



## A STUDY ON SIGNIFICANCE OF CBNAAT IN SMEAR NEGATIVE TB PATIENTS

## Pulmonary Medicine

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## ABSTRACT

**Background:** Tuberculosis is a still a major health problem worldwide, it is estimated that about one third of the world's population is infected with mycobacterium tuberculosis. While pulmonary tuberculosis is most common presentation than extra pulmonary tuberculosis. CBNAAT is cartridge based nucleic acid amplification test with a well-established role in the diagnosis of tuberculosis. There are knowledge gaps in the depth analysis of the most promising and robust diagnostic tool, gene Xpert MTB/ RIF [CBNAAT] the cycle of threshold value of the CBNAAT test and its clinical implications has not been explored much. **Material and Methods:** This study was conducted in department of Respiratory medicine of a tertiary care Hospital in Karnataka. The samples of about 81 sputum smear negative cases were subjected for the CBNAAT assay. The data obtained was tabulated using appropriate statistical tests. **Results:** Isoniazid and Rifampicin resistance was reported in 2.5% of the cases in this study. This study had shown that sensitivity and specificity of CBNAAT in various samples with culture as gold standard was 97.7% and 86.8% respectively. Positive predictive value was 89.4% and negative predictive value was 97.1% in this study. **Conclusion:** The CBNAAT has high sensitivity and specificity for diagnosis of smear negative tuberculosis cases.

## KEYWORDS

CBNAAT, Sputum culture, TB diagnostics

## INTRODUCTION

Pulmonary tuberculosis (PTB) continues as a major public health problem and is important cause of preventable mortality in developing and developed countries. Early diagnosis and prompt treatment remains as mainstay in control of tuberculosis.<sup>1</sup> During the year 2021, the global TB report had shown that around 6.4 million people developed TB disease.<sup>2</sup> The cornerstone for diagnosing TB in environments with limited resources is smear microscopy, which has a poor Positive Predictive Value (PPV) and a modest (35-80%) sensitivity. Chest X-rays are helpful but are not specific for diagnosing PTB.<sup>3</sup> Mycobacterial culture, despite being the gold standard, typically requires technical competence and takes 2-6 weeks to get a final result. Additionally, TB may present with symptoms and radiologic abnormalities that are similar to those of community-acquired pneumonia.<sup>4</sup> For the start of a treatment regimen and illness control, an early and accurate pathogen diagnosis with knowledge of its medication susceptibility patterns is essential.<sup>5</sup> Rapid molecular tests are cutting-edge diagnostic methods that potentially displace traditional culture-based drug susceptibility testing since they can concurrently test for PTB and RIF resistance with higher sensitivity than sputum smear microscopy.<sup>6</sup> CBNAAT is shown to detect the presence of TB bacilli and is also used to test the resistance to RIF.

CBNAAT was endorsed by WHO for early diagnosis of tuberculosis in less than two hours, with special emphasis on drug resistance tuberculosis, extra-pulmonary tuberculosis. It is very cost effective and rapid test which may revolutionize the diagnosis and treatment of PTB.<sup>7</sup> It is a highly specific test for rpoB gene of Mycobacterium tuberculosis, a critical gene associated with RIF resistance.<sup>8</sup>

This study was mainly undertaken in order to investigate the significance of CBNAAT in diagnosis of pulmonary tuberculosis in sputum smear negative cases.

## MATERIAL AND METHODS

This prospective study was conducted in Department of Respiratory medicine of Navodaya Medical College Hospital and Research centre, Raichur between June 2020 to July 2021. A total of 81 sputum negative pulmonary tuberculosis cases constituted the sample size. Sputum smear negative pulmonary Tuberculosis cases willing to participate in the study and clinically diagnosed new and previously treated and declared cure cases of pulmonary tuberculosis and extra-pulmonary tuberculosis cases, patients with comorbidities, smokers and alcoholics, smear negative cases were included in to the study. Patients already diagnosed with MDR TB/ XDR TB, TB patients on treatment, Bedridden; sick and moribund patients were excluded from the study.

The patients with pulmonary symptoms of cough more than 2 weeks

with weight loss , night sweat , breathlessness , haemoptysis , chest pain , fever etc , were clinically diagnosed as presumptive TB categorized into mild moderate and severe according to Bandim TB score which is based on 6 signs and 5 symptoms, which include cough, haemoptysis, dyspnoea, chest pain, night sweating, anaemic conjunctivae, tachycardia, positive finding on lung auscultation, axillary temperature >37.0, BMI <18. Then patients were subjected to X RAY and those with X RAY findings suggestive of tuberculosis were send to sputum for microscopy examination.

Also the patients with these symptoms with pleural effusion, lymph node positivity, abscess of various sites, included in this study. Various Extra pulmonary samples like pus, pleural fluid, lymph node tissue, etc sent for microscopy examination.

Smear positive and smear negative, both were further processed to CBNAAT for confirmation of MTB bacilli and Rifampicin resistance detection. Samples which were detected with MTB, either rifampicin sensitive or rifampicin resistant, further processed to first line LPA to look for isoniazid resistance. Samples with smear negative and CBNAAT positive, past H/O PTB, rifampicin resistance, isoniazid resistance, are further processed to liquid culture.

