Original Article

Diagnostic yield of CBNAAT in the diagnosis of extrapulmonary tuberculosis: A prospective observational study

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ABSTRACT

Background: Extrapulmonary Tuberculosis (EPTB) accounts for 15%–53% of all TB cases. In recent years, cartridge-based nucleic acid amplification test (CBNAAT) has emerged as an important diagnostic tool since the diagnostic yield is higher. We conducted this study to evaluate the diagnostic yield of CBNAAT in EPTB. Methods: One hundred and four patients with EPTB were included in the study. Samples were subjected to CBNAAT, AFB smear, culture for Mycobacterium tuberculosis and histopathology examination (HPE). Yield of each was estimated as compared to a composite reference standard (CRS). Results: The most common EPTB was lymph node TB (48.1%). CBNAAT was positive in 30.76% of EPTB cases. The highest yield was for bone and joint TB (35.7%), followed by lymph node TB (34%) and abdominal TB (33.3%). Taking CRS as the gold standard, sensitivity of CBNAAT was 32.3%, that of AFB culture was 33.3% and that of HPE was 87.2%. Conclusion: When taken as a single diagnostic tool, HPE had highest sensitivity in diagnosing EPTB when compared to CBNAAT and AFB culture. Use of CBNAAT alone for diagnosis of EPTB may result in missing the diagnosis. A combined modality incorporating CBNAAT, histopathology and AFB culture is the best approach for diagnosis of EPTB.

KEY WORDS: Cartridge-based nucleic acid amplification test (CBNAAT), composite reference standard (CRS), extrapulmonary tuberculosis (EPTB), India, national TB elimination program (NTEP)

INTRODUCTION

Tuberculosis (TB) is a contagious disease, predominantly involving the lungs, caused by the organism Mycobacterium tuberculosis (MTB). Traditionally, it was believed that pulmonary TB constitutes around 85% of total TB cases, whereas the remaining 15% are extrapulmonary tuberculosis (EPTB) cases.[2] But current data from around the world show a huge variation in the proportion of EPTB among all TB cases, ranging from 15% to 53%.[3] As per the 2010 annual status report of the Revised National TB Control Program (RNTCP) of India, the proportion of...
EPTB among total notified TB cases in Kerala was 26%. However, by the year 2021, the proportion of EPTB cases among notified TB cases in Kerala had increased to 40%. It is an entity that is underrecognized due to the varied and non-specific symptoms and the lack of access to diagnostic tests in peripheral hospitals and health centres. TB control programs had accorded lesser importance to EPTB as it was believed to be non-contagious, but there are studies showing the communicable nature of EPTB. India is now moving to TB elimination and the national program has been rechristened as the National TB Elimination Program (NTEP), and in the context of targets for drastic reduction of TB incidence and mortality, early diagnosis of EPTB becomes very important. Late diagnosis results in morbidity, increased mortality and disease sequelae. The laboratory diagnosis is an added hurdle, as a good number of specimens are paucibacillary or smear-negative and it is not uncommon to miss the diagnosis of EPTB.

The cartridge-based nucleic acid amplification test (CBNAAT) assay is a real-time polymerase chain reaction (PCR) cartridge-based assay for the simultaneous detection of Mycobacterium tuberculosis complex and rifampicin resistance from biological specimen samples within two hours. This technology was endorsed by the World Health Organisation (WHO) in December 2010 and is recognized as a major advancement in global TB control. The WHO had issued policy recommendations to perform the CBNAAT assay on respiratory samples in 2011 itself. By the year 2013, the policy was updated to incorporate detection of TB and rifampicin resistance from extrapulmonary samples, mainly cerebrospinal fluid (CSF), lymph nodes and other tissues. Diagnosing TB and simultaneously detecting rifampicin resistance would have a positive impact on patient care. In the recently published meta-analysis by the WHO, the sensitivity of CBNAAT in diagnosing various EPTB, like lymph node TB, CNS TB, pleural TB are 84.9%, 79.5%, and 43.7%, respectively, as compared to culture. But clinicians in India have concerns regarding the yield of CBNAAT in EPTB, as it has often been seen that the yield does not match with the data in the WHO meta-analysis. Hence, we conducted this study to assess the diagnostic accuracy of CBNAAT in EPTB in our setting.

