Diagnostic value of bronchoscopy in sputum-negative pulmonary tuberculosis patients and its correlation with clinicoradiological features

Sadia Imtiaz, Enas Mansour Batubara

Department of Internal Medicine, Division of Respiratory Medicine, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

Address for correspondence:
Dr. Sadia Imtiaz, Department of Internal Medicine, Division of Respiratory Medicine, Prince Sultan Military Medical City, PO Box 7897, Riyadh 11159, Saudi Arabia.
E-mail: sadiaimtiaz101@gmail.com

Submission: 30-10-2021
Accepted: 24-01-2022
Published: 19-04-2022

Abstract:

CONTEXT: Tuberculosis (TB) remains endemic in Saudi Arabia. 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 correlation with clinical and radiological features in sputum-negative, culture-confirmed pulmonary TB patients.

METHODS: We performed a retrospective analysis of patients with definite or 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 5 years. Patients' symptoms, radiological features, lung lobe lavaged, BAL acid-fast bacilli (AFB) stain, *Mycobacterium TB* (MTB)-PCR, and mycobacterial cultures were analyzed. Mycobacterial cultures (either sputum or BAL) were used as a reference standard.

RESULTS: Out of 154 patients, 49 (32%) were overall sputum negative and underwent a diagnostic bronchoscopy. Dry cough and fever were the most common symptoms. Uncontrolled diabetes mellitus was the most frequent comorbidity identified in 15 (31%) 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%), while transbronchial lung biopsies (TBLB) were obtained in 21 (43%). BAL mycobacterial culture and MTB PCR were positive in 35 (71%) and 23 (47%) patients, respectively. Combined BAL MTB PCR and TBLB provided rapid diagnosis in 28 (57%) patients.

CONCLUSIONS: An overall diagnostic yield of 90% was achieved with combined use of BAL MTB PCR, culture, and histopathology. Upper lobe lavage and presence of cavities on chest imaging had a higher diagnostic yield.

Keywords:

Bronchoalveolar lavage, bronchoscopy, *Mycobacterium tuberculosis* polymerase chain reaction, sputum negative, tuberculosis

Access this article online

Quick Response Code:

Website:
www.thoracicmedicine.org

DOI:
10.4103/atm.atm_487_21

Tuberculosis (TB) is a worldwide public health problem. The World Health Organization reported 1.2 million deaths in 2019, making TB one of the top 10 causes of death. Although the incidence of TB is decreasing globally, it remains one of the most significant infectious causes of morbidity and mortality.[1]

One of the pillars to the "End TB" strategy outlined by the WHO is an early and prompt diagnosis of bacteriologically confirmed

How to cite this article: Imtiaz S, Batubara EM. Diagnostic value of bronchoscopy in sputum-negative pulmonary tuberculosis patients and its correlation with clinicoradiological features. Ann Thorac Med 2022;17:124-31.

TB cases. Of all the global cases notified to WHO in 2018, 85% had pulmonary TB, of which only 55% were confirmed bacteriologically by either smear microscopy, culture, or rapid diagnostic tests. Smear microscopy is a rapid, inexpensive, and widely used diagnostic test, but it has variable sensitivity (40%–70%)[2] and limited utility in patients with little or no sputum production. Although smear-negative patients are generally considered noninfectious, this is an overestimation, considering that 12%–22% of such patients might still transmit infection.[3,4] Therefore, delayed diagnosis in such patients carries the risk of disease progression as well as public dissemination. Depending on local settings and expertise, bronchoscopy is considered the next best step in the rapid diagnosis of smear-negative TB. It not only provides the opportunity for direct visualization of the lower respiratory tract but also collects suitable samples such as bronchial washings, lavage, and biopsy when indicated.[5]

Saudi Arabia has a low prevalence of TB with an incident rate of less than 10/100,000 as reported by the WHO in 2018.[6] However, due to the large annual influx of pilgrims to holy cities and a large number of resident population belonging to high TB incidence countries, TB remains endemic in the country.[7] Pulmonary TB comprises 70% of total TB cases.[6] Smear microscopy remains the diagnostic test of choice in the kingdom from the public health point of view; however, sputum scarce or smear-negative TB cases comprise 13%–25% of pulmonary TB cases in Saudi Arabia[8] and hence carry the risk of being missed and delayed treatment.

