## Original Article

# To Compare the Diagnostic Sensitivity of ZN (Ziehl-Neelsen) Staining, CBNAAT (Cartridge Based Nucleic Acid Amplification Test) and Mycobacterium Culture of BAL (Bronchoalveolar Lavage) Fluid among Sputum Smear Negative or Non- Sputum Producing Patients with Suspected Pulmonary Tuberculosis

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## Abstract

**Background:** Compare the diagnostic sensitivity of ZN staining and CBNAAT using Mycobacterium Culture as a gold standard in BAL fluid among sputum smear negative or non- sputum producing patients with suspected pulmonary tuberculosis. **Subjects and Methods:** Our prospective observational study was conducted on 76 patients either attending Outpatient Department or being admitted in the department of Pulmonary Medicine, Teerthanker Mahaveer Medical College & Research Centre, Moradabad (UP). BAL sample obtained using a flexible fibre-optic bronchoscope from sputum smear negative or non- sputum producing patients with suspected pulmonary tuberculosis. Sample was divided into three parts and send the BAL fluid for CBNAAT, ZN staining, and Mycobacterium liquid culture and compare the diagnostic sensitivity of ZN staining and CBNAAT using Mycobacterium Culture as a gold standard in BAL fluid. **Results:** Our study was carried out on 76 patients, ZN staining detected positive and negative in BAL samples among 17.1% and 82.9% respectively. CBNAAT detected positive and negative in BAL samples among 68.72% and 31.6% respectively. Among the positive detected specimens, rifampicin resistance and sensitive were found among 4 (5.56%) and 48 (63.16%) specimens respectively.MTB detected positive and negative in BAL samples among 51.3% and 48.7% of the subjects respectively. The gold standard BAL-MTB liquid culture was used to test the efficacy of ZN staining to detect the BAL specimen. Sensitivity, specificity, PPV, NPV, and Accuracy of ZN in the detection of BAL specimen were 23.08%, 89.19%, 69.23%, 52.38%, and 55.26% respectively. Sensitivity, specificity, PPV, NPV and Accuracy of CBNAAT in detection of BAL specimen were 92.31%, 66.76%, 79.23%, 87.50% and 75% respectively. **Conclusion:** Gene Xpert MTB/RIF assay is efficient and reliable technique for the smear negative cases. Its simplicity, sensitivity, speed and automation, make this technique a very attractive tool for diagnosis of pulmonary tuberculosis in smear negative cases of TB suspects. Meanwhile it has an added advantage of detection of multi-drug resistant cases.

**Keywords:** BAL- Bronchoalveolar lavage, CBNAAT- Cartridge based nucleic acid amplification test, PTB- Pulmonary tuberculosis, ZN- Ziehl-neelsen.

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## Introduction

Tuberculosis is one of the leading causes of death known to human beings from a single infectious agent leading to numerous death and poor quality of life-impacting the entire world.[1] The WHO Global report of 2018 states around 10.0 million new cases of TB (range, 9.0–11.1 million), corresponding to 133 cases (range, 120–148) per one lakh were estimated.[2]

The most common organ or site affected by Mycobacterium tuberculosis is lungs i.e. in 90% of the subjects. Typical features comprised of fever, chest pain and cough with expectoration.[3] The development of resistant strains comprising MDR and XDR strains has posed a noteworthy task and failure to detect resistance by conventional sputum microscopy has led to an important role in the disease transmission. Newer diagnostic tests like MTB liquid culture and nucleic acid amplification tests such as line probe assay and Xpert MTB have led to quick analysis resulting in a significant decrease in the time for initiation

of treatment thereby reducing transmission rates.[4]

