

Diagnostic Value of Bronchoscopy in Sputum-Negative Presumptive Pulmonary Tuberculosis Patients and Its Clinicoradiological Profile

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Abstract:

CONTEXT: Tuberculosis (TB) remains endemic in India. Little local data have been reported on bronchoscopic evaluation of sputum-negative pulmonary TB patients, which poses a significant diagnostic and therapeutic challenge.

AIMS: To determine the diagnostic value of bronchoscopy and bronchoalveolar lavage (BAL) and its clinical and radiological profile in sputum-negative, pulmonary TB patients.

METHODS: We performed an analysis of patients with probable pulmonary TB with overall negative (smear and/or polymerase chain reaction [PCR]) or scanty sputum that had undergone bronchoscopy with BAL over a period of 11 months. Patients' symptoms, radiological features, lung lobe lavaged, BAL acid-fast bacilli (AFB) stain, *Mycobacterium TB* (MTB)-PCR, and mycobacterial cultures were analyzed. Mycobacterial culture was used as a reference standard.

RESULTS: 54 patients underwent a diagnostic bronchoscopy. Dry cough and fever were the most common symptoms. Uncontrolled diabetes mellitus was the most frequent comorbidity identified in 15 (28%) patients. Fifty-nine percent of the patients had diffuse lung infiltrates, with consolidation being the most common abnormality (41%), followed by cavitation (39%). Right upper lobe was the most frequent lung lobe lavaged (31%). BAL mycobacterial culture and MTB Polymerase Chain Reaction (PCR) were positive in 43 (80%) and 41 (76%) patients and BAL AFB was positive in 5 patients respectively. Using BAL culture as reference, male gender, predominant upper lobe disease, upper lobe lavage, and presence of cavities on chest imaging had the highest diagnostic yield (82%, 100%, 63%, and 89%, respectively) ($P = 0.02, 0.006, 0.03, \text{ and } 0.02$, respectively). There was 100% concordance among the three diagnostic modalities.

CONCLUSIONS: An overall diagnostic yield of 80% was achieved with combined use of BAL MTB PCR, culture, and AFB staining.

Keywords: Broncho alveolar lavage, bronchoscopy, *Mycobacterium tuberculosis* polymerase chain reaction, sputum negative, tuberculosis

INTRODUCTION

Tuberculosis is a significant global health issue, and efforts to improve diagnosis are crucial for effective management and control. The "End TB" strategy outlined by the World Health Organization (WHO) emphasizes early and accurate diagnosis as one of its pillars, and various studies shed light on the limitations of smear microscopy and the need for alternative diagnostic approaches. [1, 6] The fact that a substantial percentage of pulmonary TB cases are smear-negative highlights the importance of considering other diagnostic methods, such as bronchoscopy. Bronchoscopy not only allows direct visualization of the lower respiratory tract but also provides the opportunity to collect appropriate samples for testing. This can be particularly valuable in cases where smear microscopy may not be as effective, such as in patients with little or no sputum production.

Chest imaging is also highlighted as a crucial diagnostic modality for suspected pulmonary TB. While it may not have high specificity, it plays a pivotal role in differentiating between inactive and active TB. Additionally, chest imaging provides valuable information for selecting patients who may benefit from further diagnostic procedures like bronchoscopy and targeted lavage and biopsies.

The recognition that compatible clinical and radiological data may be sufficient to initiate antituberculous therapy, even before microbiological confirmation, is an important aspect of managing TB. This approach acknowledges the urgency of treatment initiation, especially in cases where delayed diagnosis could lead to disease progression and increased risk of transmission.

In summary, multifaceted approach is needed for the diagnosis of TB, involving a combination of clinical, radiological, and microbiological methods. This comprehensive approach is essential for addressing the challenges associated with TB diagnosis and working towards the "End TB" goal outlined by the WHO.

AIMS AND OBJECTIVE

- To determine the diagnostic yield of bronchoscopy in sputum-negative presumptive pulmonary TB
- To determine clinical and radiological profile of presumptive pulmonary TB patients at a single tertiary care centre in North India.

MATERIALS AND METHODS:

This was a prospective observational, single center study done in Department of Pulmonary And Critical Care Medicine in a tertiary teaching hospital in North India from December 2022 to October

The study protocol was reviewed and approved by the Institute Ethics Committee

INCLUSION CRITERIA

All Patients age >18 years with suspected Pulmonary tuberculosis (clinically/radiologically)in whom sputum is inadequate for examination (saliva or very scanty sputum) or those with sputum smear negative for acid-fast bacillus (AFB) on two samples, as per RNTCP guidelines.

