Original Article

Evaluation of the Diagnostic Utility of Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) in the Detection of Extrapulmonary Tuberculosis

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Abstract

Background: Extrapulmonary tuberculosis (EPTB) is a term used to denote infection by Mycobacterium tuberculosis affecting organs outside the lungs, such as lymph nodes, pleura, bones, and the brain. It forms a considerable percentage of tuberculosis, and it is not easily diagnosed because it is paucibacillary in nature and has diverse clinical presentations. Traditional diagnostic techniques, such as smear microscopy and culture, are less sensitive and take longer to process. The Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) is a high-speed molecular diagnostic method that can simultaneously identify Mycobacterium tuberculosis and rifampicin resistance. The current study aimed to determine the diagnostic performance of CBNAAT for detecting Mycobacterium tuberculosis in extrapulmonary samples. **Material and Methods:** This was a prospective observational study done on clinically suspected cases of extrapulmonary tuberculosis. A total of 40 cases of extrapulmonary tuberculosis were included in the study. Extrapulmonary samples were taken from the lymph node aspirate, pleural fluid, ascitic fluid, cerebrospinal fluid, pus, tissue biopsy, synovial fluid, and urine. Detection of Mycobacterium tuberculosis and rifampicin resistance was performed in all samples using the GeneXpert CBNAAT system. Descriptive statistics were used in data analysis. **Results:** Of a total of 40 specimens, 19 (47.5%) were positive to Mycobacterium tuberculosis using CBNAAT, 20 (50.0%) were negative, and 1 (2.5%) was invalid. The positive cases were 17 (89.5%) sensitive to rifampicin and 2 (10.5) resistant to rifampicin. The highest yield was realised from pus samples (66.7%) and lymph node aspirates (64.3%); a lower yield was obtained from pleural and ascitic fluids. Multibacillary samples were found to be much more positive in CBNAAT than the paucibacillary samples ($p = 0.04$). **Conclusion:** This study showed that CBNAAT is a fast and effective diagnostic procedure for detecting extrapulmonary tuberculosis and provides important supplementary information on rifampicin resistance. It is useful for early detection and treatment of EPTB, especially when combined with traditional diagnostic techniques.

Keywords: Extrapulmonary tuberculosis, Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), Mycobacterium tuberculosis, Rifampicin resistance, Molecular diagnosis.

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Introduction

Tuberculosis (TB) is a significant infectious disease globally and continues to be a major public health concern in developing countries. Global estimates reveal that millions of new TB cases occur annually, and the majority of these cases are associated with extrapulmonary tuberculosis (EPTB). EPTB is a disease that affects organs beyond the lungs, including the lymph nodes, pleura, bones, genitourinary tract, meninges, and abdomen. Even though pulmonary TB is the most frequent form of TB, extrapulmonary forms cause a significant share of TB morbidity. They are often linked to diagnostic challenges posed by their diverse clinical manifestations and paucibacillary character.[1] Extrapulmonary tuberculosis is difficult to diagnose due to the low sensitivity of the conventional diagnostic methods. The conventional approaches, such as Ziehl-Neelsen (ZN) smear microscopy and mycobacterial culture, are common but have limitations. Smear microscopy requires a high bacterial load to detect, which is not always achievable in extrapulmonary tuberculosis specimens. The culture methods, despite being regarded as the gold standard, are time-consuming and can take weeks to yield results. Such restrictions may delay disease diagnosis and the start of treatment, thereby increasing disease complications and the risk of spreading the disease.[2] Currently, molecular diagnostic methods are used to facilitate faster detection of Mycobacterium tuberculosis. The Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), or GeneXpert MTB/RIF assay, is a real-time polymerase chain reaction (PCR)-based test that simultaneously detects Mycobacterium

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tuberculosis DNA and rifampicin resistance. This test is fully automated and takes about 2 hours to produce results, making it one of the fastest diagnostic tests in clinical practice.[3] The test requires minimal laboratory facilities and eliminates the risk of cross-contamination, as the entire procedure takes place within a closed cartridge system.[4] CBNAAT has proved highly accurate in diagnosing pulmonary tuberculosis and is now also applied to extrapulmonary samples. In other studies, the GeneXpert assay has been reported to have good sensitivity and specificity for detecting tuberculosis in extrapulmonary samples, including lymph node aspirates, pleural fluid, cerebrospinal fluid, and tissue biopsies. It has been demonstrated that CBNAAT can achieve a sensitivity of over 80% and a specificity of over 90% in some extrapulmonary samples.[5] In addition, CBNAAT's capacity to detect rifampicin resistance provides a valuable opportunity to early identify multidrug-resistant tuberculosis, which is vital for determining appropriate treatment.[6] Although this method has benefits, the diagnostic value of CBNAAT in extrapulmonary tuberculosis may vary depending on the specimen type and bacterial load. Few studies have shown moderate sensitivity, particularly in paucibacillary disease, including pleural tuberculosis or tuberculous meningitis. This is why CBNAAT is frequently recommended as part of the combined diagnostic process, along with histopathology, culture, and clinical examination.[7] Since the burden of extrapulmonary TB is increasing and there is a great need to have quick and dependable diagnostic procedures, there is great clinical importance to evaluate the diagnostic value of CBNAAT in the diagnosis of EPTB. The precise treatment of tuberculosis is possible through timely and accurate diagnosis, minimising the complications of the disease, and participation in tuberculosis control programs. Therefore, the current research will help assess the diagnostic efficacy of the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) for the detection of extrapulmonary tuberculosis.

