ORIGINAL RESEARCH

To Identify the Sensitivity and Specificity of Fiberoptic Bronchoscope to Diagnose Pulmonary Tuberculosis

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ABSTRACT

Background: Tuberculosis (TB) has affected humans for most of their history and remains a major cause of mortality in adults worldwide Prevalence of Tuberculosis (TB) has been on a dangerous and positive spike for over a decade and has killed millions of people year on year. Almost, 1.3 million people in 2012 alone lost their lives to TB. As per the massive prevalence of TB, it would be incorrect to say that the disease does not poses like a pandemic. Alongside HIV, it remains a top cause of death from an infectious disease. Hence the present study was planned to evaluate the role of fiberoptic bronchoscopy in sputum negative pulmonary tuberculosis cases.

Materials and Methods: The study was carried out at Department of Pulmonary Medicine, Era's Lucknow Medical College & Hospital, Lucknow. Sputum smear negative presumptive patients of PTB. All the relevant samples were sent for Cartridge based nucleic acid amplification test (CBNAAT)/genexpert for BAL, post bronchoscopy sputum, bronchial aspirate, TBLB, Endobronchial biopsy and Transbronchial needle aspiration. Culture for Mycobacterium tuberculosis (MTB) was also obtained for all the patients. Culture is done on liquid media (MGIT).

Results: Majority of patients in the study population were adults: 21-60 years (82.6%), while only a small proportion of patients were aged ≤20 years and >60 years (8.7% each). Majority of patients in the study population presented with Cough (88.0%), Fever (78.3%), Loss of appetite (67.4%), Expectoration (63.0%) & Weight loss (56.5%). Majority of patients had negative CBNAAT (81.5%), AFB (95.7%) and Culture (77.2%) for Bronchial Aspirate. Thus indicating that fiberoptic bronchoscopy helps in establishing the diagnosis.

Conclusion: Considering the short processing time and high diagnostic efficacy, CBNAAT evaluation of bronchoalveolar lavage for detection of tuberculosis among sputum/smear negative tuberculosis cases is highly recommended.

Keywords: Tuberculosis, Fiberoptic bronchoscopy, Bronchial Aspirate.

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INTRODUCTION

Tuberculosis (TB) has affected humans for most of their history and remains a major cause of mortality in adults worldwide.[1,2] Despite the discovery of effective and affordable chemotherapy more than 50 years ago, TB deaths tolled as high as 10 million in 2019 alone,[3] increasing aggressively to reach 1.2million deaths in 2019.[4] Recent reports by World Health Organization report an year on year increase in the prevalence and deaths by TB at an estimate of 8.6 million incident cases and 1.3 million deaths in 2012 and 9.0 million new incident cases and 1.5 million deaths from the disease in the year 2013, and 10.8 million new cases and 1.8 million deaths in 2015.[5,6] This incremental trend puts up question marks on the impact of systematic efforts to curb and control the disease. As more than 90% of TB cases occur in low and middle-income countries, the literature points to a relationship between degree of advancement, basic infrastructure, quality of life in a nation and efficiency of control measures for TB.[6] The Indian scenario is much worse, with over 26% of global TB burden being represented by India.[7] In 2019, out of the estimated global annual incidence of 2.69 million TB cases, have occurred in India.[8] However, according to WHO report of 2019 TB incidence, Indian position was mostly unaffected, with a similar trend of 26% of new cases being from India out of the reported of 10.8 million new cases,[6] though the situation might be satisfying for no much increase, but what triggers a question is the massive effort to curb TB by the Indian government and public health providers, not much has been changed in respect to the prevalence of the disease in the country.

