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Diagnostic Yield of AFB smear and GeneXpert on Bronchial Washings with Fiber-Optic Bronchoscope in Patients with Sputum-Negative Pulmonary Tuberculosis

Muhammad Zaid Iqbal, Muhammad Younus, Abdus Salam, Abdul Wahab Gureja, Faiza Khalid, Muhammad Sarfraz Munawar

ABSTRACT

Objective: To determine and compare the diagnostic yield of acid-fast bacilli (AFB) smear microscopy and GeneXpert testing performed on bronchial washings in patients clinically suspected of pulmonary tuberculosis (PTB) but negative for both sputum AFB smear and GeneXpert. The study also aimed to evaluate the utility of bronchoscopic sampling as an adjunct diagnostic tool in sputum-negative PTB, where conventional methods often fail to confirm the diagnosis.

Study Design and Setting: A descriptive cross-sectional study conducted at the Department of Pulmonology, Mayo Hospital, Lahore, from 7 March 2025 to 10 June 2025.

Methods: Patients aged 18–65 years with clinical and radiological evidence suggestive of PTB but negative sputum AFB smear and GeneXpert results were included. Bronchial washings were obtained through fiber-optic bronchoscopy and analyzed using Ziehl–Neelsen staining and GeneXpert MTB assay. Statistical analysis was performed using SPSS version 27, and diagnostic yields were compared.

Results: A total of 95 patients were enrolled, with a mean age of 35.49 ± 11.03 years. Of these, 53.7% were males and 65.3% were non-smokers. GeneXpert detected Mycobacterium tuberculosis in 85.3%, while AFB smear was positive in 56.8% of bronchial wash samples. GeneXpert showed a higher diagnostic yield compared to AFB smear in sputum-negative PTB cases.

Conclusion: GeneXpert testing of bronchial washings markedly enhances the diagnostic yield for sputum-negative PTB and should be incorporated as a routine diagnostic tool in patients with strong clinical and radiological suspicion of tuberculosis despite negative sputum findings.

Keywords: Bronchoscopy, Bronchial lavage, Pulmonary tuberculosis, Sputum.

How to cite this Article:
Iqbal MZ, Younus M, Salam A, Gureja AW, Khalid F, Munawar MS. Diagnostic Yield of AFB smear and GeneXpert on Bronchial Washings with Fiber-Optic Bronchoscope in Patients with Sputum-Negative Pulmonary Tuberculosis. J Bahria Uni Med Dental Coll. 2026;16(2):519-25 DOI: https://doi.org/10.51985/JBUMDC2025730

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Received: 22-09-2025
1st Revision: 27-10-2025
Accepted: 03-03-2026
2nd Revision: 26-02-206

INTRODUCTION

Tuberculosis (TB) continues to be a major global health concern, with substantial implications for morbidity, mortality, and healthcare systems worldwide. According to the World Health Organization (WHO), in 2023, an estimated 10.8 million people were affected by TB, corresponding to an incidence rate of 134 cases per 100,000 population. Approximately 1.25 million deaths were attributed to the disease annually.[1,2] Pulmonary tuberculosis (PTB), the most prevalent form of the disease, was observed in 65.03% of cases in certain population-based studies, highlighting its widespread impact.[3] Despite remarkable progress in diagnostic technologies, the prevalence of PTB remains persistently high, especially in resource-limited countries, where delayed detection and underdiagnosis continue to

impede effective disease control. [4]

Early and accurate diagnosis of TB remains the cornerstone of global efforts to reduce its transmission and achieve effective treatment outcomes. Conventional diagnostic tools, including sputum smear microscopy and chest radiography, have long been utilized for the initial evaluation of suspected PTB. The detection of acid-fast bacilli (AFB) in respiratory specimens through Ziehl–Neelsen staining serves as the first-line method for confirming active pulmonary infection. Although sputum AFB smear microscopy is rapid, inexpensive, and highly specific, its sensitivity is limited, particularly in patients with a low bacillary load or paucibacillary disease.[5] In contrast, mycobacterial culture remains the gold standard for confirming Mycobacterium tuberculosis infection because it requires only 10 to 100 viable bacilli per milliliter to yield a positive result, compared with the 5,000–10,000 bacilli/mL required for a positive smear. However, culture is a complex and time-consuming procedure, often requiring 2–8 weeks for results and specialized laboratory infrastructure, which is not readily available in many developing settings. Additionally, the need for skilled personnel and stringent biosafety conditions further limits its widespread application. The diagnostic challenge intensifies when patients who are clinically and radiologically suggestive of PTB are unable to produce sputum or consistently yield negative smear results despite active infection.[6] This diagnostic gap contributes to delayed diagnosis, ongoing disease transmission, and the emergence of drug-resistant TB strains due to empiric or incomplete treatment. Consequently, the need for reliable alternative diagnostic approaches in sputum-scarce or sputum-negative PTB (SSN-PTB) cases has become increasingly important.[7]

