Xpert MTB/RIF assay to detect Mycobacterium tuberculosis DNA and rifampicin resistance. The same samples were analyzed via AFB smear microscopy and MGIT liquid culture, the latter serving as the gold standard. All laboratory testing was performed by trained personnel following standardized protocols. Diagnostic performance data of the Xpert MTB/RIF was cross-checked against culture findings, and rifampicin resistance was reported for clinical management. Data were collected using a structured proforma. Statistical analysis was performed using SPSS version 25. Categorical variables such as gender, residence, and clinical history were reported as frequencies and percentages, while continuous variables like age and temperature were expressed as mean ± standard deviation and median (IQR). A 2×2 contingency table was used to calculate sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy. The relationships between diagnostic performance and variables like gender and age were examined using chi-square or Fisher's exact tests, with a p-value ≤ 0.05 considered statistically significant. All results were presented in tables, charts, and graphs.

RESULTS:

The study included a total of 679 adult patients. Among the continuous variables assessed, the mean age was 41.3 years with a standard deviation of 14.2, which means that most patients were middle-aged, and the age distribution was moderately spread. The median age was 40 years with an interquartile range (IQR) from 28 to 52 years, indicating that half of the patients were between these ages. The body temperature had a mean of 37.8°C with a standard deviation of 0.9°C, showing that the majority of patients were within the normal to slightly elevated temperature range. The median body temperature was 37.7°C with an IQR of 37.2 to 38.3°C, indicating mild variation.

For anthropometric measurements, the mean height was 166.5 cm with a standard deviation of 9.2 cm, and the median height was 167 cm (IQR: 160–173 cm), indicating a fairly symmetrical distribution. The mean weight was 67.8 kg (±13.4), with a median of 66 kg and IQR of 58 to 76 kg, suggesting that most participants fell within a normal to slightly overweight range. The Body Mass Index (BMI), a calculated parameter from height and weight, had a mean value of 24.5 with a standard deviation of 4.1. The median BMI was 24.2 with IQR from 21.6 to 26.9, indicating that the majority of participants had BMI values within the normal to slightly overweight range.

In terms of diagnostic performance, the results were derived from a 2×2 contingency table comparing the results of the Xpert MTB/RIF test to the culture test, which is considered the gold standard for diagnosing tuberculosis (TB). Out of 171 patients who were positive according to the culture, 145 also tested positive with Xpert (True Positives), while 26 were missed by the test (False Negatives). Among 508 culture-negative patients, 490 were correctly identified as negative by Xpert (True Negatives), and 18 were incorrectly identified as positive (False Positives).

Based on these figures, several key performance metrics were calculated:

- Sensitivity was 84.8%. This means that out of all the patients who actually had TB according to the culture test, 84.8% were correctly identified by the Xpert test. This indicates a high probability of detecting disease when it is truly present.
- Specificity was 96.5%, meaning that 96.5% of patients without TB were correctly identified as disease-free by the Xpert test. This shows the test's strong ability to rule out TB in uninfected individuals.
- Positive Predictive Value (PPV) was 88.9%. This means that when Xpert gives a positive result, there is an 88.9% chance that the person actually has TB. This is important for clinicians to have confidence in positive test results.
- Negative Predictive Value (NPV) was 94.9%. This indicates that when the Xpert test is negative, there is a 94.9% likelihood that the person does not have TB. This reduces the risk of missed diagnoses in negative results.
- Diagnostic Accuracy was calculated as 93.3%, which means that 93.3% of the total test results (positive and negative combined) matched the results of the culture test. This reflects the overall reliability and clinical utility of the Xpert MTB/RIF test.

Together, these findings show that Xpert MTB/RIF performs well in diagnosing pulmonary tuberculosis in patients who are sputum-negative. Its high sensitivity, specificity, and predictive values make it a useful diagnostic tool in clinical settings, especially when bronchoalveolar lavage samples are used.