Materials and Methods

This cross-sectional observational study was conducted in the Department of Respiratory Medicine, in coordination with the Government Department of Microbiology. Medical College and Hospital, Nalgonda, Telangana. Institutional Ethical approval was obtained for the study as per the protocol. Written consent was obtained from all the participants of the study after explaining the nature of the study and possible outcomes in the vernacular language.

Inclusion Criteria

1. Patients with high clinical suspicion of extrapulmonary tuberculosis based on history, clinical examination, and radiological examination.
2. Adult patients aged 18 years and above
3. Cases in which samples were obtained from lymph node aspirates, pleural fluid, cerebrospinal fluid, tissue biopsies
4. Patients provided informed consent for participation in the study.

Exclusion Criteria

1. Patients receiving anti-tubercular therapy (ATT) for the current illness.
2. Patients with inadequate or insufficient specimen samples for CBNAAT analysis.
3. Patients who did not consent to participate in the study.

A total of 40 patients clinically suspected of having extrapulmonary tuberculosis (EPTB) were included in the study based on the study period duration. Patients presenting with signs and symptoms suggestive of extrapulmonary tuberculosis involving lymph nodes, pleura, bones and joints, genitourinary tract, abdomen, meninges, or other extrapulmonary sites were evaluated.

Sample Collection: Depending on the suspected site of infection, appropriate extrapulmonary specimens were taken. They consisted of lymph node aspirates, pleural fluid, cerebrospinal fluid (CSF), ascitic fluid, pus, synovial fluid, or tissue biopsy specimens obtained under aseptic conditions. All the specimens were immediately taken to the microbiology laboratory for analysis.

Diagnostic Procedure: All specimens were subjected to the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) in the GeneXpert MTB/RIF system. The test detects Mycobacterium tuberculosis complex DNA and also assesses rifampicin resistance. The process entailed combining the clinical sample with a sample reagent in a 2:1 ratio, followed by about 15 minutes of incubation. The purified sample was next resettled into a single-use cartridge of GeneXpert in the GeneXpert machine, and automated analysis was performed. Within 2 hours, results were produced.

The CBNAAT results were given as:

1. MTB identified (rifampicin susceptible or resistant)
2. MTB not detected
3. Invalid/indeterminate (in the event of the presence)

Outcome Measures: The diagnostic rate of extrapulmonary tuberculosis using CBNAAT was the primary outcome measure. The secondary outcomes were the identification of Rifampicin resistance. The distribution of positivity of CBNAAT among various extrapulmonary samples.

Statistical Analysis: The data were entered into Microsoft Excel and analysed using SPSS version 26.0. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were reported as mean ± standard deviation (SD). The diagnostic yield of CBNAAT was calculated. An association between variables was determined using the Chi-square test, and a p-value of <0.05 was considered statistically significant.

Results

The baseline demographic and clinical profile of the cases included in the study is depicted in [Table 1]. The table analysis showed that the mean age of the patients was 38.6 ± 14.2 years, with an age range of 19 to 72 years. The distribution of cases showed that the majority were in the 31–45 years age group (40.0%), followed by the 18–30 years (35.0%), 46–60 years (17.5%), and above 60 years (7.5%). The gender distribution of the cases showed male predominance, with 55% male and 45% female. The majority of cases presented with fever (80%),

followed by weight loss (70%) and night sweats (52.5%). All patients had localised symptoms at the affected extrapulmonary site, such as lymphadenopathy, abdominal distension, or neurological deficits. Evaluation of risk factors showed that diabetes mellitus was present in 6 patients (15.0%), followed by immunosuppressive therapy in (7.5%), and HIV infection in 2 patients (5.0%).