Chest imaging remains one of the cornerstone diagnostic modalities for suspected pulmonary TB. It can not only differentiate between inactive and active TB but also provides useful information to select patients for bronchoscopy and targeted lavage and biopsies. Despite low specificity of chest imaging, compatible clinical and radiological data may be sufficient enough to start antituberculous therapy while awaiting microbiological confirmation. Previously, a number of studies have demonstrated a modest correlation between radiographic features and microbiological yield, but little data have been reported from Saudi Arabia. In this study, we aim to (1) determine the diagnostic yield of bronchoscopy in sputum-negative pulmonary TB and (2) its correlation with clinical and radiological features of presumptive pulmonary TB patients at a single tertiary care center in Saudi Arabia.

Methods

Study design

This was a retrospective analysis of all patients with definite or probable pulmonary TB, who were overall sputum negative (smear and/or polymerase chain reaction [PCR]) on initial testing and underwent bronchoscopy over a period of 5 years between January 2015 and December 2019.

The study protocol was reviewed and approved by the Research and Ethics Committee of our institution.

Study population

All patients older than 14 years of age were included in the study.

Overall sputum-negative patients were defined as those with at least 3 negative sputum smears and/or PCR or those for whom suitable sputum specimen was not available for analysis.

Definite pulmonary TB was defined as culture or PCR positive in any respiratory specimen in any patient with consistent clinical and radiological features.

Probable pulmonary TB was defined as any patient with clinical and radiological picture consistent with TB but no microbiological proof and improved with antituberculous treatment.

Patients who were smear-positive, had *Mycobacterium TB* (MTB)-PCR positive from an extrapulmonary specimen, had a history of treated TB, and who received antituberculous treatment for ≥2 weeks before bronchoscopy were excluded from the study.

Data collection

Medical records of all included patients were extensively reviewed and documented on a structured data collection sheet. Clinical and demographic characteristics and laboratory results were documented. Radiological features including lobar involvement, predominant infiltrate, and presence of cavities on chest X-ray and/or computed tomography (CT) chest were reviewed by a thoracic radiologist and documented as typical or atypical for pulmonary TB.

Bronchoscopy was performed by a certified pulmonologist under topical anesthesia (lidocaine 2%) and conscious sedation (intravenous midazolam and fentanyl). The bronchoscope was advanced to targeted subsegmental bronchus guided by radiological findings. To obtain bronchoalveolar lavage (BAL), 20–30 ml of isotonic saline was infused through the bronchoscope in multiple aliquots and collected into a trap using gentle suction. Thirty percent of the total lavage return was considered adequate for analysis. BAL was sent for acid-fast bacilli (AFB) smear, mycobacterial culture, and MTB-PCR. After decontamination and centrifugation, all respiratory samples were analyzed for the presence of AFB by fluorescence microscopy followed by Ziehl–Neelsen staining. Samples were also inoculated on both liquid (BACTEC MGIT) and solid (Lowenstein–Jensen) media for ≥8 weeks. PCR for MTB was performed using GeneXpert MTB/RIF (Cepheid Inc., Sunnyvale, California, USA) according to the manufacturer's instruction.

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 ± 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. IBM SPSS Statistics for Windows, Version 25.0; July 2017; Armonk, NY: IBM Corp was used for statistical analysis.

Results

Study population

In total, 154 pulmonary TB patients treated between January 2015 and December 2019 were analyzed. Forty-nine (32%) patients fulfilled the study inclusion criteria with complete clinical and radiological data and were analyzed in detail. Among them, 41 were definite pulmonary TB, while 8 patients had negative mycobacterial cultures and were treated empirically [Figure 1]. None of the 49 patients had mycobacterial confirmation at the time of bronchoscopy.

Demographics

The mean age was 53 (± 20) years with male predominance (67%). The majority was resident Saudi population (94%). 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 (71%) and dry cough (65%) 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 (61%) patients were nonsmokers. Comorbidities were present in 38 (77%) patients. Uncontrolled diabetes mellitus was the most prevalent comorbidity (31%), followed by the history of immunosuppressive therapy received in the past 6 months (18%) 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) ($P < 0.001$).

