Section: Respiratory Medicine

Original Research Article

AUDIT OF DIAGNOSIS EFFICACY OF CBNAAT FOR EXTRAPULMONARY TUBERCULOSIS

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Abstract

Background: Diagnosis of extrapulmonary tuberculosis is challenging due to pauci bacillary nature of the disease and is mostly multidimensional involving judgmental assessment of clinical features and disease-related structural radiological images. The study was undertaken to assess the utility of CBNAAT in field conditions for evaluating suspected cases of extrapulmonary tuberculosis Cases. **Materials and Methods:** This study was a prospective Observational study conducted in a tertiary care hospital, Jamnagar, West Gujarat. Among 125 extra-pulmonary patients,34.4% were from age group 20-39 years and 68(54.4%) were males.85(68%) were newly diagnosed. Among pulmonary Smear negative 36.9% were 20-39 Years,51(78.4%) were males and 45(69%) were newly diagnosed. **Result:** Out of 125 extra pulmonary TB patients, CBNAAT detected MTB in 50%, 44.44%, 34.71%, 15%, 10%, 10%, 0.0%, and 0.0% respectively in articular, pus, lymph node, CSF, pleural fluids, gastric fluids, pericardial and urinary TB. CBNAAT MTB detection was 66.67%, 50%, 50%, 0.0%, 33.33%, and 0.0% in pus aspirated from psoas abscess, breast abscess, chest wall swelling, splenic abscess, gluteal abscess, and occipital swelling respectively. In our current study, the diagnostic accuracy of CBNAAT for extrapulmonary TB was 63.3% and 76.9%, respectively, and for smear-negative cases, they are 80% and 91%, respectively. **Conclusion:** The overall sensitivity and specificity were found to be 63.3% and 76.9%, respectively. Notably in our study, the assay performed better in smear-negative cases, with a sensitivity of 80% and specificity of 91%. These findings indicate the potential of the GeneXpert MTB/RIF assay in detecting TB cases that are missed by conventional smear microscopy, particularly in the context of extrapulmonary TB.

INTRODUCTION

Tuberculosis (TB) continues to be a major global health concern, with a significant burden on healthcare systems and patient outcomes. Rapid and accurate diagnosis of TB is crucial for the timely initiation of appropriate treatment and effective disease control. Despite significant progress, tuberculosis (TB) continues to be a global public health problem. In 2015 around 10.4 million people fell ill because of TB and 1.4 million died from TB. Over 95% of TB deaths happen in low- and middle-income countries. India shares nearly one-fourth of the global TB burden.[1] In recent years, the GeneXpert MTB/RIF (CBNAAT) assay has emerged as a promising diagnostic tool for TB detection, offering improved sensitivity and specificity compared to conventional methods.

The GeneXpert MTB/RIF assay is a nucleic acid amplification test that simultaneously detects Mycobacterium tuberculosis (MTB) and resistance to rifampicin (RIF), a key anti-TB drug. It utilizes real-time polymerase chain reaction (PCR) technology to amplify specific target genes, providing rapid and automated results within a few hours. The assay has been extensively evaluated in various clinical settings and has demonstrated high diagnostic accuracy in both pulmonary and extra-pulmonary TB.

The Cepheid Xpert MTB/RIF assay (Cepheid, Sunnyvale CA), was developed for rapid diagnosis of TB. It can detect both TB and rifampicin resistance.[2] The test is basically based on a heminested PCR test that detects the presence of Mycobacterium tuberculosis complex bacilli (MTB).[3] The target is an 81-base-pair region of the

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rpoBgene which is the rifampicin resistance-determining region (RRDR). This is a single-use cartridge-based system making it easy to operate, also called CBNAAT (Cartridge Based Nucleic Acid Amplification Test). There is no cross-contamination and result can be obtained in only 100 min which can dramatically reduce the time for diagnosis of TB. In a recent meta-analysis, Xpert as an initial replacement for smear microscopy showed a pooled sensitivity of 89% and specificity of 99%, and as an add-on test following negative smear microscopy, pooled sensitivity and specificity were 67% and 99% respectively.[4] The interpretation of the CBNAAT result is done on the basis of the Cycle of Threshold (CT) value in PCR as high, medium, low, and very low. CT value is a continuous variable and is inversely correlated with the concentration of the starting material.

The study was undertaken to show the diagnostic efficacy of CBNAAT for evaluating suspected cases of extrapulmonary tuberculosis even in field/peripheral areas.

MATERIALS AND METHODS

This study was a prospective Observational study conducted in a tertiary care hospital in Jamnagar, West Gujarat from

Study Participants

All presumptive cases of tuberculosis visiting the outpatient/ inpatient during the study period from whom respiratory samples (bronchial washing, endotracheal tube secretions and sputum), pleural samples (pleural fluid and biopsies) and others (samples from extra-pulmonary sites, lymph node biopsies, tissue samples, etc.) could be retrived constitute the study participants. A total of 190 samples were collected

All the patients who were suspected of EPTB and who were willing to participate were included in the study. patients who did not give consent were excluded

Institutional Ethics Committee clearance was obtained and informed consent was obtained from all patients

Data Analysis

Smear microscopy and CBNAAT results were compared using liquid culture(MGIT) as the gold standard. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with 95% confidence intervals (CIs) for both diagnostic tests by type of specimen. The yield of CBNAAT, smear microscopy, and culture were calculated by the type of specimen

RESULTS

[Table 1] shows among 165 extra-pulmonary patients,34.4% were 20-39 years and 68(54.4) were males, and 85(68) were newly diagnosed. In pulmonary 36.9% were 20-39 Years,51(78.4) were males and 45(69) were newly diagnosed.