MATERIALS AND METHODS

This was a prospective observational study conducted in a tertiary care hospital in Thiruvananthapuram, south Kerala from December 2018 to May 2020. All patients who were diagnosed with EPTB, initiated on Anti tuberculosis therapy (ATT) and who were willing to give consent were included in the study. Patients who were not willing to participate in the study, patients with established pulmonary tuberculosis, and those with presumptive EPTB for whom the Xpert® MTB/RIF assay (Cepheid Inc., CA, USA) was not done were excluded from the study. Institutional Ethics Committee clearance was obtained (KIMS/IHEC/ RM-DNB05/2018) and informed consent was obtained from all patients.

The primary objective of the study was to estimate the diagnostic yield of Xpert® MTB/RIF assay in patients who were diagnosed as having EPTB presenting to a tertiary care centre, with reference to a composite reference standard (CRS) which was defined by clinical, radiological, laboratory and histopathological findings and treatment response to ATT at the end of six months.

The sample size was calculated based according to the previous study on the diagnostic yield of Xpert® MTB/RIF assay, assuming that the proportion of positives would be 50%, and with 95% confidence levels and 20% relative precision, the sample size was calculated as 96. Consecutive patients who satisfied the inclusion and exclusion criteria were enrolled in the study after obtaining informed consent [Figure 1]. As per the hospital protocol, samples collected from all suspected EPTB patients were sent for Xpert® MTB/RIF assay along with smear for acid-fast bacilli (AFB), AFB culture and histopathological studies. The clinical, radiological, laboratory and other relevant data from patients satisfying the inclusion criteria were collected from direct interaction with patients as well as from medical records using a structured study questionnaire. This patient data was entered into study proforma, along with the result of their Xpert® MTB/RIF assay, smear AFB, AFB culture and histopathology. All microbiological and histopathological examination was performed in a laboratory accredited by the National Accreditation Board for Testing and Calibration Laboratories (NABL). The laboratory has an inherent quality control and the Xpert® MTB/RIF assay machine was subjected to annual titration by the manufacturer and is certified on an annual basis. Treatment response to ATT was followed up at the end of six months by reviewing the clinical, radiological and laboratory parameters. Since the yield of AFB culture in EPTB was low, a CRS as mentioned earlier was taken as the surrogate gold standard.

![Figure 1: Flowchart explaining the patient flow in the study](image-url)
Data collected was tabulated using Microsoft Excel and analysed using Statistical Package for the Social Sciences version 16.0. Results of continuous measurements were represented using mean ± SD, and results of categorical measurements were represented using frequencies and percentages. Association between categorical variables was assessed using the Chi-squared test. Sensitivity, specificity and 95% confidence interval (CI) were estimated. A P value less than 0.05 was considered statistically significant.

**RESULTS**

Hundred four patients were recruited for this study: 53.8% were males and 46.2% were females. Mean age of the study population was 40.8±6.3 years with age ranging from 9 to 89 years. The most common comorbidity observed in the study population was diabetes mellitus (18.3%); 14.4% of the study population had a smoking history and 16.3% had a history of alcoholism. The mean ESR was 41.5±30.6 mm/hour. The most common EPTB found in our study population was lymph node TB (48.1%) followed by TB pleural effusion (15.4%), abdominal TB (14.4%), bone and joint TB (13.5%) and central nervous system (CNS) TB (4.8%). The least common EPTB was urogenital TB.

In the study population, sensitivity and specificity of Xpert® MTB/RIF assay when compared to CRS was 32.3% and 100%, respectively [Table 2]. Xpert® MTB/RIF assay when compared with AFB culture had a sensitivity of 55.2% and a specificity of 75%, while it was 33.3% and 76.9% when compared to histopathologic examination.

As compared to CRS, sensitivity of AFB staining, AFB culture and HPE were 9.1%, 33.3% and 87.2%, respectively, in the study population [Table 3]. Xpert® MTB/RIF assay when combined with AFB culture and histopathologic evidence together as a diagnostic modality gave a sensitivity of 95.5%.

The maximum yield for Xpert® MTB/RIF assay was for bone and joint TB (35.7%) in the study population followed by that for lymph node TB (34%). Xpert® MTB/RIF assay was positive in 33.3% of abdominal TB cases and 31.3% of TB pleural effusion (pleural tissue). No Xpert® MTB/RIF assay–positive cases were found in CNS TB or urogenital TB cases. Histopathology examination (HPE) showed granulomatous inflammation in 92.9% of TB pleural effusion (pleural tissue) and 91.7% of lymph node TB. No HPE positive cases were reported among patients with CNS TB [Table 4]. Cases of CNS TB was diagnosed clinically, along with consistent radiological and CSF findings and a decision to initiate ATT by neurologist.