Ziehl-Neelsen stain is a very fast, low cost and easy method. This method requires at least 10,000 bacilli per ml of sputum for confirmation of tuberculosis. This test has specificity 99% and sensitivity of only 20-80%. The major drawback of smear microscopy is the failure to detect the rifampicin resistance.[5] The gold standard method for diagnosis mycobacterium culture needs only 10 to 100 viable organisms for the detection of bacteria. Though, a culture is a comparatively slow and complex technique and requires specialized laboratories and skilled staff. The mycobacterium takes days to grow in liquid media which is faster than solid media requiring four to eight weeks to grow.[6] A newer rapid automated technique like CBNAAT (Cartridge based nucleic acid amplification test) detecting Drug resistance tuberculosis within two hours respectively. CBNAAT was recommended as an extra test for sputum smear-negative specimens and first-line diagnostic test in MDR/RR–TB and HIV related TB.[7]

### Aim and Objectives
**Aim:**
To compare the diagnostic sensitivity of ZN staining, CBNAAT and Mycobacterium culture of BAL fluid among sputum smear-negative or non-sputum producing patients with suspected pulmonary tuberculosis.

### Objectives:
1. Diagnostic role of CBNAAT in BAL (Bronchoalveolar lavage) fluid for suspected Pulmonary Tuberculosis.
2. To compare the diagnostic sensitivity of ZN staining and CBNAAT using Mycobacterium Culture as a gold standard in BAL fluid.

## Subjects and Methods

The present prospective observational study was conducted on 76 patients either attending Outpatient Department or being admitted (Inpatient Department) in the department of Pulmonary Medicine, Teerthanker Mahaveer Medical College & Research Centre, Moradabad after taking clearance from the ethical committee. Study duration was one year.
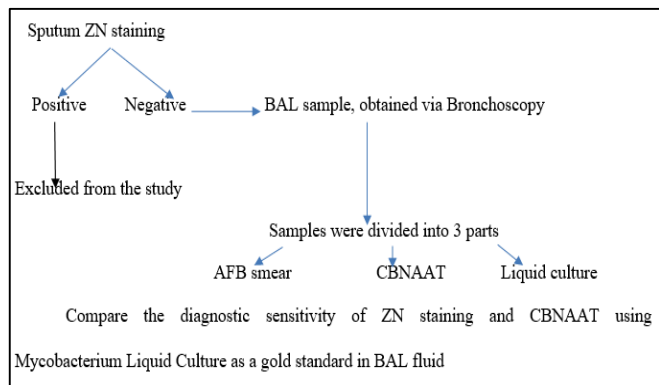


### Inclusion Criteria:
1. Age 18 years and above.
2. Patients with clinical and radiological features suspected of pulmonary tuberculosis but sputum smear-negative or not able to expectorate sputum.

### Exclusion Criteria:
1. Patients not giving consent
2. Patients on Anti Tubercular Treatment.
3. Patients with contraindications of bronchoscopy like:

Patients with hypoxia (SpO2<90% at room air), associated malignant arrhythmia, unstable cardiac status, bleeding disorder and hemodynamically unstable patients.

### Investigations
HB %, TLC, DLC, Chest X- ray PA view, Sputum ZN staining for 2 samples (If present), CT-Thorax (if needed)

## Results

The present prospective observational study was conducted among 76 patients of either sex attending or being admitted in the department of pulmonary medicine. Out of 76 patients, 25 (32.9%) and 51 (67.1%) were females and males respectively [Table 1].

**Table 1: Gender and age distribution of the study subjects**

| Variables | N | % |
|---|---|---|
| Gender | | |
| Male | 51 | 67.1 |
| Female | 25 | 32.9 |
| Total | 76 | 100 |

ZN staining detected positive and negative in BAL samples among 17.1% and 82.9% of the subjects respectively [Table 2].

**Table 2: Distribution of ZN staining in BAL samples**

| Variables | N | % |
|---|---|---|
| Detected | 13 | 17.1 |
| Not detected | 63 | 82.9 |
| Total | 76 | 100.0 |

CBNAAT detected positive and negative in BAL samples among 68.72% and 31.6% of subjects respectively. Among the positive detected specimens, rifampicin resistance and sensitive were found among 4 (5.56%) and 48 (63.16%) specimens respectively [Table 3].