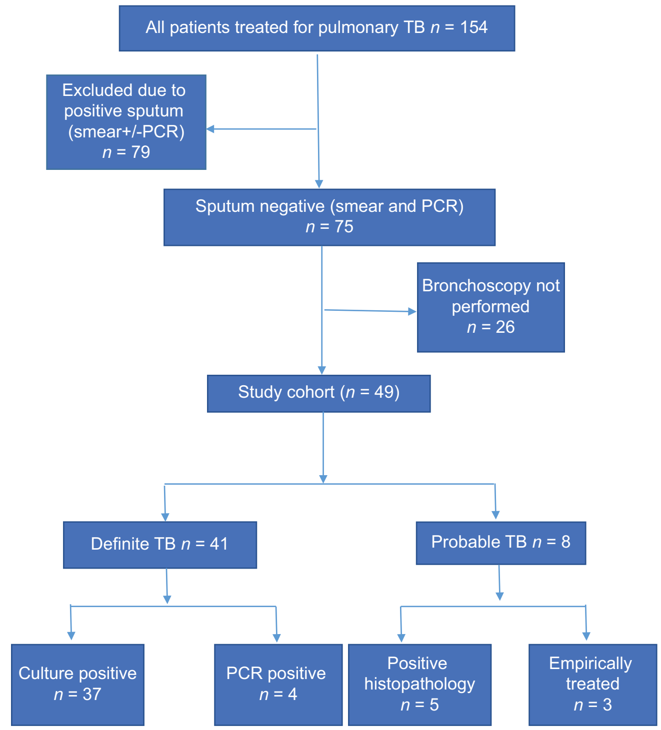

Figure 1: Distribution of study cohort

Table 1: Baseline clinical and laboratory characteristics of study population

Characteristics	Study population (*n*=49), *n* (%)
Age (years), mean±SD	53±20
Gender	
Male/female	33 (67)/16 (33)
Ethnicity	
Saudi	46 (94)
Filipin	2 (4)
Indian	1 (2)
Smoking status	
Nonsmoker/smoker	30 (61)/19 (39)
Symptoms	
Asymptomatic	9 (18)
Fever	35 (71)
Cough	32 (65)
Weight loss>10 kg	15 (31)
Hemoptysis	1 (2)
Comorbid illnesses	
None	12 (24)
Diabetes mellitus	15 (31)
Immunosuppressant	10 (20)
End stage renal disease	6 (12)
Intravenous drug abuse	2 (4)
Retroviral disease	1 (2)
ESR (mean±SD)	56±45
CRP (mean±SD)	103±73

SD=Standard deviation, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein

The mean erythrocyte sedimentation rate (ESR) was 56 (±45) and the mean C-reactive protein (CRP) was 103 (±73) mg/L. Ten patients had ESR values more than 100 and had extensive bilateral lung infiltrates suggestive of severe disease. Although no gender differences were seen in baseline clinical characteristics, female patients had significantly less mean ESR (66 vs. 35, *P*: 0.006) and CRP values (116 vs. 66, *P*: 0.03) compared to male patients.

Radiological findings

All 49 patients had abnormal radiology. CT chest was available for review in 45 patients, while the rest had typical findings for TB (upper lobe cavity, nodules, and consolidation) on chest X-ray (hence CT was deemed unnecessary). Twenty-nine (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 20 (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 and had higher ESR than those without ($P = 0.008$).

Table 3 summarizes the bronchoscopic and microbiological data. The right upper lobe was the most frequent lung lobe lavaged (31%). Transbronchial lung biopsies (TBLB) were also obtained for 21 (43%) patients, 13 of whom had typical histopathological features of mycobacterial infection but only 2 were culture positive from the biopsy. Among 8 culture-negative (probable pulmonary TB) patients, 5 were diagnosed based on compatible histopathology and 3 were treated empirically.

Out of 49 enrolled patients, 37 (75%) had positive mycobacterial cultures (20 from both sputum and BAL, 15 from BAL alone, and 2 from sputum alone), 4 (8%) had positive BAL PCR only, and 8 (16%) remained culture negative [Figure 2].

BAL culture was positive in 35/49 (71%) followed by BAL MTB PCR in 23/49 (47%) patients, while the lowest diagnostic yield was seen with BAL AFB smear (10%). Bronchoscopy also helped identify 8 (16%) patients who were exclusively culture positive from BAL.

Using BAL PCR and culture, a diagnostic yield of 80% (39/49) was achieved which, with the addition of TBLB/histopathology, improved to 90% [Table 4]. Furthermore, bronchoscopy led to an incremental increase in the diagnosis of 46% in patients who ultimately had negative sputum cultures. Since sputum mycobacterial culture results were not available at the time of bronchoscopy, BAL MTB PCR and TBLB provided an early diagnosis in 28 (57%) patients.