Informed consent was mandatory by the patient/attendant

EXCLUSION CRITERIA

Patients with smear positive for AFB

Those with extrapulmonary tuberculosis

Those on antitubercular treatment for suspected PTB (clinical/radiological)

The patients who did not give consent

METHOD

After fulfilling of above mentioned inclusion and exclusion criteria, total 54 patients were enrolled in this study.

Bronchoscopy was performed under topical anesthesia (lidocaine 2%) and conscious sedation (intravenous midazolam and fentanyl). The bronchoscope was guided to the targeted subsegmental bronchus based on radiological findings. BAL was performed, where 20–30 ml of isotonic saline was infused through the bronchoscope in multiple aliquots and collected into a trap using gentle suction. BAL samples were subjected to analysis for acid-fast bacilli (AFB) smear, mycobacterial culture, and MTB-Polymerase Chain Reaction (PCR).

Respiratory samples, after decontamination and centrifugation, were analyzed for the presence of AFB by fluorescence microscopy with Ziehl–Neelsen staining. Inoculation of samples on liquid (BACTEC MGIT) media for ≥ 8 weeks was performed. PCR for MTB was conducted using GeneXpert MTB/RIF (Cepheid Inc., Sunnyvale, California, USA) according to the manufacturer's instructions.



Figure: Flexible Fibreoptic Bronchoscope

Statistical analysis

Descriptive statistics were used to summarize demographic and other clinical, radiological, and laboratory characteristics of the participants. Frequencies and percentages (%) were obtained for qualitative variables, whereas quantitative variables were presented as means \pm standard deviations or as median and interquartile range (IQRs). Student's *t*-test and ANOVA test were used for continuous variables with normal distribution and Chi-squared test was used for comparison of categorical variables. $P < 0.05$ was considered statistically significant.

RESULT

Demographics

Total 54 patients were enrolled in the study .The mean age was 53 (\pm 20) years with male predominance (67%). Only 10 (20%) patients reported a previous contact with TB patients. None of them had a previous history of TB.The characteristics of the study population are illustrated in Table 1. Low-grade fever (67%) and dry cough (61%) were the most commonly reported symptoms. Hemoptysis was the presenting complaint in only one patient. Eighteen percent of patients were completely asymptomatic and were identified on incidental radiological findings. Thirty three (61%) patients were nonsmokers. Comorbidities were present in 38 (77%) patients. Uncontrolled diabetes mellitus was the most prevalent comorbidity (28%), followed by the history of immunosuppressive therapy received in the past 6 months (20%) and end-stage renal disease (on intermittent hemodialysis) in 6 patients. Patients without comorbidities were significantly younger (31 ± 14 years) than those with comorbidities (66 ± 14 years) ($P < 0.001$).

Table 1: Baseline clinical and laboratory characteristics of study population

Characteristics	Study population (n=54), n (%)
Age(years) Mean +SD	53 \pm 20
Gender:	
Male	36(67%)
Female	18(33%)
Smoking Status	
Smoker	21 (39)
Non smoker	33 (61)
Symptoms	
1.fever	9 (18)
2.cough	36 (67)
3.weight loss	33 (61)
4.asymptomatic	16 (31)
5.hemoptysis	1 (2)
Comorbidities	
None	13 (24)
Diabetes mellitus	15 (28)
Immunosuppressant	10(20)
End stage renal disease	6 (12)

Radiological findings

All 54 patients had abnormal radiology. Thirty two (59%) patients had bilateral, diffuse pulmonary infiltrates with predominantly upper lobe involvement [Table 2]. Among those with unilateral disease, the right lung was more commonly affected (75%). Consolidation was the most common abnormality seen in 22(41%) patients. Cavities were seen in 39% of patients, while 31% had concomitant mild to moderate pleural effusion. Patients with cavities on chest imaging were significantly more symptomatic

Table2: Radiological characteristics of study population

Findings	Population(n=54),n (%)
Extent	
Bilateral	32 (59)
Unilateral	22 (41)
Side	
Right	40 (75)
Left	14 (25)
Lunglobes	
Upper	19 (35)
Middle	5(6)
Lower	10(18)
Morethan1 lobe	20 (41)
Radiographic/parenchymal findings	
Consolidation	22 (41)
Cavitation	21 (39)
Tree-in-bud	16 (33)
Largenodules(>1cm)	7(14)
Miliarynodules	3(6)
Pleuraleffusion	15 (31)
Thoraciclymphadenopathy	13 (26)

Table 3 summarizes the bronchoscopic and microbiological data. The right upper lobe was the most frequent lung lobe lavaged with MTB culture yielding positive results in 43 patients.11 patients with negative cultures but presumptive symptoms were treated empirically.