Various techniques are available for the early diagnosis of suspected sputum-negative PTB (SSN-PTB). Fiber-optic bronchoscopy for bronchial washings is a desirable diagnostic tool for SSN-PTB. The lower respiratory tract can be assessed through fiber-optic bronchoscopy, and acquired bronchial washings can be analyzed on sensitive molecular tests as GeneXpert MTB /RIF assay, a nucleic acid amplification cartridge-based test that detects the DNA of Mycobacterium tuberculosis and resistance to rifampicin. [8, 9] Fiber-optic bronchoscopy can be performed as an outpatient procedure without the need for general anesthesia, and it is considered a safe procedure with an estimated complication rate of 1.1% and a mortality rate of 0.02%.[10] Gaude et.al reported that 93.5% of the proven cases of PTB were detected through GeneXpert, 86% through AFB culture, and 41.9% through AFB smear microscopy. The sensitivity and specificity of GeneXpert were 92.5% and 79.37% on bronchial samples, respectively.[3]

In high-burden countries such as Pakistan, the diagnostic challenges are compounded by the large proportion of patients presenting with negative sputum smears despite having radiological evidence of disease. The integration of bronchial washings with GeneXpert testing may substantially enhance case detection and guide timely initiation of therapy, thereby reducing disease transmission and associated mortality. Therefore, this study was designed to determine the diagnostic yield of AFB smear microscopy and GeneXpert testing on bronchial washings in patients with sputum-negative PTB. It also aims to assess the effectiveness of bronchoscopic sampling as an adjunct diagnostic approach to confirm the diagnosis in such patients. By providing evidence on the comparative performance of these diagnostic modalities, this research seeks to support the optimization of diagnostic protocols for PTB in high-burden regions and contribute to improved clinical decision-making in suspected sputum-negative tuberculosis.

METHODOLOGY

This descriptive cross-sectional study was conducted at the Department of Pulmonology, Mayo Hospital, Lahore, over a duration from 7 March 2025 to 10 June 2025.

Prior to participation, each patient was fully informed about the purpose, procedure, and potential risks of the study, following which written informed consent was obtained. Confidentiality was assured by assigning unique identification codes to each participant and removing any direct personal identifiers from the data. Personal information, including names, contact numbers, and addresses, was collected solely for follow-up purposes and was kept strictly confidential. Ethical approval for the study was obtained from the Institutional Review Board of King Edward Medical University (KEMU), reference number 54/RC/KEMU, dated 9 January 2025.

The non-probability consecutive sampling technique was used to retrieve the participants presenting at the outdoor patient department of the Department of Pulmonology, Mayo Hospital, Lahore. The sample size was calculated based on an assumed diagnostic yield of 86% for GeneXpert, with a 95% confidence interval and a 7% margin of error. [3]

Participants eligible for inclusion comprised male and female patients aged 18 to 65 years who exhibited clinical manifestations suggestive of pulmonary tuberculosis (PTB). These symptoms included a persistent cough lasting more than two weeks, fever, unintentional weight loss, hemoptysis, night sweats, or radiological evidence consistent with PTB. Enrollment was restricted to individuals whose sputum samples tested negative for both AFB smear microscopy and GeneXpert MTB/RIF assay on two consecutive occasions.

Patients were excluded if they had a prior history of anti-tuberculous treatment, or were already diagnosed with lung carcinoma, bacterial pneumonia, or any other chronic pulmonary disease capable of clinically or radiologically mimicking tuberculosis. Moreover, individuals with bleeding disorders, unstable cardiac conditions, or any medical

contraindication to undergoing bronchoscopy were also excluded to ensure patient safety and minimize procedural risk.