Table 2: Radiological characteristics of study population

Findings	Population (*n*=49), *n* (%)
Extent	
Bilateral	29 (59)
Unilateral	20 (41)
Side	
Right	37 (75)
Left	12 (25)
Lung lobes	
Upper	17 (35)
Middle	3 (6)
Lower	9 (18)
More than 1 lobe	20 (41)
Radiographic/parenchymal findings	
Consolidation	20 (41)
Cavitation	19 (39)
Tree-in-bud	16 (33)
Large nodules (>1 cm)	7 (14)
Miliary nodules	3 (6)
Pleural effusion	15 (31)
Thoracic lymphadenopathy	13 (26)

Table 3: Bronchoscopic and microbiological data of treated pulmonary tuberculosis patients

Bronchoscopy	Patients (*n*=49)
BAL, *n* (%)	
Right upper	15 (31)
Right middle	7 (14)
Right lower	10 (20)
Left upper	7 (14)
Left lower	4 (8)
More than 1 lobe	6 (12)
TBLB	21 (43)
Microbiology	
Positive BAL MTB culture	35/49
Positive BAL PCR	23/49
Positive BAL AFB smear	5/49
Positive TBLB culture	2/49
Negative yield	8/49

BAL=Bronchoalveolar lavage, TBLB: Transbronchial lung biopsies, MTB: Mycobacterium tuberculosis, AFB=Acid-fast bacilli, PCR=Polymerase chain reaction

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, had lower mean ESR values (34 vs. 65), 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 reference, male gender, predominant upper lobe disease, upper lobe lavage, and presence of cavities on chest imaging had the highest diagnostic

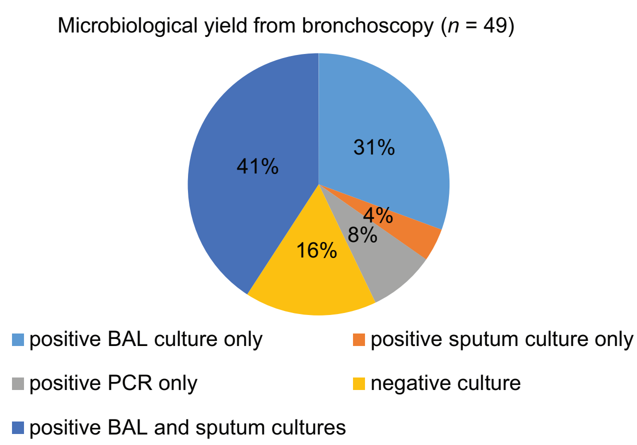

Figure 2: Microbiological yield from bronchoscopy and bronchoalveolar lavage

Table 4: Rapid and overall diagnostic yield from combination of bronchoscopic techniques

Procedure	Investigation	Rapid diagnosis (*n*=49), *n* (%)	Overall diagnostic yield, *n* (%)
BAL only	BAL AFB smear + BAL MTB PCR + BAL AFB culture	23 (47)	39 (80)
BAL + TBLB	BAL AFB smear + BAL AFB culture + BAL MTB PCR + TBLB histology	28 (57)	44 (90)
BAL + (TBLB + PCR + culture)	BAL AFB smear + BAL MTB PCR + BAL AFB culture + TBLB histology + TBLB MTB PCR + TBLB AFB culture	28 (57)	44 (90)

BAL=Bronchoalveolar lavage, TBLB: Transbronchial lung biopsies, MTB: Mycobacterium tuberculosis, AFB=Acid-fast bacilli, PCR=Polymerase chain reaction

yield (82%, 100%, 63%, and 89%, respectively) ($P = 0.02$, 0.006, 0.03, and 0.02, respectively).

Discussion

Several international studies have evaluated the diagnostic role of bronchoscopy in smear-negative/sputum scarce pulmonary TB[5,9-14] with variable diagnostic yields (47%–90%). This variability is attributed to different studies' designs, population studied, and the applied diagnostic methods (smear, PCR, culture, and biopsy). The role of bronchoscopy in lieu or addition to induced sputum has also been debated in the literature, with some studies reporting no additional diagnostic benefit of bronchoscopy,[15,17] while others suggesting 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 reported lower diagnostic yield due to the bacteriostatic effect of topical lidocaine, bronchoscopy remains the single most important diagnostic modality for the evaluation of sputum-negative patients. It not only provides an opportunity for direct visualization of airways leading to targeted sampling and exclusion of other diagnoses but also provides rapid diagnosis and an additional diagnostic yield of 21%–32% in sputum culture-negative patients.[9,12] Moreover, it provides a unique advantage of combining different diagnostic modalities (smear, PCR, cultures, and biopsies) to obtain a diagnostic sensitivity as high as 84% in sputum-negative patients.[13,14]