CBNAAT is a hemi-nested real time PCR. CBNAAT utilizes molecular beacon technology for detection of rifampicin resistance. Molecular beacons are nucleic acid probes that specifically bind to "wild type" sequence of rpoB gene, rifampicin susceptible gene. When the probe binds to such a sequence, a fluorescent signal is lighted up indicating the presence of rifampicin susceptible TB. If the probe fails to bind, then it is considered as rifampicin resistant TB. The results were interpreted as M.TB not detected, M.TB detected, RIF resistance not detected and M.TB detected, RIF resistance detected.

## RESULTS

The mean age of the study group was 44.2 years. About 60.5% of the cases were males. Past history of tuberculosis was present in 8.6% of the cases in this study. Bilateral lesions were present in 16.0% of the cases and cavitory lesions were present in 22.1% of the cases.

**Table 1: Rifampicin Sensitivity Among CBNAAT Positive Participants**

| Rifampicin sensitivity | Frequency | Percentage |
|------------------------|-----------|------------|
| CBNAAT negative        | 33        | 40.7       |
| Resistant              | 2         | 2.5        |
| Sensitive              | 46        | 56.8       |
| Total                  | 81        | 100        |

Among 81 patients who had CBNAAT positive result, 56.8% of them were sensitive to rifampicin.

**Table2: Isoniazid Sensitivity Among CBNAAT Positive Participants**

| Isoniazid sensitivity | Frequency | Percentage |
|-----------------------|-----------|------------|
| CBNAAT negative       | 33        | 40.7       |
| Resistant             | 2         | 2.5        |
| Sensitive             | 46        | 56.8       |
| Total                 | 81        | 100        |

Among 81 patients who had CBNAAT positive result, 46 (56.8%) of them were sensitive to isoniazid.

**Table 3: Isoniazid And Rifampicin Sensitivity**

|           |           | Rifampicin      |                 | Total     |
|-----------|-----------|-----------------|-----------------|-----------|
|           |           | Resistant n (%) | Sensitive n (%) |           |
| Isoniazid | Resistant | 0               | 2 (4.3)         | 2 (2.5)   |
|           | Sensitive | 2 (100)         | 44 (95.7)       | 46 (56.8) |
| Total     |           | 2 (100)         | 46 (100)        | 81 (100)  |

None of the cases were resistant to both Isoniazid and Rifampicin in this study. But 4.3% of the cases resistant to Isoniazid were sensitive to Rifampicin.

**Table 4: Predictive Accuracy Of CBNAAT**

| CBNAAT   | Culture         |                 | Total     |
|----------|-----------------|-----------------|-----------|
|          | Resistant n (%) | Sensitive n (%) |           |
| Positive | 42 (97.7)       | 5 (13.2)        | 2 (2.5)   |
| Negative | 1 (2.3)         | 33 (86.8)       | 46 (56.8) |
| Total    | 43 (100)        | 38 (100)        | 81 (100)  |

$\chi^2$  value= 59.162      df=1      p value=0.000, Sig

| Parameters                | Percentage |
|---------------------------|------------|
| Sensitivity               | 97.7       |
| Specificity               | 86.8       |
| Positive predictive value | 89.4       |
| Negative predictive value | 97.1       |

The sensitivity of CBNAAT in sputum negative cases was 97.7%, specificity was 86.8%, positive predictive value was 89.4% and negative predictive value was 97.1%.

## DISCUSSION

This study was taken up mainly to assess the significance of CBNAAT in sputum negative tuberculosis cases. The mean age of sputum smear negative cases was 44.2 years in this study and majority were males. Past history of tuberculosis was present in 8.6% of the cases only. Bilateral lesions and cavitary lesions were also present in the cases. A study by Sachdeva et al reported that, the mean age of the patients was 42 years and females outnumbered males. Cavitary lesions were seen in 4.36% of CBNAAT MTB and 16.66% of the CBNAAT MTB not detected cases.<sup>9</sup>

This study had shown rifampicin resistance in 2.5% of the cases and isoniazid resistance in 2.5% of the cases. About 95.7% of the cases were sensitive both for rifampicin and isoniazid. In a study by Sreekanth et al, the rifampicin resistance was detected in 1.86% of the cases only.<sup>10</sup>

The sensitivity of CBNAAT in sputum smear negative cases was 97.7%, specificity was 86.8%, positive predictive value was 89.4% and negative predictive value was 97.1% in this study. In a study by Sreekanth et al, the CBNAAT was able to pick up 12 cases out of 78 sputum smear negative cases. The sensitivity, specificity, PPV and NPV was 100%, 84.6%, 71% and 100% in comparison with sputum smear examination.<sup>10</sup> A study by Sukumar et al reported that, the sensitivity was 87.93%, specificity was 95.45, positive predictive value was 98.07% and negative predictive value was 75.0% in sample of broncho alveolar lavage.<sup>11</sup>

## CONCLUSION

This study concludes that, CBNAAT had high sensitivity and specificity for sputum smear negative cases. CBNAAT will be a viable option in resource scarce settings where culture and DST are not available. CBNAAT is robust in accurate diagnosis of tuberculosis of pulmonary and extra pulmonary samples.

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