**DISCUSSION**

In this study with 104 participants, mean age of the study population was 40.8 years, with a slight male predominance of 53.8%. It was similar to that observed in studies by Chakravorty et al.[14] (20–39 years), and Yadav DK and Veena M [15] (21–30 years). As per NTEP reports, TB is more common in males in India, with 62% of notified TB patients in India being males.[5]

The most common EPTB in our study population was found to be lymph node TB (48.1%) followed by TB pleural effusion (15.4%). Likewise lymph node TB was the most common type of EPTB described by SK.
The studies from the same state of Kerala have shown a much lower sensitivity for CBNAAT. Jose et al.\textsuperscript{[20]} conducted a study in north Kerala (n = 1145) and observed the sensitivity of CBNAAT to be 12.6%. A newer technology, Truenat, which is also a nucleic acid amplification test (chip-based), and the sensitivity of Truenat has been studied by Kurien et al. in Kerala in pleural tissue (n = 114) showing a sensitivity of 51.11% and in pleural fluid with a sensitivity of 20%.\textsuperscript{[27]}

As understood from the above studies, the sensitivity range of CBNAAT is highly variable in EPTB. The reasons for this variability can be due to the difference of smear positivity status, variations in sampling, the quality of sample and tissue processing. Along with this the type of tissue assessed with CBNAAT also varies from study to study.

This also emphasizes the problems with a gold standard for comparison for assessing newer tests for EPTB. Culture, which could be an ideal gold standard, often has low yield, and sometimes lower yield than the newer test, when it comes to the diagnosis of EPTB. The transparent nature along with the feasibility of reproducibility and the ability to deal with imperfect reference standard make CRS a

Table 3: Diagnostic yield of various modalities

| Variables        | Number | Percentage (%) |
|------------------|--------|----------------|
| AFB Staining     |        |                |
| Positive         | 9      | 9.78           |
| Negative         | 83     | 90.22          |
| CBNAAT           |        |                |
| Positive         | 32     | 30.8           |
| Negative         | 72     | 69.2           |
| Histopathology   |        |                |
| Positive         | 75     | 85.2           |
| Negative         | 13     | 14.8           |
| AFB Culture      |        |                |
| Positive         | 29     | 32.6           |
| Negative         | 60     | 67.4           |

Table 4: Type of EPTB and various diagnostic modalities

| Type of EPTB        | AFB Stain | AFB Culture | CBNAAT | HPE  |
|---------------------|-----------|-------------|--------|------|
| Lymph node TB       | 7         | 14          | 13     | 26   |
| CNS TB              | 0         | 0           | 0      | 26   |
| TB pleural effusion | 0         | 0           | 0      | 26   |
| Abdominal TB        | 1         | 6.7         | 4      | 26.7 |
| Bone and joint TB   | 1         | 7.1         | 7      | 50   |
| Urogenital TB       | 0         | 0           | 0      | 0    |

Sharma et al.\textsuperscript{[16]} and observed in studies conducted by Komanapalli S et al.\textsuperscript{[17]} (94%, 138/272 cases), Armand et al.\textsuperscript{[18]} (57%, 16/28 cases) and Moure et al. (38.2%, 34/89 cases).\textsuperscript{[19]}

The highest proportion of EPTB diagnosed by CBNAAT was bone and joint TB (35.7%) followed by lymph node TB (34%). The form of EPTB with the highest sensitivity with CBNAAT was lymph node TB in the WHO meta-analysis\textsuperscript{[11]} and in many other studies, whereas in our study, it had lesser sensitivity for detection of lymph node TB when compared to bone and joint TB. Out of the 50 cases of lymph node TB, only 17 cases had a positive result on CBNAAT. The rest of the 33 cases were detected by other modalities, emphasising the use of other diagnostic modalities apart from CBNAAT, even in presumptive cases of lymph node TB. CBNAAT was negative in all cases of CNS TB and urogenital TB in our study population. In a study done by Hillemann D et al.\textsuperscript{[20]} all samples of CNS TB (0/19) were negative for CBNAAT, which was similar to that observed in our study, and it underlies the fact that diagnosis of CNS TB can often be missed if CBNAAT alone is used for diagnosis. In a study conducted by Scott et al.,\textsuperscript{[21]} CBNAAT was positive in 25% (1/4) of bone and joint TB and 8% (3/37) of CNS TB, whereas Komanapalli S et al.\textsuperscript{[17]} found CBNAAT positivity in 50.7% (138/272) of lymph node TB.