In the present study, we found a higher prevalence of smear-negative patients (49%) in our cohort in contrast with the reported local prevalence of 13%–25%.[8,19] Moreover, local epidemiological studies have established a higher incidence of pulmonary TB in the non-Saudi population,[7,8] whereas 94% of our patients were Saudi citizens. This might be due to referral bias since our center is a military tertiary care hospital, which caters to a specific population (soldiers and their dependents), where the majority of patients are referred for further diagnostic evaluation of suspected pulmonary TB once smear results are negative. Higher mean age (54 years) and male predominance in our cohort are in line with previously published data.[20,21]

The majority (82%) of our patients presented with classical, but nonspecific signs and symptoms of pulmonary TB, while 18% were asymptomatic. Dry cough lasting more than 4 weeks was the most common presenting complaint. Although less frequent than smear-positive cases,[22,23] symptoms are largely considered unhelpful in the diagnosis of smear-negative pulmonary TB, especially in areas with low TB prevalence.[24] Lack of expectoration is the only symptom that has been consistently found to be a positive predictor of smear-negative TB in several prediction models.[25-27] However, the clinical utility of these prediction scores is limited due to the heterogeneity of the population studied, underlying HIV prevalence, and lack of reference standards.

Among those who were asymptomatic, 8 were either on immunosuppressive/biological therapy for underlying disease and were found to have incidental radiological findings or were referred to rule out pulmonary TB before initiation of immunosuppressive drugs. Comorbidities (such as diabetes, alcohol abuse, and immunosuppression) increase the risk of TB in general, they are not particularly predictive of smear negative, culture positive TB except HIV where the prevalence of smear negative TB may reach as high as 40% and portends poor prognosis.[22,28] However, only one patient in our cohort was seropositive for HIV.

Bilateral, diffuse, upper, and lower lobe distribution was the most common pattern seen in our patients (43%), followed by upper lobe distribution (37%). The presence of upper lobe disease was significantly associated with a positive culture from BAL ($P = 0.006$). Although upper lobe infiltration, with or without cavity, is the classical radiological finding in smear-positive patients,[29] no single radiographic feature is considered diagnostic in smear-negative patients.[22] In fact, several radiographic prediction models incorporate a combination of findings to reliably predict active TB in this specific population.[29,30] The presence of lobar consolidation, tree-in-bud with micronodular pattern, lack of cavitation, lower lobe involvement, miliary infiltrates, and mediastinal lymphadenopathy have all been described in smear-negative patients.[24,25,31] Similar radiographic features were seen in our study, except a significant number of our patients (61%) had cavities on CT imaging. The presence of cavitation on CT imaging was independently associated with positive mycobacterial yield from bronchoscopy ($P = 0.02$).

In the present study, bronchoscopy led to the diagnosis of TB in 44 (90%) of 49 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 (71%), followed by BAL TB PCR (47%), while BAL AFB smear was positive in 5 (10%) patients only. Moreover, in those patients with negative sputum cultures, bronchoscopy led to an incremental increase in the diagnosis in 24 of 49 patients (49%), which is slightly higher than a recent study conducted by Ahmad *et al*.[9] A retrospective analysis of 190 HIV-negative, suspected pulmonary TB patients with negative sputum smear and cultures found a similar diagnostic yield of BAL culture and BAL PCR (31.6% and 30.5%, respectively). In another study by Jacomelli *et al*.,[13] BAL AFB culture alone was found to have a low sensitivity (50%) in smear-negative patients; however, the role of BAL PCR was not evaluated. This study also concluded that a combination of different diagnostic methods should be employed to enhance diagnostic yield in this patient population. Worldwide, BAL MTB-PCR is reported to have an excellent diagnostic yield with sensitivity above 90% and specificity approaching 100% in high burden countries[33-35] and above 80% sensitivity and 90% specificity in low-to-intermediate burden countries.[9,32,36] In our study, we found a lower diagnostic yield of BAL MTB-PCR (47%) than reported previously.[32,33,37] However, BAL MTB-PCR was the only positive finding in 4 patients. 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.