Demographic information, including age, gender, symptom duration, and smoking status, was recorded. The pre-bronchoscopy workup included a complete blood count (CBC), electrocardiography (ECG), and a coagulation profile. The bronchoscopy of the patients was performed by three different consultant pulmonologists with an experience of more than 5 years in performing bronchoscopy. The procedure was carried out under topical anesthesia with 4% lignocaine spray to the nasopharynx and oropharynx, supplemented by 2% lignocaine solution applied to the bronchoscope's working channel to anesthetize the airways. Mild sedation was administered when indicated to improve patient comfort. The bronchoscope was advanced under direct visualization, and bronchial washings were collected from the most affected segment or lobe, as determined by radiographic or CT imaging. Approximately 30 mL of sterile normal saline was instilled, and the aspirated fluid was collected into sterile containers. Two separate 30 mL aliquots of bronchial washing were obtained and sent promptly to the Department of Microbiology for laboratory analysis. One aliquot was subjected to Ziehl–Neelsen staining for AFB smear microscopy, while the other was analyzed using the GeneXpert MTB/RIF assay (Cepheid, USA), following the manufacturer's instructions. The GeneXpert test simultaneously detects Mycobacterium tuberculosis DNA and mutations associated with rifampicin resistance. All specimens were processed by trained laboratory personnel.

Data was entered and analyzed using SPSS version 27.0. Continuous variables, such as age and duration of symptoms, were summarized using measures of central tendency and dispersion, specifically the mean ± standard deviation (SD). Categorical variables, including gender, smoking status, and the outcomes of AFB smear microscopy and GeneXpert MTB/RIF assay, were expressed as frequencies and percentages. For inferential analysis, cross-tabulation was performed to compare the diagnostic results of AFB smear and GeneXpert testing. The chi-square ($\div^2$) test was applied following appropriate post-stratification of categorical variables to assess the association between diagnostic modalities and other relevant factors. The level of statistical significance was predefined at a p-value of < 0.05.

RESULT

A total of 95 patients fulfilling the inclusion criteria were enrolled in the study. The mean age of the participants was 35.49 ± 11.03 years. Out of the total, 51 (53.7%) were males and 44 (46.3%) were females. The majority of participants, 62 (65.3%), were non-smokers, whereas 24 (25.3%) were active smokers, and 9 (9.4%) were ex-smokers. Regarding symptom duration, 66 (69.5%) patients reported having symptoms for less than 21 days, while 29 (30.5%) had symptoms persisting for more than 21 days. (Table 1) The AFB smear was positive in 54 (56.8%) of the 95 patients, while GeneXpert detected Mycobacterium tuberculosis in 81 (85.3%) patients, demonstrating a markedly higher diagnostic yield. The difference in diagnostic positivity between the two methods was statistically significant ($p < 0.05$). (Table 2)

For AFB smear microscopy, the highest positivity rate was observed among participants aged below 25 years (60.0%), followed by those aged 25–45 years (55.4%) and above 45 years (57.1%). Regarding gender distribution, 26 (59.1%) of females and 28 (54.9%) of males had positive AFB smears, showing no significant association ($p = 0.681$). Among smokers, ex-smokers demonstrated the highest smear positivity (66.7%) compared to non-smokers (56.5%) and active smokers (54.2%). However, the relationship between smoking status and AFB smear results was not statistically significant ($p = 0.807$). Similarly, the duration of symptoms (<21 days vs. >21 days) had no statistically relevant impact on AFB positivity ($p = 0.828$), though those with shorter symptom duration (<21 days) showed a slightly higher yield (57.6%). (Table 3) For the GeneXpert assay, diagnostic positivity was consistently higher across all demographic categories compared with AFB smear microscopy. Among the three age groups, <25 years (84.0%), 25–45 years (85.7%), and >45 years (85.7%), the yield was uniformly high, suggesting that age did not significantly influence GeneXpert detection ($p = 0.979$). Female participants exhibited a marginally higher GeneXpert positivity (86.4%) compared with males (84.3%), though the difference was not statistically significant ($p = 0.779$). In relation to smoking status, non-smokers (87.1%) and active smokers (87.5%) demonstrated similar positivity rates, whereas ex-smokers (66.7%) exhibited a comparatively lower detection rate (*p*