Three major goals can be attributed to control and cure TB; early detection, drug compliance and proper treatment.[9] Unfortunately, most of the high burden countries are have poor infrastructure for the diagnosis of infectious diseases owing to inadequacy of resources. The only diagnostic technique for TB, suitable to peripheral levels of health services, is serial sputum smear microscopy with Ziehl Neelsen (ZN) staining.[10] Sputum smear microscopy is not only time consuming but has also shown a high false negative rate ranging from 16 to 50% despite the clinical profile and radiological lesions being consistent with diagnosis of pulmonary tuberculosis.[11] Attempts to improve the quality of sputum smear examination have been made from time to time but did not reveal any significant improvement in false positivity as well as false negativity rate despite increasing the complexity of investigational procedures.[12-14] In the event of negative-sputum in presence of symptoms, it is essential that the diagnostic tool is sensitive enough to provide an accurate diagnosis within a reasonable time. There are alternative approaches like culture sensitivity, however, AFB culture takes around 4-6 weeks, and during this time a false negative patient remains without treatment and thus increases the chance of spread of disease in the community. Anti-Tuberculosis Treatment (ATT) is typically initiated experimentally, which frequently results in unwarranted drug toxicity risk and unnecessary expense. Because cases are classified as "tuberculosis suspects," diseases like bronchogenic cancer and widespread lung disorders are sometimes overlooked. However, 64% of sputum-negative suspects may require chemotherapy within a year if they are not treated.[15] Mathematical modelling for predicting active disease has been used to determine active TB disease in individuals with presumptive sputum negative tuberculosis.[16,17] The use of a fibreoptic bronchoscope (FOB) is one of the alternative techniques that has been the subject of the most research among sputum-negative patients[13,18–21]. In terms of the relationship between sputum smear negative PTB patients' clinical and radiological profiles, fiberoptic bronchoscopy (FOB) has become an effective diagnostic tool. In addition to identifying patients who are more likely to experience disease progression, fiberoptic bronchoscopy satisfies the fundamental requirement for the early

stage diagnosis of patients who do not meet the usual bacteriological criteria for PTB confirmation.[22] In cases with endobronchial TB, which the HRCT cannot detect, FOB has proven to be the most reliable detection method. FOB may also be superior in the differential diagnosis of tuberculosis with other frequently occurring diseases such pneumonia or lung cancer.[23] Because of its more aggressive nature in reporting cases with bronchial washing specimens with AFB smears or MTB polymerase chain reaction (PCR), and tissue specimens from bronchoscopic or transbronchial biopsies, FOB is considered useful for the diagnosis of sputum smear-negative PTB despite being relatively expensive and invasive. As a result, FOB has made it possible to quickly diagnose patients with PTB before confirmation from sputum cultures could be obtained. FOB, however, raises the possibility of spreading illnesses like TB and other diseases. Because they are expensive, they are not readily available in many nations. Early FOB seems to be the best course of action for patients with suspected SSN-PTB in industrialised nations with unlimited resources. The picture is changing quickly because to the shifting economic climate and the accessibility of fiberoptic bronchoscope facilities in developing nations; therefore, it is crucial to assess the efficacy of this technology in smear-negative scenarios in Indian contexts. Our study's goal is to determine the fiberoptic bronchoscope's sensitivity and specificity for diagnosing pulmonary tuberculosis.

MATERIALS AND METHODS

Study design

The present study was carried out as a cross-sectional study.

Patients and sample collection

The study was carried out at Department of Pulmonary Medicine, Era's Lucknow Medical College & Hospital, Lucknow. For this cross-sectional study 92 subjects were enrolled and ethical clearance was obtained from the Institutional Ethical Committee, Era's Lucknow Medical College & Hospital, Lucknow. After obtaining an informed consent, demographic information, duration and nature of complaints were noted. Sputum examination for Acid-Fast Bacillus (AFB) was conducted in each participant twice, first-spot sample, and second-early morning sample. The examination was carried out by Ziehl–Neelsen staining technique. All the patients were clinically examined and necessary laboratory/radiographic investigations were also done. If the sputum smear was found positive, patient was immediately registered under DOTS and ATT and was excluded from the study, however if the sputum smear was negative, bronchoscopy was planned and the patient was included in the study. Fiberoptic bronchoscopy was used to examine bronchial tree and obtain Bronchoalveolar lavage (BAL) fluid, Bronchial aspirate, Transbronchial lung biopsy (TBLB), Endobronchial biopsy, Transbronchial needle aspiration (TBNA), Post bronchoscopy sputum. All the relevant samples were sent for Cartridge based nucleic acid amplification test (CBNAAT)/genexpert for BAL, post bronchoscopy sputum, bronchial aspirate, TBLB, Endobronchial biopsy and Transbronchial needle aspiration. Culture for Mycobacterium tuberculosis (MTB) was also obtained for all the patients. Culture is done on liquid media (MGIT).