Table 1: Baseline Demographic and Clinical Characteristics of Study Patients

Characteristic	Category	Mean ± SD or (%)
Age (years)		38.6 ± 14.2 (Range: 18-72)
Age Distribution	18 - 30 years	14 (35.0%)
	31- 45 years	16 (40.0%)
	46 - 60 years	7 (17.5%)
	> 60 years	3 (7.5%)
Gender	Male	22 (55.0%)
	Female	18 (45.0%)
Clinical Presentation	Fever	32 (80.0%)
	Weight loss	28 (70.0%)
	Night sweats	21 (52.5%)
	Localized symptoms*	40 (100%)
Risk Factors	Diabetes Mellitus	6 (15.0%)
	HIV Positive	2 (5.0%)
	Immunosuppressive Therapy	3 (7.5%)
	No known risk factors	29 (72.5%)

*Localized symptoms varied according to site of involvement (lymphadenopathy, abdominal distension, neurological deficit)

The distribution of extrapulmonary specimens is presented in [Table 2]. The analysis showed that the most frequent specimen submitted for CBNAAT analysis was lymph node aspirate (35.0%), followed by pleural fluid (25.0%), ascitic fluid (12.5%), cerebrospinal fluid (10.0%), and pus samples (7.5%). In one case, each sample from the synovial fluid and urine was obtained in the study.

Table 2: Distribution of Extrapulmonary Tuberculosis Specimen Types

Specimen Type	Number of Samples (n)	Percentage (%)
Lymph Node Aspirate	14	35.00
Pleural Fluid	10	25.00
Ascitic Fluid	5	12.50
Cerebrospinal Fluid (CSF)	4	10.00
pus	3	7.50
Tissue Biopsy	2	5.00
Synovial Fluid	1	2.50
Urine	1	2.50
Total	40	100.0

The overall CBNAAT results for Mycobacterium tuberculosis detection are shown in [Table 3]. Out of the 40 samples tested, 19 samples (47.5%) were positive for MTB, while 20 samples (50.0%) were negative. One sample (2.5%) yielded an invalid or indeterminate result, which was excluded from further analysis.

Table 3: CBNAAT results for detection of Mycobacterium Tuberculosis

CBNAAT Result category	Number Of Samples (n)	Percentage %)
MT B Detected	19	47.5
MTS Not Detected	20	50.0
Invalid / Indeterminate*	1	2.5
Total	40	100.0

*The invalid result was excluded from further analysis of rifampicin resistance.

Among the 19 CBNAAT-positive samples, the rifampicin resistance is shown in [Table 4]. In the majority of cases (17, 89.5%), rifampicin was sensitive, whereas 2 samples (10.5%) showed rifampicin resistance, indicating possible multidrug-resistant tuberculosis. No indeterminate rifampicin resistance results were observed.

Table 4: Rifampicin Resistance Status Among CBNAAT-Positive Samples (n=19)

Rifampicin Resistance Status	Number of Samples (n)	Percentage (%)
Rifampicin Sensitive	17	89.5
Rifampicin Resistant	2	10.5
Rifampicin Indeterminate	0	0.0
Total	19	100.0

The diagnostic yield of CBNAAT according to specimen type is depicted in Table 5. The highest yield was observed in pus samples with 66.7% positive results, and tissue biopsy and CSF analysis yielded 50% positive results. A moderate yield was noted in ascitic fluid (40.0%) and pleural fluid (30.0%), while no positive cases were detected in synovial fluid or urine samples. Overall, the diagnostic yield of CBNAAT in the study population was 47.5%.

Table 5: Diagnostic yield of CBNAAT according to specimen type

Specimen Type	Total Samples (n)	MTB Detected (n)	Diagnostic Yield (%)
Lymph Node Aspirate	14	9	64.3
Pleural Fluid	10	3	30.0
Ascitic Fluid	5	2	40.0
Cerebrospinal Fluid (CSF)	4	2	50.0
Pus	3	2	66.7
Tissue Biopsy	2	1	50.0
Synovial Fluid	1	0	0.0
Urine	1	0	0.0
Total	40	19	47.5

[Table 6] presents the correlation between CBNAAT positivity and sample characteristics. CBNAAT positivity was also significantly higher in multibacillary samples (66.7%) than in paucibacillary samples (37.5%), and the difference was significant (p = 0.04). Though higher positivity was observed in sufficient samples (51.4%) than in suboptimal samples (25.0%), the difference was not significant (p = 0.29). No prior anti-tubercular therapy was reported in any of the patients; thus, all samples were assigned to the no prior ATT group. In general, the findings show that CBNAAT is a suitable diagnostic method to quickly detect extrapulmonary tuberculosis with a higher diagnostic performance in specimens with elevated bacillary load and in specific specimen types like lymph node aspirates and pus.