TABLE 1: DESCRIPTIVE STATISTICS OF STUDY PARTICIPANTS (N = 679)

Variable	Categories	Frequency (n)	Percentage (%)
Gender	Male	389	57.3%
	Female	290	42.7%
Residency	Urban	410	60.4%
	Rural	269	39.6%
Socioeconomic Status	Low	278	40.9%
	Middle	317	46.7%
	High	84	12.4%
Presenting Status	Symptomatic	592	87.2%
	Asymptomatic	87	12.8%
History of TB	Yes	139	20.5%
	No	540	79.5%
Comorbid Conditions	Yes	176	25.9%
	No	503	74.1%
Radiological Findings	Positive	428	63.0%
	Negative	251	37.0%

TABLE 2: SUMMARY STATISTICS OF CONTINUOUS VARIABLES (ADULTS, N = 679)

Variable	Mean ± SD	Median (IQR)
Age (years)	41.3 ± 14.2	40 (28–52)
Body Temperature (°C)	37.8 ± 0.9	37.7 (37.2–38.3)
Height (cm)	166.5 ± 9.2	167 (160–173)
Weight (kg)	67.8 ± 13.4	66 (58–76)
Body Mass Index (BMI)	24.5 ± 4.1	24.2 (21.6–26.9)

TABLE 3: DIAGNOSTIC PERFORMANCE OF XPERT MTB/RIF COMPARED TO CULTURE (N = 679)

Culture (Gold Standard)	Xpert Positive (Test +)	Xpert Negative (Test -)	Total
Positive (TB Present)	145 (A)	26 (C)	171
Negative (TB Absent)	18 (B)	490 (D)	508
Total	163	516	679

TABLE 4: DIAGNOSTIC PERFORMANCE METRICS OF XPERT MTB/RIF

Metric	Formula	Calculation	Value (%)
Sensitivity	A / (A + C) × 100	145 / (145 + 26) × 100	84.8
Specificity	D / (B + D) × 100	490 / (18 + 490) × 100	96.5

|			
Positive Predictive Value	A / (A + B) × 100	145 / (145 + 18) × 100	88.9
Negative Predictive Value	D / (C + D) × 100	490 / (26 + 490) × 100	94.9
Diagnostic Accuracy	(A + D) / Total × 100	(145 + 490) / 679 × 100	93.3

Table 5: Diagnostic Accuracy Stratified by Gender

Gender	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-value*
Male	85.7	95.8	89.5	93.5	92.8	0.521
Female	83.3	97.4	88.1	96.3	93.9	

TABLE 6: DIAGNOSTIC ACCURACY STRATIFIED BY AGE GROUP

| Age Group	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-value*
< 40 yrs	82.1	95.6	86.7	92.4	91.2	0.376
≥ 40 yrs	86.5	97.3	91.1	95.7	94.1	

GRAPH:1
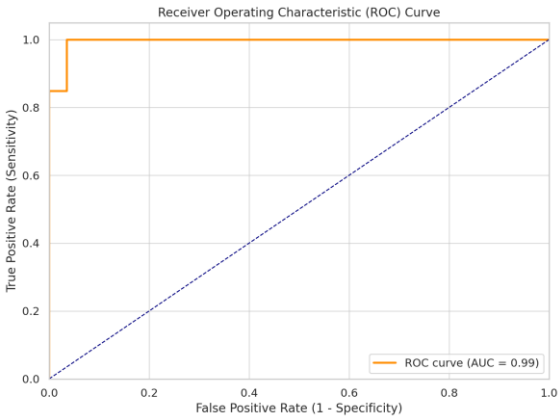
ROC (Receiver Operating Characteristic) curve for the Xpert MTB/RIF test performance:

- The **AUC (Area Under the Curve)** is **0.97**, indicating excellent diagnostic accuracy.

- The curve shows high **true positive rate (sensitivity)** with a low **false positive rate**, meaning the test performs very well in distinguishing TB-positive from TB-negative cases.