Statistical analysis

All the differences in sociodemographic and categorical data were analyzed using Mean ± SD, Chi-Square test and Student’t’ test. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. A statistically significant P value of <0.05 was considered.

RESULTS

[Table 1] summarizes the demographic characteristics of patients. The Mean ± SD of the cases 38.65±14.25 (18-72) years respectively. Majority of patients in the study population

were adults: 21-60 years (82.6%), while only a small proportion of patients were aged ≤20 years and >60 years (8.7% each). A higher proportion of males (62.0%) were found in the study population. Majority of patients in the study population presented with Cough (88.0%), Fever (78.3%), and Loss of appetite (67.4%), Expectoration (63.0%) & Weight loss (56.5%). Hemoptysis (33.7%), Night-time sweat (19.6%), H/o Tuberculosis (17.4%) and Breathlessness (16.3%) were also reported summarized in table 2. Overall, Upper Consolidation was the most common (30.4%) X-ray finding, followed by Cavity (17.4%), Lower Consolidation (16.3%) and Middle Consolidation (15.2%), Cavity and Consolidation (12.0%) & bilateral consolidation (8.7%) [Figure 1].

Most common Bronchoscopy finding was Hyperemia (43.5%), followed by Hyperemia & Anthracotic patch (13.0%), Mucous pooling (9.8%), Hyperemia & Bronchial Stenosis (6.5%), Anthracotic patch (5.4%), Hyperemia & Mucus Pooling (5.4%), Anthracotic patch & Mucosal Edema (3.3%), Hyperemia, Mucous Pooling & Anthracotic patch (2.2%) & Lower Lobe Mass (1.1%), while remaining 11 cases (12.0%) had normal bronchoscopy findings [Figure 2]. Majority of patients were tested positive for Bronchoalveolar Lavage CBNAAT (51.1%) and Culture (55.4%). Though a large proportion of patients also tested positive for BAL-AFB (48.9%), a majority of them were tested negative (51.1%).

Majority of patients had negative CBNAAT (81.5%), AFB (95.7%) and Culture (77.2%) for Bronchial Aspirate. None of the methods yielded any additional tuberculosis case. Majority of patients had negative CBNAAT (93.5%), AFB (96.7%) and Culture (91.3%) for sputum smear post-bronchoscopy. None of the methods yielded any additional tuberculosis case summarized in [Table 3].

Most common final diagnosis of the study population was Drug Sensitive Tuberculosis (50.0%), followed by No Tuberculosis (42.4%). Only a small proportion of patients were diagnosed with Drug resistant TB (5.4%). While, non-tuberculous Mycobacteria and Adenocarcinoma were reported in one case (1.1%) each. Of 51 cases positive for tuberculosis, 5 (9.8%) were drug resistant tuberculosis and remaining 46 (90.2%) were drug-sensitive tuberculosis. Among cases negative for tuberculosis, 1 (2.4%) each was diagnosed as non-tuberculous mycobacterium and adenocarcinoma respectively on culture. A total of 39 (95.1%) were culture negative cases. Diagnostic accuracy of CBNAAT was 97.8%. Sensitivity, Specificity, PPV, NPV values were found to be 100.0%, 95.1%, 96.2%, 100.0% respectively fig 3. Diagnostic accuracy of AFB was 89.1%. Sensitivity, Specificity, PPV, NPV values were found to be 84.3%, 95.1%, 95.6%, 83.0% respectively [Table 4].