**Table 3: Distribution of BAL-CBNAAT samples**

| Variables | N | % |
|---|---|---|
| Rifampicin resistance (Detected) | 4 | 5.56 |
| Rifampicin sensitive (Detected) | 48 | 63.16 |
| Not detected | 24 | 31.6 |
| Total | 76 | 100.0 |

In Liquid culture, MTB detected positive and negative in BAL samples among 51.3% and 48.7% of the subjects

respectively [Table 4].

**Table 4: Distribution of BAL-MTB liquid culture samples**

| Variables | N | % |
|---|---|---|
| Detected | 39 | 51.3 |
| Not detected | 37 | 48.7 |
| Total | 76 | 100.0 |

BAL-MTB liquid culture was used as gold-standard to test the diagnostic efficacy of ZN staining to detect the BAL specimen. MTB liquid culture detected 39 positive specimens whereas ZN staining detected only 13 positive specimens.MTB liquid culture negative in 37 specimens whereas ZN staining negative in 63 specimens. Sensitivity, specificity, PPV, NPV and Accuracy of ZN in detection of BAL specimen were 23.08%, 89.19%, 69.23%, 52.38% and 55.26% respectively [Table 5].

BAL-MTB liquid culture was used as gold standard to test the diagnostic efficacy of CBNAAT to detect the BAL specimen. MTB liquid culture detected 39 positive specimens whereas CBNAAT detected 52 positive specimens.MTB liquid culture negative in 37 specimens whereas CBNAAT staining negative in 24 specimens. Sensitivity, specificity, PPV, NPV and Accuracy of CBNAAT in detection of BAL specimen were 92.31%, 66.76%, 79.23%, 87.50% and 75% respectively [Table 6].

**Table 5: Diagnostic efficacy of ZN staining samples in relation to BAL-MTB liquid culture samples**

| | | BAL-MTB Liquid Culture | | Total | Chi square | p value |
|---|---|---|---|---|---|---|
| | | Detected | Not Detected | | | |
| ZN Staining | Detected | 9 | 4 | 13 | 2.02 | 0.16 |
| | Not detected | 30 | 33 | 63 | | |
| | Total | 39 | 37 | 76 | | |
| Sensitivity | | Specificity | PPV | NPV | | Accuracy |
| 23.08% | | 89.19% | 69.23 | 52.38 | | 55.26% |

**Table 6: Diagnostic efficacy of BAL-CBNAAT samples in relation to BAL-MTB liquid culture samples**

| | | BAL-MTB Liquid Culture | | Total | Chi square | p value |
|---|---|---|---|---|---|---|
| | | Detected | Not Detected | | | |
| BAL-CBNAAT | Detected | 36 | 16 | 52 | 21.15 | <0.01 |
| | Not detected | 3 | 21 | 24 | | |
| | Total | 39 | 37 | 76 | | |
| Sensitivity | | Specificity | PPV | NPV | | Accuracy |
| 92.31% | | 66.76% | 79.23% | 87.50% | | 75% |

# Discussion

Due to the high prevalence of TB in India, there is a need for a rapid diagnostic method to initiate early treatment and cure the diseased individuals thereby to reduce the TB burden.[8] Sputum negative cases comprise about half of every single new instance of pulmonary tuberculosis. Despite the fact that the relative transmission pace of smear-negative TB is lower than that of smear-positive cases, it is as yet answerable for 17% of transmission. Low sensitivity of direct microscopy and going for culture is a tedious procedure for the confirmation of tuberculosis. In this manner, it is the need of the hour to develop new techniques for fast detection of the Koch's bacillus in pauci-bacillary samples.[9] Under RNTCP, effective implementation of sputum smear microscopic examination was done via Primary health centers by the government of India. The initial step in the identification of mycobacterium bacillus is by ZN staining followed by a culture which takes approximately 2-6 weeks.[10] Bronchoscopy offers an advantage in confirmation of PTB in individuals who have a dry cough or those in which smear results are negative.[11,12] Therefore the present study was conducted "To measure the diagnostic sensitivity of BAL by CBNAAT, ZN staining and compare it with BAL-MTB cultures in smear-negative and sputum-scarce suspected PTB".