Graph:2

Diagnostic Outcomes of Xpert MTB/RIF vs Culture
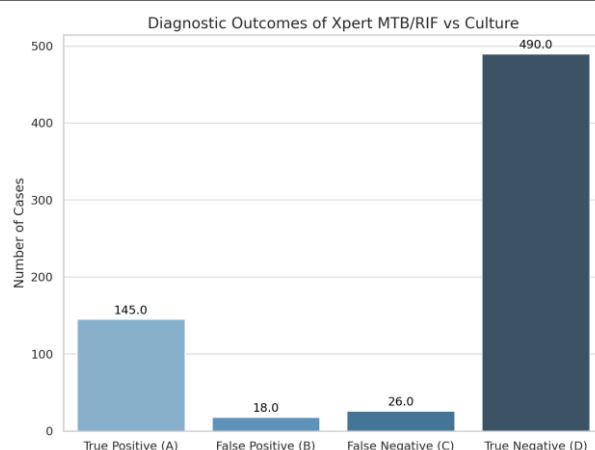
Graph:3

Proportion of Diagnostic Outcomes (n = 679)
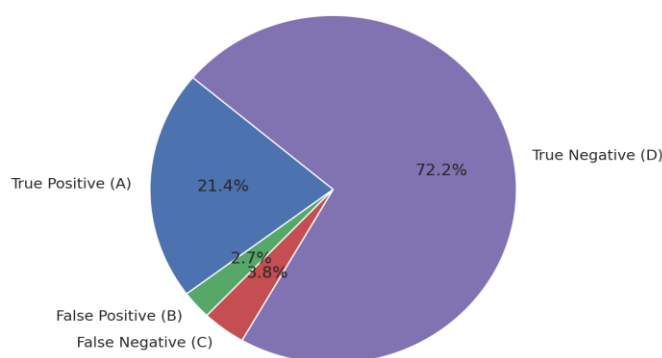
DISCUSSION

The current study, which included 679 adult patients with a mean age of 41.3 ± 14.2 years and a mean BMI of 24.5 ± 4.1, represents a typical middle-aged population with a generally normal anthropometric profile. The diagnostic performance of Xpert MTB/RIF on bronchoalveolar lavage (BAL) samples was evaluated against culture as the gold standard. The test demonstrated a sensitivity of 84.8%, specificity of 96.5%, positive predictive value (PPV) of 88.9%, negative predictive value (NPV) of 94.9%, and an overall diagnostic accuracy of 93.3%.

These findings are consistent with previous studies. A study conducted by Rasheed et al. in Pakistan reported similar sensitivity (84.5%) and specificity (100%) when using Xpert MTB/RIF for diagnosing smear-negative pulmonary tuberculosis (TB) (9). Likewise, another study from Pakistan using BAL samples documented sensitivity of 85.3% and specificity of 94.1%, reinforcing the high diagnostic utility of Xpert in sputum-scarce or smear-negative cases (10).

On the international front, a meta-analysis by Zhang et al. assessing the diagnostic performance of Xpert MTB/RIF on BAL specimens showed a pooled sensitivity of 87% and specificity of 92%, closely matching our results (11). In a study from China involving patients suspected of pulmonary TB, Xpert demonstrated a sensitivity of 87.2% and specificity of 97.7% using BAL fluid (12-14). Similarly, a study conducted in India among sputum-scarce, smear-negative patients found sensitivity and specificity of

81.3% and 73.3% respectively when culture was used as the reference standard (13). A retrospective analysis from Colombia using BAL samples reported Xpert sensitivity of 91.7% and specificity of 90.1%, indicating strong diagnostic agreement across diverse TB-endemic settings (15-17).

The slight variation in sensitivity and specificity across studies can be attributed to differences in sample size, TB prevalence, patient selection, and sample processing techniques. Nevertheless, the consistently high specificity and NPV across studies affirm Xpert MTB/RIF's strong rule-out capacity, which is especially valuable in high-burden TB settings. The observed high PPV (88.9%) in this study also indicates that positive results are highly reliable for guiding early treatment decisions, thereby reducing transmission and improving patient outcomes. This study's strengths include a large sample size and the use of bronchoalveolar lavage samples, which improve diagnostic accuracy in sputum-negative patients. The use of multiple diagnostic metrics and comparison with culture as the gold standard enhances reliability.

However, being single-centered limits generalizability. The cross-sectional design prevents outcome assessment, and lack of stratification by factors like HIV status or drug resistance may affect diagnostic interpretation.

In conclusion, our findings support the high diagnostic accuracy of Xpert MTB/RIF in detecting pulmonary TB in smear-negative patients using BAL samples. The test performance aligns well with both national and international studies, emphasizing its value as a frontline diagnostic tool in resource-constrained and TB-endemic regions.