The most common type of EPTB detected by AFB culture was bone and joint TB (50%) followed by abdominal TB (44.4%). AFB culture had growth in 38.5% cases of TB pleural effusion and 26.5% cases of lymph node TB. AFB culture was negative for all CNS TB and urogenital TB cases in our study population. Scott et al.\textsuperscript{[21]} observed that 10.8% (4/37) of CNS TB had growth in AFB culture while none for bone and joint TB. This is probably due to the paucibacillary nature of the disease.

In our study, sensitivity and specificity of CBNAAT was 32.3% and 100%, respectively, when compared to CRS which was taken as the gold standard. The sensitivity for EPTB is highly variable in different studies, ranging from 25% to 96%, as observed by Lawn et al.\textsuperscript{[22]} in a systematic review.

There are studies from different parts of the world with varying sensitivity of CBNAAT, as shown by Tortoli et al., where they conducted a retrospective study in Italy (n = 1476) and found the sensitivity and specificity of CBNAAT to 81.3% and 99.8%, respectively, when compared to CRS.\textsuperscript{[23]} Another study from Turkey conducted by Zeka et al.\textsuperscript{[13]} (n = 48) showed the sensitivity and specificity of CBNAAT against CRS to 52.1% and 100%, respectively, among EPTB samples. Scott et al.\textsuperscript{[21]} from South Africa (n = 1045) found the sensitivity of CBNAAT against culture as 59%. A similar result was observed by Moure et al.\textsuperscript{[19]} from Spain (n = 149), where sensitivity of CBNAAT was found to be 58.3%. Another study by Hillemann D et al.\textsuperscript{[20]} from Germany (n = 521) found the sensitivity of CBNAAT to be 77.3% when compared against culture.

Studies from India have also shown varying sensitivity for CBNAAT. Vadwai et al.\textsuperscript{[22]} (n = 283) observed sensitivity of CBNAAT against CRS as 81%, whereas a study by S Suzana et al.\textsuperscript{[24]} involving 494 samples found that sensitivity of CBNAAT was 62%. Another study by Krishna V et al. had observed the sensitivity of CBNAAT against CRS to be 68.5%.\textsuperscript{[25]}

The studies from the same state of Kerala have shown a much lower sensitivity for CBNAAT. Jose et al.\textsuperscript{[20]} conducted a study in north Kerala (n = 1145) and observed the sensitivity of CBNAAT to be 12.6%. A newer technology, Truenat, which is also a nucleic acid amplification test (chip-based), and the sensitivity of Truenat has been studied by Kurien et al. in Kerala in pleural tissue (n = 114) showing a sensitivity of 51.11% and in pleural fluid with a sensitivity of 20%.\textsuperscript{[27]}
perfect gold standard.[29] However, the use of CRS may often result in cases not having TB included as TB in studies. To overcome this limitation of CRS, in our study, we followed up on every case till six months after initiating ATT to look for response to ATT. Whenever an alternate diagnosis was made subsequent to inadequate response, such cases were excluded from the study.

Hence from our study, it is clear that the general consensus regarding sensitivity of CBNAAT according to the WHO meta-analysis[31] may not be applicable to our part of country. Along with the paucibacillary nature of EPTB and the health-conscious behaviour of our population, early visit to healthcare facility for seeking medical attention can lead to early detection of EPTB through other diagnostic modalities as well.

**Policy implications**

The National TB Elimination Program (NTEP) guidelines in India accord maximum importance to nucleic acid amplification tests (NAATs) for the diagnosis of EPTB. As per the NTEP algorithm, for every presumptive EPTB for which a sample is available, a NAAT should be done. It is only if NAAT is not available that a culture is done.[29] In the scenario that has been discussed, only a third of cases would be diagnosed as TB based on the NAAT. Hence this study has implications on how planning should be done by the national program and government for investing for the diagnosis of EPTB. CBNAAT and AFB culture together had a sensitivity of 51.1%, whereas a combination of CBNAAT and AFB culture with histopathological examination increased the yield of diagnosis to 95.5%. With many states of India showing an increasing trend in proportion of EPTB, this becomes even more important.

**CONCLUSION**

In our study, the sensitivity and specificity of CBNAAT against CRS was found to be 32.3% and 100%, respectively. When taken as an individual diagnostic tool, histopathology had highest sensitivity in diagnosing EPTB in the study population, as compared to CBNAAT and AFB culture, thereby emphasising the importance of a tissue diagnosis. Perhaps it is high time we redefine the gold standard for the diagnosis of EPTB. CRS could be the answer for this vexing question.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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