Table 1: Age & Gender Profile of study population

SN	Demographic Variable	Frequency (n=92) (No.)	Percentage (%)
1-	**Age Group**		
	≤20 years	8	8.7
	21-40 years	45	48.9
	41-60 years	31	33.7
	>60 years	8	8.7
	Mean±SD age (Range) years	**38.65±14.25 (18-72) years**	
2-	**Gender**		
	Female	35	38.0
	Male	57	62.0

Table 2: Distribution of study population according to Presenting Symptoms

SN	Presenting Symptoms	Frequency (n=92) (No.)	Percentage (%)
1-	Cough	81	88.0
2-	Night time Sweat	18	19.6

3-	Fever	72	78.3
4-	Hemoptysis	31	33.7
5-	Weight Loss	52	56.5
6-	Expectoration	58	63.0
7-	Loss of Appetite	62	67.4
8-	Breathlessness	15	16.3
9-	H/o Tuberculosis	16	17.4

Table 3: Bronchoalveolar Lavage (BAL) Fluid Analysis of study population

SN	Test	Negative		Positive	
		No.	%	No.	%
1-	**Bronchoalveolar Lavage (BAL) Fluid Analysis**				
	CBNAAT	45	48.9	47	51.1
	AFB	47	51.1	45	48.9
	Culture	41	44.6	51	55.4
2-	**Bronchial Aspirate Analysis**				
	CBNAAT	75	81.5	17	18.5
	AFB	88	95.7	4	4.3
	Culture	71	77.2	21	22.8
3-	**Post-Bronchoscopy Sputum**				
	CBNAAT	86	93.5	6	6.5
	AFB	89	96.7	3	3.3
	Culture	84	91.3	8	8.7

Table 4: Diagnostic efficacy of AFB against Culture

AFB*	Culture*	
	Positive	Negative
Positive	39	8
Negative	2	43

Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
95.1	84.3	83.0	95.6	89.1

*Positivity assessed in any of the BAL, Bronchial aspirate and Post-Bronchoscopy specimen