Table 1: Demographic Characteristics

Variables	Frequency (Percentage)
Age (Years) (Mean ± S.D.)	35.49 ± 11.03
Gender	
Male	51 (53.7%)
Female	44 (46.3%)
Smoking	
Non-smoker	62 (65.3%)
Active smoker	24 (25.3%)
Ex-smoker	9 (9.4%)
Duration of Symptoms (Days)	
<21 days	66 (69.5%)
>21 days	29 (30.5%)

Table 2: Diagnostic Yield Summary

Diagnostic Test	Positive	Negative
AFB Smear	54 (56.8%)	41 (43.2%)
GeneXpert	81 (85.3%)	14 (14.7%)

Table 3: Stratification of AFB Smear with Demographics

Variables	AFB Smear		Correlation	p-value
	Positive	Negative		
Age groups (Years)			0.152	0.927
<25	15 (60.0%)	10 (40.0%)		
25-45	31 (55.4%)	25 (44.6%)		
>45	8 (57.1%)	6 (42.9%)		
Gender			0.169	0.681
Male	28 (54.9%)	23 (45.1%)		
Female	26 (59.1%)	18 (40.9%)		
Smoking			0.428	0.807
Non-smoker	35 (56.5%)	27 (43.5%)		
Active smoker	13 (54.2%)	11 (45.8%)		
Ex-smoker	6 (66.7%)	3 (33.3%)		
Duration of Symptoms (Days)			0.047	0.828
<21 days	38 (57.6%)	28 (42.4%)		
>21 days	16 (55.2%)	13 (44.8%)		

Table 4: Stratification of GeneXpert with Demographics

Variables	GeneXpert		Correlation	p-value
	Positive	Negative		
Age groups (Years)			0.043	0.979
<25	21 (84.0%)	4 (16.0%)		
25-45	48 (85.7%)	8 (14.3%)		
>45	12 (85.7%)	2 (14.3%)		
Gender			0.079	0.779
Male	43 (84.3%)	8 (15.7%)		
Female	38 (86.4%)	6 (13.6%)		
Smoking			2.739	0.254
Non-smoker	54 (87.1%)	8 (12.9%)		
Active smoker	21 (87.5%)	3 (12.5%)		
Ex-smoker	6 (66.7%)	3 (33.3%)		
Duration of Symptoms (Days)			2.042	0.153
<21 days	54 (81.8%)	12 (18.2%)		
>21 days	27 (93.1%)	2 (6.9%)		

= 0.254). The duration of symptoms showed an observable but statistically insignificant trend, with patients symptomatic for more than 21 days (93.1%) yielding slightly higher positivity compared to those symptomatic for less than 21 days (81.8%) (p = 0.153). (Table 4)

DISCUSSION

The present study evaluated the diagnostic yield of acid-fast bacilli (AFB) smear microscopy and GeneXpert MTB/RIF testing on bronchial washings among patients clinically and radiologically suspected of pulmonary tuberculosis (PTB) but who were sputum smear- and GeneXpert-negative. The findings demonstrated that GeneXpert on bronchial washing samples provided a significantly higher diagnostic yield (85.3%) compared to AFB smear microscopy (56.8%), confirming its superior sensitivity in detecting Mycobacterium tuberculosis in patients with sputum smear-negative pulmonary tuberculosis (SSN-PTB). These results underscore the crucial role of bronchoscopic sampling combined with molecular diagnostics in improving early and accurate detection of tuberculosis in challenging diagnostic scenarios.