In the present study, out of 76 patients, 25 (32.9%) and 51 (67.1%) were females and males respectively. Similar dominance of males was shown by study done by Abhay Uppe et al,[13] in their study. There were 121 (60.5%) males and 79 (39.5%) females in study done by Abhay Uppe et al.[13] Sanjay Avashia et al1 in their study revealed that 56.9% were male and 43.1% were female. Mushtaq Ahmad et al,[14] in his study found that males constituted 85.3% of patients.

Mycobacterium Culture of BAL fluid

The current study confirmed the important value of BAL via FOB in the sputum smear-negative and not producing sputum subjects. Mycobacterium Culture detected positive and negative in BAL samples among 51.3% and 48.7% of the subjects respectively in the present study. Similar results were reported by Mushtaq Ahmad et al,[14] 60 out of 190 patients (31.6%) were identify BAL in PTB cases. This outcome is predictable with results from past examinations that analyzed the significance of BAL or washings in negative instances of PTB in sputum smear. In 1982, on 65 patients suspected of having active PTB who were either sputum smear-negative or had no sputum to test, Soe et al,[15] conducted a FOB. In bronchial aspirate, they registered a positive diagnostic yield of 38% (Soe et al., 1982).[15]

Altaf Bachh et al,[16] they found bronchial washings to be the only diagnostic tool in 48.33% of cases in 75 suspected sputum smear-negative pulmonary TB cases. Krishnan et al,[17] in 2017, they recorded a bronchial wash yield of 26.9 percent AFB smear and 44.23 percent culture in a recent

cross-sectional analysis. Only rarely reported higher yields of up to 86.6 percent (Kalawat et al., 2010).[18]

## ZN staining of BAL fluid

In the present study, ZN staining detected positive and negative BAL samples among 17.1% and 82.9% of the subjects respectively. BAL-MTB liquid culture was used as gold standard to test the diagnostic efficacy of ZN staining to detect the BAL specimen. MTB liquid culture detected 39 positive specimens whereas ZN staining detected only 13 positive specimens. MTB liquid culture detected 37 negative specimens whereas ZN staining detected 63 negative specimens. Sensitivity, specificity, PPV, NPV, and Accuracy of ZN in the detection of BAL specimen was 23.08%, 89.19%, 69.23%, 52.38%, and 55.26% respectively.

Abdul Hashim KP et al,[19] revealed that in comparison with culture used as the gold standard, sensitivity, specificity, PPV, and NPV for smear microscopy for sputum samples were recorded as 65.6%, 100%, 100%, and 85.7% respectively. In their research, Monika Agrawal et al20 found culture used as a gold standard, sensitivity, specificity, PPV and NPV for Smear microscopy for BAL samples were reported as 22.2%, 100%, 100%, and 85.3% respectively, consistent with other studies as shown in [Table 7].

**Table 7: Comparison of Sensitivity, Specificity, PPV and NPV of smear microscopy in BAL samples in different studies**

| Study | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|-------|-----------------|-----------------|---------|---------|
| Present study | 23.08 | 89.19 | 69.23 | 52.38 |
| Pierrae et al,[21] | 25 | 95.8 | 45.5 | 90.1 |
| Dewald et al,[22] | 41 | 98.6 | 94.1 | 75.8 |
| Kanwal et al,[23] | 39.53 | 100 | 100 | 11.86 |
| Monika Agrawal et al,[20] | 22.2 | 100 | 100 | 85.3 |

## CBNAAT of BAL fluid

Mycobacterial cultures for detection of Mycobacterium tuberculosis use either solid "(Lowenstein Jensen media)" or "liquid broth system (MGIT 960)". LJ medium is highly specific but is expensive, laborious requires trained personnel, not widely available and takes 6-8 weeks to give the results. Though results by MGIT 960 medium come earlier as compared to LJ medium, delay in diagnosis in smear-negative especially drug-resistant strains can have serious consequences for the patient as well as the community.[24] The Xpert MTB/RIF tests, in any case, a straight forward measure that can be performed with negligible training. The results are produced within a couple of hours.[25] At present, costs for the Gene Xpert system are similar to those required to set up an automated liquid culture system for tuberculosis but as this test is offered at