Table 6: Correlation of CBNAAT Positivity with Sample Characteristics

Sample Characteristic	Category	Total Samples (n)	MTB Detected (n, %)	p-value
Sample Type	Paucibacillary	24	9 (37.5%)	
	Multibacillary	15	10 (66.7%)	0.04*
Sample Adequacy	Adequate	35	18 (51.4%)	0.29
	Suboptimal	4	1 (25.0%)	
Prior ATT History	No Prior ATT	40	19 (47.5%)	–
	On ATT (Excluded)	0	0	

Discussion

Extrapulmonary tuberculosis (EPTB) is an important contributor to the global burden of the disease and is of considerable diagnostic difficulty as most extrapulmonary specimens are paucibacillary and show a variety of clinical features.[1,2] The current study analysed the diagnostic potential of the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) for Mycobacterium tuberculosis in extrapulmonary samples. CBNAAT was found useful in this study, as it identified M. tuberculosis in 47.5% of the samples, making it an effective tool for diagnosing suspected cases of EPTB. The mean age distribution of the study population was 38.67 ± 14.19 years. This indicates that most patients were in the young to middle-aged age group. The same age distribution is reported in previous research, in which extrapulmonary tuberculosis is found to occur primarily among middle-aged, economically productive individuals in the population.[8,9] The present study found a slight male predominance (55%), which is in line with the previous epidemiological studies that found higher TB incidences in males of the population, perhaps because of increased exposure and socio-behavioural factors.[1,10] Fever, weight loss, night sweats, etc., were clinically presented as the most frequent systemic symptoms in the study population. These constitutional symptoms are often associated with tuberculosis and have been observed in previous studies assessing extrapulmonary disease.[2,11] Besides, each patient reported local symptoms that depended on the infection site, indicating the varied clinical presentation of EPTB. Lymph node aspirates were the most prevalent specimen type in the current study (35%), followed by pleural and ascitic fluids. These observations are consistent with past research indicating that the most prevalent form of extrapulmonary tuberculosis is tuberculous lymphadenitis.[8,12] Our study has a total CBNAAT positivity rate of 47.5%, which compares with the results of other researchers, who reported detection rates of 40 to 60% based on specimen type and bacillary load.[5,13] The CBNAAT diagnostic yield varied depending on the type of specimen analysed.

The higher positivity rates in our study were as follows: higher in lymph node aspirates (64.3%) and pus samples (66.7%) than in pleural fluid (30%). This difference could be attributed to differences in bacillary load across extrapulmonary samples, with fluid specimens such as pleural or ascitic fluid typically containing fewer organisms, thereby making molecular tests less sensitive.[5,14] Previous studies have reported similar results when assessing GeneXpert's performance in extrapulmonary tuberculosis. The other interesting result of this study was that bacillary load showed a strong correlation with CBNAAT positivity, with multibacillary samples demonstrating a higher detection rate than paucibacillary samples (p = 0.04). This observation is in line with past studies showing that molecular diagnostic techniques perform better when the bacterial

concentration in the specimen is higher.[13,15] Although adequate samples showed higher positivity than suboptimal samples, the difference was not statistically significant. Therefore, the quality of the specimen may be a determinant of diagnostic yield, but it is not necessarily the only determinant. CBNAAT can also be used to rapidly detect rifampicin resistance, a significant indicator of multidrug-resistant tuberculosis. In the same study, CBNAAT-positive cases revealed that 10.5% were resistant to rifampicin, which is similar to other studies that have been done in the high TB burden countries.[6,16] Early detection of drug resistance enables clinicians to initiate appropriate treatment plans promptly, thereby improving patient outcomes and reducing the transmission of resistant strains. Finally, in this study, the evidence from our study is consistent with existing research evidence that CBNAAT is an appropriate diagnostic tool in extrapulmonary tuberculosis because it is fast and has reasonable sensitivity to detect M. tuberculosis Nevertheless, because of variable sensitivity in certain paucibacillary specimens, CBNAAT would preferably be combined into a diagnostic procedure alongside the traditional diagnostic techniques and clinical assessment to enhance diagnostic accuracy.[5,7]

Conclusion

The current study, within its limitations, found that the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) is a fast and efficient diagnostic method for detecting extrapulmonary tuberculosis (EPTB). CBNAAT had a moderate overall diagnostic yield, with higher positivity in samples such as lymph node aspirates and pus samples. Early detection of rifampicin resistance was also possible through the test, and the appropriate therapy must be administered as quickly as possible. CBNAAT plays a significant role in early diagnosis, although sensitivity varies across specimen types, especially in paucibacillary samples. Hence, CBNAAT is advised as a valuable supplement to the traditional diagnostic tools to improve the diagnosis and treatment of extrapulmonary tuberculosis.

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Conflicts of interest

There are no conflicts of interest.

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