Omer et.al had reported that 91.7% of patients had positive results for TB on bronchoalveolar lavage through fiber-optic bronchoscopy with 100% true negative (p = 0.000). Furthermore, it was a significant procedure with a sensitivity of 91.67% and a specificity of 100%.[6] Wan et.al had diagnosed 84.4% of patients with PTB through bronchoscopy, with the sensitivity, specificity, positive predictive value,

and negative predictive value being 76.9%, 68.2%, 92.9%, and 35.3%, respectively.[11] Oh et. al found that among the patients without any findings on the microbiology for the pulmonary TB on the sputum, microbiological growth was confirmed in 49.1% of the patients after the bronchoscopy on TB culture, and additional resistance was confirmed in 10.5% of the patients.[12] Nusrullah et.al reported that the bronchial washings achieved through the bronchoscopy and subjected to AFB staining among the patients with SSN-PTB the diagnostic yield achieved was 57.5%.[13] Bronchoscopy has long been recognized as a safe, minimally invasive, and highly effective diagnostic technique for PTB, particularly in patients with SSN-PTB, where conventional diagnostic methods often fail. Its ability to directly visualize bronchial structures and obtain targeted samples, such as bronchial washings or bronchoalveolar lavage, markedly enhances the likelihood of detecting Mycobacterium tuberculosis. The bronchoscopy-based sampling provides a significantly higher diagnostic yield than both regular and induced sputum methods, especially in paucibacillary disease. The procedure enables the collection of high-quality specimens from the site of maximal radiological involvement, thereby improving test sensitivity for AFB smear microscopy, GeneXpert MTB/RIF assay, and culture. Consequently, the integration of fiber-optic bronchoscopy into diagnostic protocols for SSN-PTB has proven instrumental in facilitating early, accurate, and microbiologically confirmed diagnoses, ultimately improving patient outcomes.[14, 15]

The low sensitivity of direct AFB smear in comparison to GeneXpert, despite being cost-effective and specific, remains a challenge in TB diagnosis. Otutu et.al showed that 36.7% were positive for smear microscopy and 63.3% were positive for GeneXpert, concluding that GeneXpert demonstrated a higher prevalence rate of detected Mycobacterium tuberculosis in sputum samples compared to the AFB smear microscopy. (16) Ahmed et al. also reported comparable results, indicating that 69.1% of the smears were AFB-positive with characteristics suggesting tuberculous infection. This percentage rose to 91% following GeneXpert Analysis. In cases with indeterminate cytology, 55.8% were AFB-positive, which increased to 83.7% upon the use of GeneXpert.[17] The conventional method for detecting Mycobacterium tuberculosis has long been acid-fast bacilli (AFB) smear microscopy, a technique that remains the cornerstone of tuberculosis (TB) diagnosis in many resource-limited settings. This method is valued for its simplicity, rapid turnaround time, and low operational cost, making it suitable for large-scale screening programs. However, despite these advantages, AFB smear microscopy is significantly limited by its sensitivity and specificity, particularly in paucibacillary or sputum-scarce cases, where the bacterial load is insufficient for microscopic visualization. The diagnostic process is also subject to observer variability. [18, 19]

In contrast, the advent of molecular diagnostic techniques, particularly the GeneXpert MTB/RIF assay, has revolutionized tuberculosis detection by providing a rapid, sensitive, and automated alternative to conventional microscopy. The GeneXpert system utilizes nucleic acid amplification technology to identify specific DNA sequences of M. tuberculosis directly from clinical specimens, including sputum and bronchial washings. Its ability to detect minute quantities of bacterial DNA allows it to accurately diagnose TB even in cases with low bacterial loads, thereby addressing one of the principal limitations of AFB smear microscopy. Moreover, the GeneXpert assay simultaneously detects mutations in the rpoB gene, enabling the identification of rifampicin resistance, a key marker for multidrug-resistant TB (MDR-TB), within approximately two hours. The molecular foundation of GeneXpert not only enhances analytical sensitivity but also eliminates much of the subjectivity associated with smear interpretation, ensuring greater reproducibility and consistency of results across laboratories. These features render GeneXpert a more reliable and efficient diagnostic tool, particularly in high-burden regions where rapid detection is critical for infection control.[20]

Despite its clear advantages, the widespread implementation of GeneXpert faces several challenges, especially in low-income and resource-constrained countries. The high cost of cartridges and instruments, the need for stable electricity and temperature-controlled environments, and the shortage of trained laboratory personnel limit its accessibility and scalability. Addressing these logistical and financial constraints through international funding, government investment, and local capacity building will be essential to ensure equitable access to molecular diagnostics. Expanding GeneXpert testing, particularly in secondary and tertiary care centers, could dramatically improve early TB detection, facilitate prompt initiation of therapy, and reduce transmission, thereby strengthening tuberculosis control programs in endemic regions.[21, 22]