Another advantage of bronchoscopy is the rapid diagnosis (within 3 days) of pulmonary TB and avoiding delay in the initiation of treatment. This was achieved in 28 of 49 (57%) patients in our study. This is of particular importance, especially in patients with atypical radiological findings and a broad list of differential diagnoses. A number of studies have evaluated the role of transbronchial biopsies in the diagnosis of smear-negative patients.[5,13,38,39] Routine use of biopsies is not advocated due to potential procedural risks and lack of a superior diagnostic yield when compared to other diagnostic modalities.[38,39] However, they should be obtained if another diagnosis (for instance malignancy, fungal infection) is equally likely especially in low TB prevalence areas with atypical radiological findings to prevent underdiagnosis of life-threatening conditions.[13] Moreover, the complementary role of biopsies in enhancing diagnostic yield is well established.[13,38]

To our knowledge, 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. As a result, upper lobe lavage had a higher diagnostic yield than middle and lower lobes. Interestingly, 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]

Our study had several limitations. First, it was a retrospective study with small sample size. Hence, selection bias was unavoidable. Second, we did not have a control group to compare baseline clinical and radiological characteristics. Third, we did not evaluate the role of induced sputum and 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 to enhance the diagnostic yield in smear/sputum-negative patients. However, this practice is not a routine at our center. Finally, the lack of routine use of sputum MTB-PCR in our study population was another drawback. Both WHO and ATS/IDSA/CDC guidelines recommend sputum MTB-PCR on initial sputum samples[40,41] for simultaneous rapid detection of MTB and drug resistance. However, the diagnostic accuracy of BAL MTB-PCR is higher than sputum PCR in smear-negative patients (96% vs. 58%).[42,43] Therefore, our results of BAL

PCR yield should be read with caution since sputum PCR was not performed on all patients.