Out of 54 enrolled patients,43 (80%) had positive mycobacterial cultures.BAL culture was positive in 43/54(80%) followed by BAL MTB PCR in 41/54 (76%) patients, while the lowest diagnostic yield was seen with BAL AFB smear (10%). Bronchoscopy also helped identify 11 (20%) patients who were exclusively culture negative from BAL.

Table3:Bronchoscopic andmicrobiological data of treated pulmonary tuberculosis patients

Bronchoscopy	Patients(n=54)
BAL,n (%)	
Rightupper	16 (31)
Rightmiddle	7(14)

Rightlower	10 (20)
Leftupper	7(14)
Leftlower	4(8)
Morethan1 lobe	6(12)
YIELD OF BRONCHOSCOPY	
Positive BAL MTBculture	43/54(80%)
Positive BAL PCR	41/54(76%)
Positive BAL AFB smear	5/54(10%)
Negative culture	11/54(20%)

BAL=Bronchoalveolar lavage, MTB:Mycobacterium tuberculosis, AFB=Acid-fast bacilli, PCR=Polymerase chainreaction

Although there was no statistically significant difference in clinical and radiological characteristics between culture-positive and culture-negative patients, those who had negative BAL cultures were less symptomatic and had predominantly upper lobe involvement. Seventy percent of patients had positive BAL mycobacterial cultures when predominant infiltrate was consolidation and tree-in-bud, while 87% of patients with cavities on chest imaging yielded positive MTB PCR from BAL.

Using BAL culture as the standard of reference, male gender, predominant upper lobe disease, upper lobe lavage, and presence of cavities on chest imaging had the highest diagnostic yield (82%, 100%, 63%, and 89%, respectively) ($P = 0.02, 0.006, 0.03, \text{ and } 0.02$, respectively). All patients in whom AFB were positive also had positive CBNAAT and culture and patient in whom CBNAAT was positive also had positive culture. So there was 100% concordance among the 3 diagnostic test.

In our study the diagnostic yield of bronchoscopy with all modalities combined was 80%.

Discussion

In the present study, bronchoscopy led to the diagnosis of TB in 43 (80%) of 54 sputum-negative patients, a diagnostic yield that is comparable to previous studies.[9,13,32] We found that BAL AFB culture had the highest diagnostic yield (80%), followed by BAL TB PCR (76%), while BAL AFB smear was positive in 5 (10%) patients only. Since none of our patients had a previous history of treated or untreated TB, positive PCR from BAL was considered diagnostic of active TB and hence antituberculous treatment was initiated.

International studies have evaluated the diagnostic role of bronchoscopy in smear-negative/sputum-scarce pulmonary TB. The diagnostic yields in these studies vary (47%–90%), and this variability is attributed to differences in study design, the population studied, and the diagnostic methods used (smear, PCR, culture, and biopsy) [5,9-14]. There is a debate in the literature regarding the role of bronchoscopy compared to or in addition to induced sputum. Some studies report no additional diagnostic benefit of bronchoscopy, [15, 17], while others suggest a higher yield and an incremental increase in the diagnosis of induced sputum-negative patients [11, 18]. Despite being operator dependent, less cost-effective, and having

reported lower diagnostic yield due to the bacteriostatic effect of topical lidocaine, bronchoscopy remains the single most important diagnostic modality for evaluating sputum-negative patients.

It offers the advantage of direct visualization of airways, leading to targeted sampling and exclusion of other diagnoses. Bronchoscopy provides a rapid diagnosis and an additional diagnostic yield of 21%–32% in sputum culture-negative patients. [9, 12] Bronchoscopy has the unique advantage of combining different diagnostic modalities (smear, PCR, cultures, and biopsies). This combination can result in a diagnostic sensitivity as high as 84% in sputum-negative patients, providing a more comprehensive approach to diagnosis. [13, 14] The majority of patients (82%) presented with classical but nonspecific signs and symptoms of pulmonary TB. A significant portion (18%) of patients were asymptomatic. Dry cough lasting more than 4 weeks was identified as the most common presenting complaint among symptomatic patients. Symptoms are described as largely considered unhelpful in the diagnosis of smear-negative pulmonary TB, particularly in areas with low TB prevalence. [22, 23, 24]. Lack of expectoration is noted as the only symptom consistently found to be a positive predictor of smear-negative TB in several prediction models. [25–27] Among those who were asymptomatic, eight patients were either on immunosuppressive/biological therapy for an underlying disease and were found to have incidental radiological findings.