This research carries significant clinical and public health implications, particularly for resource-limited and high TB burden settings such as Pakistan, where early and accurate diagnosis remains a persistent challenge. Although fiber-optic bronchoscopy and GeneXpert MTB/RIF testing are relatively more costly and require specialized infrastructure compared to conventional sputum smear microscopy, their substantially higher diagnostic yield justifies their use in patients suspected of having SSN-PTB. In these cases, reliance solely on traditional diagnostic techniques often results in delayed detection, continued disease transmission, and worse clinical outcomes. The integration of bronchial washing analysis with GeneXpert testing not only enhances diagnostic sensitivity but also provides the added advantage of detecting rifampicin resistance, which is critical for guiding appropriate treatment regimens. The World Health Organization (WHO) has already endorsed the incorporation

of GeneXpert technology into national tuberculosis control programs, and the findings of this study further reinforce its pivotal role in improving diagnostic accuracy and timeliness. By expanding access to these molecular diagnostics, particularly in secondary and tertiary care facilities, healthcare systems can strengthen case detection, initiate earlier treatment, and ultimately contribute to reducing TB transmission and mortality in high-burden populations.[23, 24]

A major strength of this study lies in its focus on a clinically challenging subset of patients, those with sputum smear and GeneXpert-negative PTB for whom diagnosis is often delayed or missed. By employing bronchial washing specimens obtained through fiber-optic bronchoscopy, the study provides valuable insight into the diagnostic utility of this minimally invasive yet highly effective procedure. The use of both AFB smear microscopy and GeneXpert MTB/RIF assay on the same bronchial samples allows for a direct comparison of conventional and molecular diagnostic methods, enhancing the reliability of findings. Importantly, the study's findings are directly applicable to resource-limited, high TB-burden settings, such as Pakistan, and offer practical recommendations for integrating bronchoscopy-based molecular testing into existing tuberculosis diagnostic frameworks.

Limitations: This study has certain limitations that should be acknowledged when interpreting the findings. Being conducted at a single tertiary care center, the results may not be fully generalizable to the broader population, as regional variations in disease prevalence, diagnostic facilities, and patient characteristics may influence outcomes. Furthermore, the study did not include mycobacterial culture, which is internationally recognized as the gold standard for confirming tuberculosis and determining drug susceptibility. The exclusion of culture-based testing was primarily due to constraints of time, resources, and laboratory capacity, which limited the ability to perform a direct comparison of sensitivity, specificity, and predictive values between GeneXpert, AFB smear microscopy, and culture.

CONCLUSION

In conclusion, the findings of this study demonstrate that in patients with a high clinical and radiological suspicion of PTB but who are negative for sputum AFB smear and GeneXpert, the analysis of bronchial washing specimens significantly enhances the overall diagnostic yield. The GeneXpert MTB/RIF assay performed on bronchial washings was able to identify Mycobacterium tuberculosis in a substantially greater proportion of cases compared with AFB smear microscopy, thereby highlighting its superior sensitivity, particularly in paucibacillary or sputum-scarce forms of PTB. Beyond its diagnostic sensitivity, GeneXpert offers additional advantages, including the rapid detection of rifampicin resistance, which enables earlier initiation of appropriate therapy and reduces the risk of delayed or ineffective treatment. In contrast, while AFB smear microscopy continues to serve as a cost-effective and highly specific diagnostic tool, its limited sensitivity underscores the need to integrate more advanced molecular diagnostics within routine clinical protocols. Expanding access to bronchoscopy services and GeneXpert testing at secondary and tertiary care centers—particularly in high-burden and resource-limited settings can play a pivotal role in improving early case detection. Furthermore, regular training of healthcare personnel, capacity building in diagnostic laboratories, and integration of molecular testing with national tuberculosis control programs are essential steps to enhance diagnostic efficiency and ensure timely treatment. Collectively, such measures could contribute significantly to reducing diagnostic delays, limiting disease transmission, and ultimately strengthening tuberculosis control strategies in high-prevalence regions.

Conflicts of Interest: Nil

Source of Funding: Nil

Acknowledgement: We acknowledge the faculty of the Department of Pulmonology, Mayo Hospital, Lahore for their support and the patients for their contribution to this study.

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