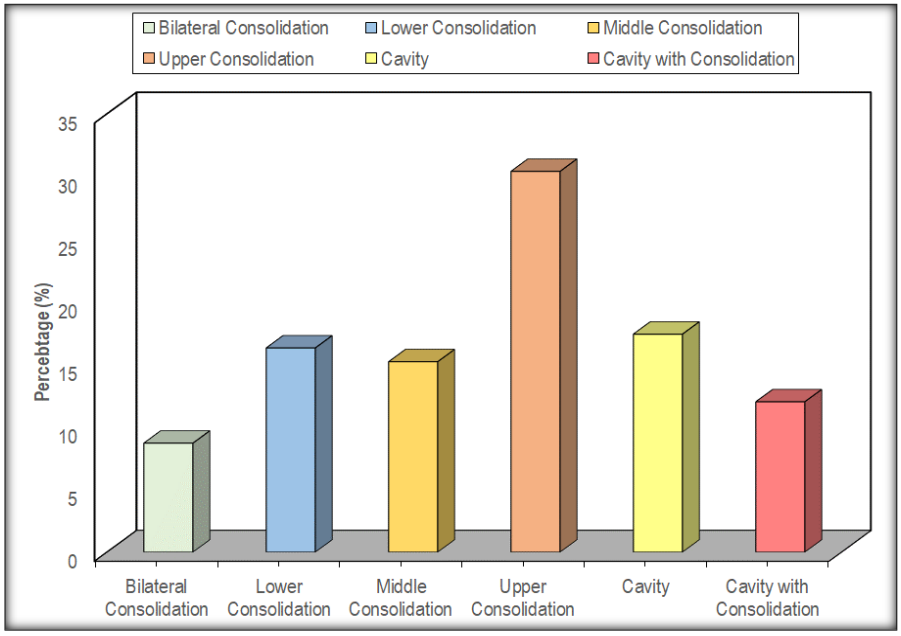

Figure 1: X-ray Findings of study population

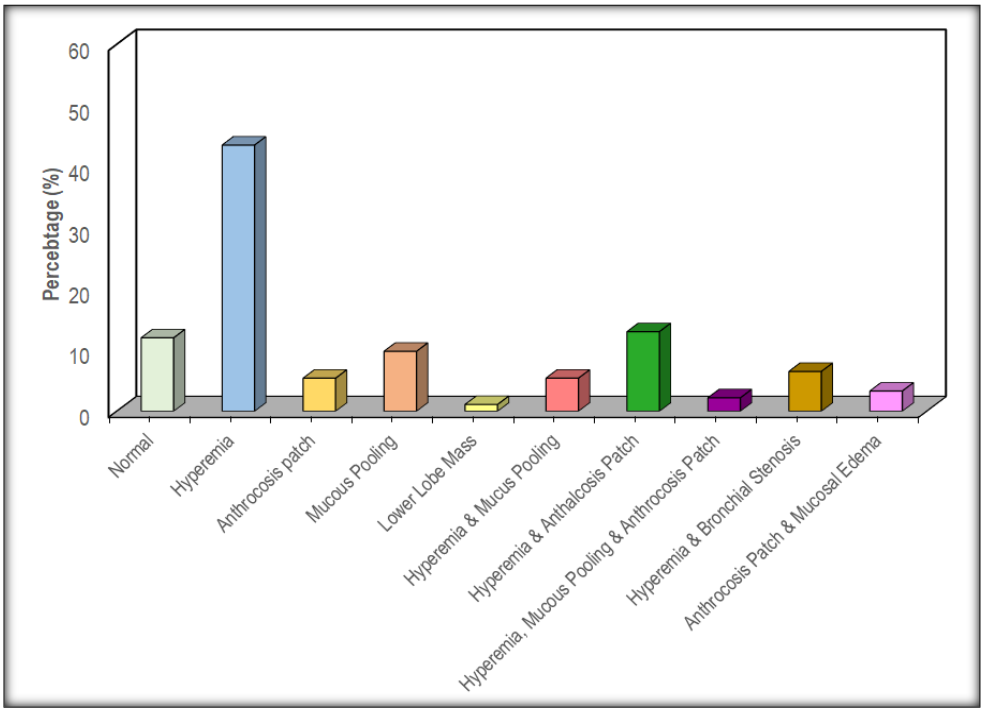

Figure 2: Bronchoscopy Findings of study population

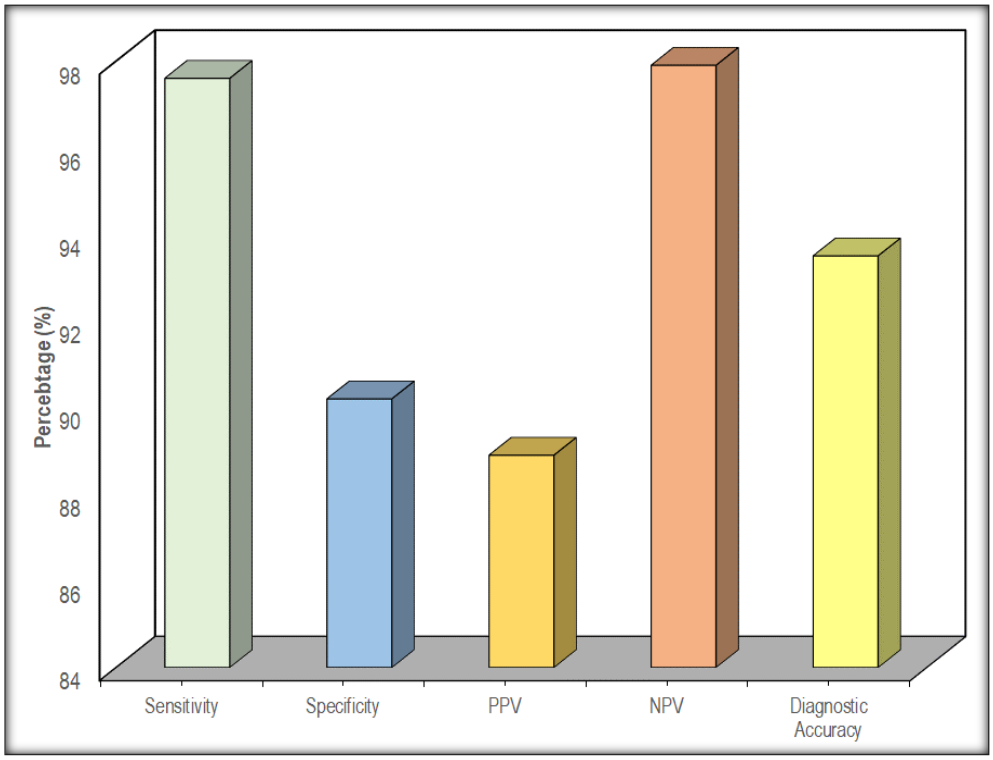

Figure 3: Diagnostic accuracy of CBNAAT

DISCUSSION

Tuberculosis is one of the unresolved disease that has remained untamed despite concerted efforts by health professionals throughout the world. Primary treatment of tuberculosis is sometimes started on symptomatic manifestation itself. Sputum smear positivity is the criteria for screening, however, it is often marred with false negativity.[11,24] On the other hand there are a number of conditions including malignancy that often have clinical manifestations similar to tuberculosis and are clinically misdiagnosed as pulmonary tuberculosis.[25-27] In

such a situation, a clinically suspected sputum negative tuberculosis patient needs further exploration for the underlying disease responsible for the clinical manifestation, moreover, in a scenario when sputum negative patient on subsequent assessments proves out to be a confirmed case of tuberculosis.[21] In such a scenario advanced and confirmatory diagnostic methods like PCR and fiberoptic bronchoscopy play an instrumental role.[21,28]

Hence the present study was planned to evaluate the role of fiberoptic bronchoscopy in sputum negative pulmonary tuberculosis cases.

A total of 92 clinically suspected sputum negative tuberculosis cases were enrolled in the study. The cases were aged from 18 to 72 years, with majority being <40 years of age (57.6%). Mean age of the patients was 38.65±14.25 years. Majority of patients were males (62%). In India, tuberculosis is seen to affect almost all the age groups. However, the burden is higher in young and productive ages. Similar to findings of present study, where there was a dominance of male patients <40 years of age and mean age was below 40 years, Baby