WHO centers for TB control so they are available free of charge to the patient. Although it is routinely performed for identification of pulmonary tuberculosis by using frozen sputum or BAL specimens, research has shown that it may be a valuable aid in the identification of mycobacteria in other body fluids like Cerebrospinal Fluid (CSF), pleural and ascetic fluid and will have wider applicability in future.[26]

In the present study, CBNAAT detected positive and negative BAL samples among 68.72% and 31.6% of the subjects respectively. Among the positive detected specimens, rifampicin resistance and sensitive were found among 4 (5.56%) and 48 (63.16%) specimens respectively. BAL-MTB liquid culture was used as a gold standard to test the diagnostic efficacy of CBNAAT to detect the BAL specimen. MTB liquid culture detected 39 positive specimens whereas CBNAAT detected 52 positive specimens. MTB liquid culture detected 37 negative specimens whereas CBNAAT staining detected 24 negative specimens. Sensitivity, specificity, PPV, NPV, and Accuracy of CBNAAT in the detection of BAL specimen was 92.31%, 66.76%, 79.23%, 87.50%, and 75% respectively in the present study. Similar results were reported by Kanwal Fatima Khalil et al,[23] in their study whose sensitivity and specificity of 91.86% and 71.42% respectively. Our study results were comparable to those of a recent meta-analysis stating Xpert's pooled sensitivity in smear positive-culture PTB as 98 percent, and sensitivity for smear-negative TB was 67 percent and specificity was 99 percent.

Monika Agrawal et al20 found sensitivity, specificity, PPV and NPV of GeneXpert were 81.4%, 93.4%, 73.3% and 95.7% respectively. In the other studies, GeneXpert sensitivity and specificity for the BAL sample were from 81%-92% and 71%-100% which is in conjunction with our study as shown in [Table 8]. Although the specificity is 93.4 percent in the analysis of Monika Agrawal et al,[20] it is because three culture samples are positive for MOTT and GeneXpert detects only MTB For two other cases, while MTB growth is in cultivation, it may have been too small for the GeneXpert to detect the DNA from the MTB complex. This indicates that with MTB or MOTT, a patient with a negative GeneXpert may still have TB. GeneXpert's NPV quality is high in our study compared to the study conducted by Kanwal et al,[23] as LJ media has been used in their study while the liquid culture approach has been used in our and other studies.

The strength of the present study was its prospective design. Our study highlights that CBNAAT has high sensitivity and specificity for the diagnosis of smear-negative and not producing sputum of suspected PTB cases as compared to smear microscopy when compared with culture as a gold standard. The limitation of the study was that it was limited by its small sample size. Furthermore, bronchoscopy may not be feasible in a resource-limited setting with limited expertise.

**Table 8: Comparison of diagnostic tests of CBNAAT in BAL samples in different studies**

| Study | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| Present study | 92.31 | 66.76 | 79.23 | 87.50 |
| Pierrae et al,[21] | 80 | 98.6 | 88.9 | 97.2 |
| Dewald et al,[22] | 92.3 | 87.7 | 80 | 95.5 |
| Kanwal et al,[23] | 91.86 | 71.42 | 97.53 | 41.66 |
| Monika Agrawal et al,[20] | 81.4 | 93.4 | 73.3 | 95.7 |

## Conclusion

In summary, our study confirmed the usefulness of the Xpert® MTB/RIF assay (CBNAAT), compared to Smear Microscopy, for the early diagnosis of suspected pulmonary TB requiring fibre-optic bronchoscopy, performed on per procedure samples. Gene Xpert MTB/RIF assay is efficient and reliable technique for the rapid smear negative cases. Its simplicity, sensitivity, speed and automation, make this technique a very attractive tool for diagnosis of Mycobacterium tuberculosis from smear negative cases of TB suspects. Meanwhile it has an added advantage of detection of multi-drug resistant cases.

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