Conclusion

We found bronchoscopy and BAL to be a useful diagnostic modality in sputum-negative patients. The combined use of BAL MTB-PCR and BAL mycobacterial cultures helped to identify 49% of patients who had negative sputum smear and AFB cultures. Male gender, upper lobe infiltrates, presence of cavities on chest imaging, and upper lobe lavage were independently associated with higher diagnostic yield from bronchoscopy when BAL culture was used as a reference, but similar results were not obtained with BAL MTB-PCR. Therefore, we recommend, whenever available, bronchoscopy to be performed in smear/sputum-negative patients for early diagnosis of pulmonary TB.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization (WHO). Global Tuberculosis Report 2020 [internet]. Geneva: WHO; 2020. Available from: https://www.who.int//iris/bitstream/handle/10665/336069/9789240013131-eng.pdf. [Last accessed 13 March 2021].
2. Mase SR, Ramsay A, Ng V, Henry M, Hopewell PC, Cunningham J, *et al.* Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: A systematic review. Int J Tuberc Lung Dis 2007;11:485-95.
3. Tostmann A, Kik SV, Kalisvaart NA, Sebek MM, Verver S, Boeree MJ, *et al.* Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. Clin Infect Dis 2008;47:1135-42.
4. Behr MA, Warren SA, Salamon H, Hopewell PC, Ponce de Leon A, Daley CL, *et al.* Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. Lancet 1999;353:444-9.
5. 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.
6. World Health Organization (WHO). Tuberculosis Country Profiles (Saudi Arabia). Geneva: WHO; 2019. Available from: https://www.who.int/tb/country/data/profiles/en/. [Last accessed on 2021 Apr 15].
7. Al-Hajoj S, Varghese B. Tuberculosis in Saudi Arabia: The journey across time. J Infect Dev Ctries 2015;9:222-31.
8. Abouzeid MS, Zumla AI, Felemban S, Alotaibi B, O'Grady J, Memish ZA. Tuberculosis trends in Saudis and non-Saudis in the Kingdom of Saudi Arabia – A 10 year retrospective study (2000-2009). PLoS One 2012;7:e39478.
9. Ahmad M, Ibrahim WH, Sarafandi SA, Shahzada KS, Ahmed S, Haq IU, *et al.* Diagnostic value of bronchoalveolar lavage in the subset of patients with negative sputum/smear and mycobacterial culture and a suspicion of pulmonary tuberculosis. Int J Infect Dis 2019;82:96-101.
10. Shin JA, Chang YS, Kim TH, Kim HJ, Ahn CM, Byun MK. Fiberoptic bronchoscopy for the rapid diagnosis of smear-negative pulmonary tuberculosis. BMC Infect Dis 2012;12:141.
11. Iyer VN, Joshi AY, Boyce TG, Brutinel MW, Scalcini MC, Wilson JW, *et al.* Bronchoscopy in suspected pulmonary TB with negative induced-sputum smear and MTD(®) Gen-probe testing. Respir Med 2011;105:1084-90.
12. Worodria W, Davis JL, Cattamanchi A, Andama A, den Boon S, Yoo SD, *et al.* Bronchoscopy is useful for diagnosing smear-negative tuberculosis in HIV-infected patients. Eur Respir J 2010;36:446-8.
13. Jacomelli M, Silva PR, Rodrigues AJ, Demarzo SE, Seicento M, Figueiredo VR. Bronchoscopy for the diagnosis of pulmonary tuberculosis in patients with negative sputum smear microscopy results. J Bras Pneumol 2012;38:167-73.
14. Prasad R, Singh A. Role of bronchoscopy in diagnosis of smear-negative pulmonary tuberculosis. Egypt J Bronchol 2019;13:1-5.
15. McWilliams T, Wells AU, Harrison AC, Lindstrom S, Cameron RJ, Foskin E. Induced sputum and bronchoscopy in the diagnosis of pulmonary tuberculosis. Thorax 2002;57:1010-4.
16. Luo W, Lin Y, Li Z, Wang W, Shi Y. Comparison of sputum induction and bronchoscopy in diagnosis of sputum smear-negative pulmonary tuberculosis: A systemic review and meta-analysis. BMC Pulm Med 2020;20:146.
17. Brown M, Varia H, Bassett P, Davidson RN, Wall R, Pasvol G. Prospective study of sputum induction, gastric washing, and bronchoalveolar lavage for the diagnosis of pulmonary tuberculosis in patients who are unable to expectorate. Clin Infect Dis 2007;44:1415-20.
18. Schoch OD, Rieder P, Tueller C, Altpeter E, Zellweger JP, Rieder HL, *et al.* Diagnostic yield of sputum, induced sputum, and bronchoscopy after radiologic tuberculosis screening. Am J Respir Crit Care Med 2007;175:80-6.
19. Memish ZA, Bamgboye EA, Abuljadayel N, Smadi H, Abouzeid MS, Al Hakeem RF. Incidence of and risk factors associated with pulmonary and extra-pulmonary tuberculosis in Saudi Arabia (2010-2011). PLoS One 2014;9:e95654.
20. Al-Orainey I, Alhedaithy MA, Alanazi AR, Barry MA, Almajid F. *M. tuberculosis* incidence trends in Saudi Arabia over 20 years: 1991-2010. Ann Thorac Med 2013;8:148-52.
21. Almutairi FM, Tayeb T, Alhakeem R, Saeed AB, Assiri A, McNabb SJ. Distribution and determinants of tuberculosis in the Kingdom of Saudi Arabia from 2005 to 2012. J Epidemiol Glob Health 2018;7 Suppl 1:S23-8.
22. Campos LC, Rocha MV, Willers DM, Silva DR. Characteristics of patients with smear-negative pulmonary tuberculosis (TB) in a region with high TB and HIV prevalence. PLoS One 2016;11:e0147933.
23. Tozkoparan E, Deniz O, Ciftci F, Bozkanat E, Bicak M, Mutlu H, *et al.* The roles of HRCT and clinical parameters in assessing activity of suspected smear negative pulmonary tuberculosis. Arch Med Res 2005;36:166-70.
24. Siddiqi K, Lambert ML, Walley J. Clinical diagnosis of smear-negative pulmonary tuberculosis in low-income countries: The current evidence. Lancet Infect Dis 2003;3:288-96.
25. Kanaya AM, Glidden DV, Chambers HF. Identifying pulmonary tuberculosis in patients with negative sputum smear results. Chest 2001;120:349-55.
26. Soto A, Solari L, Díaz J, Mantilla A, Matthys F, van der Stuyft P. Validation of a clinical-radiographic score to assess the probability of pulmonary tuberculosis in suspect patients with negative sputum smears. PLoS One 2011;6:e18486.
27. Samb B, Henzel D, Daley CL, Mugusi F, Niyongabo T, Mlika-Cabanne N, *et al.* Methods for diagnosing tuberculosis among in-patients in eastern Africa whose sputum smears are negative. Int J Tuberc Lung Dis 1997;1:25-30.
28. World Health Organization (WHO). Improving the Diagnosis and treatment of Smear-Negative Pulmonary and Extrapulmonary