and Nair,[29] also reported majority of patients as males (60%) and reported the mean age to be only 35.15 years. An even higher proportion of males (85.3%) and an even younger mean age (33 years) was also reported by Ahmad et al,[30] in their study. Peposhi et al,[31] in their study reported the mean age of patients to be slightly higher (44.1 years) but reported a dominance of males (65.3%) as seen in present study. Though Sanjeevaiah et al. did not report the mean age of patients, however, they also found majority of patients to be males (58.9%) and described the age range of patients as 11 to 68 years. All these studies show that tuberculosis may affect almost at all age groups, particularly males in young age.

The symptomatic profile of the patients was dominated by presence of cough (88.0%) and fever (78.3%) – two of the primary symptomatic conditions of tuberculosis. Other conditions like loss of appetite (67.4%), expectoration (63%), weight loss (56.5%), hemoptysis (33.7%), night time sweat (19.6%), breathlessness (16.3%) and past history of tuberculosis (17.4%) were also suggestive of a clinical diagnosis of tuberculosis. Although Sanjeevaiah et al,[32] in their study reported cough with expectoration (66.7%), fever/night sweats (56.1%) and weight loss (54.4%) as the most common presenting complaints, however, in relatively fewer patients as compared to present study. Baby and Nair,[29] on the other hand reported cough (85%) and fever (65%) as the most common presenting complaints. Thus, the presence of clinical symptoms was higher in present study as compared to all these studies. In fact, there are some studies,[30] that have included as high as 85% of asymptomatic patients too. Compared to these studies the present study had a higher proportion of symptomatic patients. The reason for this could be the fact that in present study we included only sputum negative symptomatic presumptive patients of PTB.