Bilateral, diffuse, upper, and lower lobe distribution was the most common pattern observed in 43% of patients. The presence of upper lobe disease was found to be significantly associated with a positive culture from bronchoalveolar lavage (BAL) ($P = 0.006$). While upper lobe infiltration with or without cavity is considered the classical radiological finding in smear-positive patients, no single radiographic feature is considered diagnostic in smear-negative patients. [22] Radiographic prediction models for smear-negative patients often incorporate a combination of findings to reliably predict active TB in this specific population. Various radiographic features have been described in smear-negative patients, including lobar consolidation, tree-in-bud with micronodular pattern, lack of cavitation, lower lobe involvement, miliary infiltrates, and mediastinal lymphadenopathy. [24, 25, 31] In the study, a significant number of patients (61%) had cavities on CT imaging. The presence of cavitation on CT imaging was independently associated with a positive mycobacterial yield from bronchoscopy ($P = 0.02$).

Bronchoscopy offers the advantage of swiftly diagnosing pulmonary tuberculosis (TB) within three days, preventing delays in treatment initiation, particularly in cases with unusual radiological findings and a diverse range of potential diagnoses. In our study, 57% of patients (28 out of 54) benefited from this rapid diagnostic capability. The use of transbronchial biopsies has been evaluated in diagnosing smear-negative patients in various studies. [5, 13, 38, 39] While routine biopsy usage is not universally recommended due to procedural risks and comparable diagnostic yields to other methods, [38, 39] it becomes crucial when alternative diagnoses, such as malignancy or fungal infection, are equally likely. This precaution is especially relevant in regions with low TB prevalence and unusual radiological presentations to avoid overlooking life-threatening conditions. Furthermore, the established role of biopsies in complementing diagnostic accuracy is well recognized. [13, 38]

Only a few studies have evaluated the role of clinical and radiological characteristics with bronchoscopic yield. [9, 10] In our study, specific clinical and radiological characteristics were not significantly associated with positive BAL culture except for the presence of cavities and upper lobe infiltrates. Hence upper lobe lavage had a higher diagnostic yield than middle and lower lobes. Similar results were not seen when BAL MTB-PCR was used as a reference. **Ahmad et al.** found a significant association of upper zone disease with positive mycobacterial yield on bronchoscopy, [9] while **Shin et al.** found tree-in-bud to be

significantly associated with active disease on HRCT chest.[10] **Sadia Imtiaz, Enas Mansour Batubara et al** did a similar study in Saudi Arabia. In the study of 154 patients 32% (49 individuals) were initially sputum negative and underwent diagnostic bronchoscopy. The most prevalent symptoms were dry cough and fever, and the most common comorbidity identified was uncontrolled diabetes mellitus in 31% of patients. Among the findings, 59% of patients exhibited diffuse lung infiltrates, with consolidation as the primary abnormality in 41%, followed by cavitation in 39%. The right upper lobe was the most frequently lavaged lung lobe (31%), and transbronchial lung biopsies (TBLB) were obtained in 43% of cases. BAL mycobacterial culture and MTB PCR were positive in 71% and 47% of patients, respectively. A rapid diagnosis was achieved in 57% of patients through the combined use of BAL MTB PCR and TBLB. Our study had following limitations. We did not evaluate the role of postbronchoscopic sputum samples in the diagnosis of sputum-negative patients. The current guidelines from the American Thoracic Society and the Centre for Disease Control and Prevention [40] recommend the collection of postbronchoscopic sputum samples for enhancing the diagnostic yield in smear/sputum-negative patients. However, this practice is currently not done routinely at our centre. The diagnostic sensitivity of BAL MTB PCR is slightly lower than Culture in our study, this may be due to technical difficulties in test procedure.

Conclusion

Bronchoscopy and Broncho alveolar lavage (BAL) emerged as valuable diagnostic tools in patients with negative sputum results. Through the combined utilization of BAL acid-fast bacilli (AFB), BAL Mycobacterium tuberculosis polymerase chain reaction (MTB-PCR), and BAL mycobacterial cultures, a noteworthy 80% of patients with negative or scanty sputum were successfully identified. Factors independently linked to a higher diagnostic yield from bronchoscopy, using BAL culture as a reference, included male gender, upper lobe infiltrates, the presence of cavities on chest imaging, and upper lobe lavage. Consequently, we advocate for the performance of bronchoscopy in smear/sputum-negative patients whenever possible, aiming for early detection of pulmonary tuberculosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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