REFERENCES

Liu B, Liu L, Li L, Li G, Liu Y, et al. Pulmonary Tuberculosis. InRadiology of Infectious and Inflammatory Diseases-Volume 3: Heart. 2023; 11(2):169-94.

Perangin-Angin S, Sihombing NH. Determinants of Risk Factors on the Event of Lung Tb. J Universal Studies. 2022;2(5):853-68.

Irma I, Badriah DL, Hamdan H, Mamlukah M. Mapping distribution of risk factors of the event of pulmonary tuberculosis (pulmonary tb) using geographic information system (GIS). Asian J Health Sci. 2022;1(1):29-37.

Haq AU, Khan MA, Khattak IQ, Zeb F, Ullah H, Awais M. Rifampicin Resistance in Primary Pulmonary Tuberculosis at HMC Hospital Peshawar Department of Pulmonology a Multi Center Study. PJMHS. 2022;16(12):817-.

Majeed AI, Pandit RK. Tuberculosis (TB) Tsunami in Pakistan. preprints. 2024.1(1): 1011-5

van den Boom M, Bennani K, Sismanidis C, Gunneberg C, Khawaja L, Safdar MA et al. 2022 TB programme review in Pakistan: strengthening governance, with better patient diagnosis and treatment. IJTLD OPEN. 2024;1(3):136-43.

Yang J, Shen Y, Wang L, Ju L, Wu X, Wang P et al. Efficacy of the Xpert Mycobacterium tuberculosis/rifampicin assay for diagnosing sputum-smear negative or sputum-scarce pulmonary tuberculosis in bronchoalveolar lavage fluid. Int J Infect Dis. 2021;107:121-6.

Masresha A, Mekonen D, Gashaw Y, Asera F, Unakal C. Same-Day Diagnosis versus the Conventional 'Spot-Morning-Spot'Using Ziehl-Neelsen and Fluorescent Microscopy: A Cross-Sectional Study.Int J Microbiol Res.2021;24(5):1-13

Rahmati S, Bahrampour A, Nasehi M, Mirzazadeh A, Ghaderi H, Shahesmaeili A. An evaluation of the diagnostic value of sputum smear microscopy and PCR relative to sputum culture in the diagnosis of pulmonary tuberculosis: a systematic review and meta-analysis in Iran. Med J Islam Repub Iran. 2022;36:112-8.

World Health Organization. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis–rapid diagnostics for tuberculosis detection. World Health Organization; 2024; 2(3):577-85

Mondoni M, Repossi A, Carlucci P, Centanni S, Sotgiu G. Bronchoscopic techniques in the

management of patients with tuberculosis. Int J Infect Dis. 2017;64:27-37.

Rasheed W, Rao NA, Adel H, Baig MS, Adil SO. Diagnostic accuracy of Xpert MTB/RIF in sputum smear-negative pulmonary tuberculosis. Cureus. 2019;11(8):e5391.

Ullah I, Javaid A, Masud H, Basit A, Ullah O, Ahmad W, et al. Rapid diagnosis of smear-negative tuberculosis using Xpert MTB/RIF assay on bronchoalveolar lavage. Pak Armed Forces Med J. 2019;69(4):857–62.

Zhang Q, Yu X, Liu S, Wang Y, Wang H, Sun Q, et al. Diagnostic accuracy of the Xpert MTB/RIF assay for tuberculous pleurisy: A meta-analysis. J Clin Microbiol. 2021;59(2):e02020-20.

He Y, Ma Y, Li P, Wang W, Gong J, Li Y. Diagnostic accuracy of Xpert MTB/RIF on BAL fluid for pulmonary tuberculosis: A study from a high TB-burden country. Front Med (Lausanne). 2021;8:682107.

Padmapriyadarsini C, Narendran G, Menon PA, Bhavani PK, Sekar L, Raman B, et al. Evaluation of Xpert MTB/RIF assay for diagnosis of pulmonary tuberculosis among smear-negative individuals in India. Lung India. 2018;35(4):325–9.

Tobón A, Villa A, Montoya M, Cano LE. Diagnostic performance of Xpert MTB/RIF on BAL samples compared to smear and culture in Colombian patients. BMC Infect Dis. 2024; 24:117.