On X-ray, bilateral consolidation was seen in 8 (8.7%) cases. A total of 15 (16.3%), 14 (15.2%) and 28 (30.4%) patients respectively showed unilateral consolidation in lower, middle and upper zone lungs. Cavitation was seen in 16 (17.4%) cases, while Cavity with Consolidation was seen in 11 (12.0%) cases. These findings are suggestive of active tuberculosis as suggested by Joshi et al. (2012),[33] Joshi et al. (2007),[34] expressed questions about the specificity of chest X-rays and were of the opinion that chest radiography for TB lacked specificity in yet another investigation. Additionally, illnesses like histoplasmosis, tropical eosinophilia, pneumoconiosis, siderosis, sarcoidosis, hypersensitivity pneumonitis, and vasculitis have radiologic abnormalities that are suggestive of TB.[27] Hence, although the radiological picture corroborated the clinical diagnosis yet they cannot be considered confirmatory.

AFB Ziehl neelsen stianing assessment and culture of bronchoalveolar lavage on Lowenstein-Jensen medium have been proposed as a useful modality for evaluation of sputum AFB negative tuberculosis cases.[18,19,21] In present study too, we carried out AFB Ziehl neelsen stianing and found that 45 (48.9%) cases were positive whereas MGIT confirmed the diagnosis of pulmonary tuberculosis in 51 (55.4%) cases. AFB Ziehl neelsen stian is one of

the useful modalities for confirming sputum negative tuberculosis as pulmonary tuberculosis as indicated in previous studies,[18,19,21] and findings of present study confirmed that. In present study, CBNAAT confirmed the diagnosis in as many as 47 (51.1%) cases. The findings showed that BAL evaluation by CBNAAT yielded maximum positive cases. Compared to present study, Archana et al,[35] showed a much higher positivity rate for all the three modalities. In their study, AFB was positive in 64.2% cases, CBNAAT was positive in 75.8% and MGIT was positive in 76.7% cases. Thus, they found CBNAAT to yield more positivity than AFB but found this positivity rate to be slightly lower as compared to culture (MGIT). In the present study, we found similar results, where CBNAAT had higher positivity as compared to AFB while was slightly lower as compared to culture. Lu et al,[36] in another study found positivity rates to be lower than present study, but found CBNAAT to yield maximum positivity (26.9%) than culture (25.2%) as observed in present study. A higher positivity rate for CBNAAT as compared to culture and AFB was also seen by Gowda et al,[37] in their study who observed the AFB, Culture and Xpert positivity in 10%, 26.7% and 40% cases respectively. As such nucleic acid amplification method is considered to be the most accurate molecular measurement method for diagnosis of tuberculosis and present study showed it to be highly sensitive for TB diagnosis.

In present study, fiberoptic BAL evaluation was quite discriminating and helped in establishing the diagnosis in 57.6% cases, and non-tuberculous were seen in 42.4% cases. Thus indicating that fiberoptic bronchoscopy helps in establishing the diagnosis. However, as many as 39 cases had normal fiberoptic bronchoscopy findings, and were non tuberculous cases. It must be taken into account that this finding does not mean that the cases were normal otherwise. Thus it should be considered as a limitation of fiberoptic bronchoscopy and emphasizes the need for further exploration using improvised evaluation tools. Molecular techniques such as CBNAAT could be recommended in such cases. However, despite this limitation, fiberoptic bronchoscopy was able to reduce the burden of undiagnosed pulmonary tuberculosis to a substantial extent (55.4%). Thus establishing the role of fiberoptic bronchoscopy as a helpful aid in evaluation of sputum negative pulmonary tuberculosis cases.

CONCLUSION

The findings of study showed that fiberoptic bronchoscopy is a useful method to make confirmed diagnosis of tuberculosis among clinically suspected but sputum/smear negative tuberculosis cases. Bronchoalveolar lavage is a useful specimen that helps in confirmation of tuberculosis in maximum number of cases. Among different evaluation methods against culture positive tuberculosis, CBNAAT had a definite edge over AFB. Considering the short processing time and high diagnostic efficacy, CBNAAT evaluation of bronchoalveolar lavage for detection of tuberculosis among sputum/smear negative tuberculosis cases is highly recommended.

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