Tuberculosis among adults and Adolescents. Recommendations for HIV Prevalent and Resource-Constrained Settings. Geneva: WHO; 2007. Available form: https://apps.who.int/iris/handle/10665/69463. [Last accessed on 2021 Apr 30].
29. Yeh JJ, Yu JK, Teng WB, Chou CH, Hsieh SP, Lee TL, *et al.* High-resolution CT for identify patients with smear-positive, active pulmonary tuberculosis. Eur J Radiol 2012;81:195-201.
30. Nakanishi M, Demura Y, Ameshima S, Kosaka N, Chiba Y, Nishikawa S, *et al.* Utility of high-resolution computed tomography for predicting risk of sputum smear-negative pulmonary tuberculosis. Eur J Radiol 2010;73:545-50.
31. Caliskan T, Ozkisa T, Aribal S, Kaya H, Incedayi M, Ulcay A, *et al.* High resolution computed tomography findings in smear-negative pulmonary tuberculosis patients according to their culture status. J Thorac Dis 2014;6:706-12.
32. Theron G, Peter J, Meldau R, Khalfey H, Gina P, Matinyena B, *et al.* Accuracy and impact of Xpert MTB/RIF for the diagnosis of smear-negative or sputum-scarce tuberculosis using bronchoalveolar lavage fluid. Thorax 2013;68:1043-51.
33. Khalil KF, Butt T. Diagnostic yield of Bronchoalveolar Lavage gene Xpert in smear-negative and sputum-scarce pulmonary tuberculosis. J Coll Physicians Surg Pak 2015;25:115-8.
34. Sharma SK, Kohli M, Yadav RN, Chaubey J, Bhasin D, Sreenivas V, *et al.* Evaluating the diagnostic accuracy of Xpert MTB/RIF assay in pulmonary tuberculosis. PLoS One 2015;10:e0141011.
35. Tueller C, Chhajed PN, Buitrago-Tellez C, Frei R, Frey M, Tamm M. Value of smear and PCR in bronchoalveolar lavage fluid in culture positive pulmonary tuberculosis. Eur Respir J 2005;26:767-72.
36. Lee HY, Seong MW, Park SS, Hwang SS, Lee J, Park YS, *et al.* Diagnostic accuracy of Xpert® MTB/RIF on bronchoscopy specimens in patients with suspected pulmonary tuberculosis. Int J Tuberc Lung Dis 2013;17:917-21.
37. Kilaru SC, Chenimilla NP, Syed U, Momin K, Kilaru H, Patil E, *et al.* Role of Xpert MTB/RIF in Bronchoalveolar lavage fluid of sputum-scarce, suspected Pulmonary TB patients. J Clin Tuberc Other Mycobact Dis 2019;14:7-11.
38. Mok Y, Tan TY, Tay TR, Wong HS, Tiew PY, Kam JW, *et al.* Do we need transbronchial lung biopsy if we have bronchoalveolar lavage Xpert(®) MTB/RIF? Int J Tuberc Lung Dis 2016;20:619-24.
39. Tamura A, Shimada M, Matsui Y, Kawashima M, Suzuki J, Ariga H, *et al.* The value of fiberoptic bronchoscopy in culture-positive pulmonary tuberculosis patients whose pre-bronchoscopic sputum specimens were negative both for smear and PCR analyses. Intern Med 2010;49:95-102.
40. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, *et al.* Official American Thoracic Society/Infectious Diseases Society of America/centers for disease control and prevention clinical practice guidelines: Diagnosis of tuberculosis in adults and children. Clin Infect Dis 2017;64:111-15.
41. World Health Organization. WHO Consolidated Guidelines on Tuberculosis. Module 3: Diagnosis–Rapid Diagnostics for Tuberculosis Detection. Geneva: WHO; 2020. Available from: https://www.who.int/publications/i/item/who-consolidated -guidelines-on-tuberculosis-module-3-diagnosis---rapid-diagnostics-for-tuberculosis-detection. [Last accessed on 2021 Apr 30].
42. Sarmiento OL, Weigle KA, Alexander J, Weber DJ, Miller WC. Assessment by meta-analysis of PCR for diagnosis of smear-negative pulmonary tuberculosis. J Clin Microbiol 2003;41:3233-40.
43. Hamdi A, Fida M, Deml SM, Abu Saleh O, Wengenack NL. Utility of *Mycobacterium tuberculosis* PCR in ruling out active disease and impact on isolation requirements in a low prevalence setting. J Clin Tuberc Other Mycobact Dis 2020;21:100181.