Table 1: Socio-demographic and clinical characteristics of the patients

Variables	Frequency	
Age	Extrapulmonary (n=125)	Smear negative Pulmonary (n=65)
1-19	32(25.6)	9(13.8)
20-39	43(34.4)	24(36.9)
40-59	33(26.4)	21(32.3)
.>60	17(13.6)	11(16.9)
Gender		
Male	68(54.4)	51(78.4)
Female	57(45.6)	14(21.54)
Type of Extra-pulmonary TB		
New	85(68)	45(69)
Previously treated	40(32)	20(21)

Table 2: Diagnostic yield of CBNAAT

CBNAAT Result	Extrapulmonary TB									Total
	Pleural Fluid	LN	Pus	CSF	Pericardial	Synovial	Ascitic	Gastric	Urine	
MTB detected	02 (10%)	10 (35.71%)	08 (44.44%)	03 (15%)	00 (0.0%)	05 (50%)	00 (0.0%)	01 (10%)	00 (0.0%)	29 (23.2%)
MTB NOT detected	18 (90%)	18 (64.29%)	10 (55.56%)	17 (85%)	05 (100%)	05 (50%)	10 (100%)	09 (90%)	05 (100%)	96 (76.8%)
Total	20	28	18	20	05	10	10	10	05	125
	(100%	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)

In this study out of 125 extra pulmonary TB patients, CBNAAT detected MTB in 50%, 44.44%, 34.71%, 15%, 10%, 10%, 0.0%, and 0.0% respectively in articular, pus, lymph node, CSF, pleural fluids, gastric fluids, pericardial and urinary TB.

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Table 3: CBNAAT Diagnostic yield in pus (aspirated from a different system)

	Pus from different System						
CBNAAT	**Psoas abscess**	**Breast abscess**	**Chest wall swelling**	**Splenic abscess**	**Gluteal abscess**	**Occipital swelling**	**Total**
MTB detected	4 (66.67%)	1 (50%)	2(50%)	0(0.0%)	1(33.33%)	0(0.0%)	8(44.44%)
MTB not detected	2(33.33%)	1(50%)	2(50%)	2(100%)	2(66.67%)	1(100%)	10(55.56%)
Total (n=28)	6	2	4	2	3	1	18

CBNAAT MTB detection was 66.67%, 50%, 50%, 0.0%, 33.33%, and 0.0% in pus aspirated from psoas abscess, breast abscess, chest wall swelling, splenic abscess, gluteal abscess, and occipital swelling respectively.

Table 4: Sensitivity and Specificity of CBNAAT compared to Liquid culture

	Sensitivity, %	**Specificity**	**PPV**	**NPV**
Overall	63.3	76.9	62	89
Pus	80	85	38.7	98
Pleural fluid	70	97	55	92
Smear negative	80	91	50.3	96

Overall sensitivity and specificity of CBNAAT are 63.3% and 76.9% and for Smear negative it were 80 and 91.

Table 5: shows the distribution of the EPTB site and CBNAAT in EPTB, this can be compared with various studies.[6,7]

EPTB	**Doris Hillemann et al,[6]**			**Tortoli Enrico et al,[7]**			**Present study**	
	CBNAAT			**CBNAAT**			**CBNAAT**	
	MTB+ve	**MTB-ve**	**MTB -I**	**MTB+ve**	**MTB-ve**	**MTB –I**	**MTB+ve**	**MTB -ve**
Pleural fluid	03 (2.65%)	103 (91.15%)	07 (6.19%)	08 (2.42%)	318 (96.36%)	04 (1.22%)	02 (10%)	18 (90%)
Pus	-----	-----	----	48 (24.62%)	143 (73.33%)	04 (2.05%)	08 (44.44%)	10 (55.56%)
CSF	0 (0.0%)	19 (100%)	0 (100%)	13 (9.77%)	115 (86.47%)	05 (3.76%)	03 (15%)	17 (85%)
Gastric fluid	08 (26.67%)	22 (73.33%)	0 (0.0%)	48 (21.43%)	176 (78.57%)	00 (0.0%)	01 (10%)	09 (90%)
Urine	06 (6.59%)	82 (89.01%)	03 (4.40%)	15 (11.54%)	115 (88.46%)	00 (0.0%)	0 (0.0%)	04 (100%)

DISCUSSION

Table -1 shows the socio-demographic and clinical profile of patients, in which 125 (65.7) were EPTB patients and 65 (34%) were PTB patients this is compared with the Xinyu Zhang study,[5] (66%-EPTB, and 25% were pulmonary TB patients). The difference could be regional variation in the prevalence of the type of disease and broader group of pulmonary TB (smear positive and smear negative) in the Xinyu Zhang study.

CBNAAT MTB detection in pleural fluids was 10% in the present study and 2.65% in Doris Hillemann's study and 2.42% in Tortoli Enrico's study.[6,7]

CBNAAT MTB detection in pus as 45% in the present study and 24.62% in Tortoli Enrico study.[7]

CBNAAT MTB detection in CSF was 15% in the present study and 0.0% in Doris Hillemann's study and 9.77% in Tortoli Enrico's study.

CBNAAT MTB detection in gastric fluids was 10% in the present study and 26.67% in Doris Hillemann's study and 21.43% in Tortoli Enrico's study.

CBNAAT MTB detection in urine was 0.0% in the present study and 6.59% in Doris Hillemann's study and 11.54% in Tortoli Enrico's study

Variability could be due to differences in pathological morphology in different types of extrapulmonary TB and variable multiplying properties of MTB in different regions.

In our current study, the diagnostic accuracy of CBNAAT for extrapulmonary TB was 63.3% and 76.9%, respectively, and for smear-negative cases, they are 80% and 91%, respectively. These results indicate that CBNAAT has moderate sensitivity and high specificity for diagnosing extrapulmonary TB. However, the sensitivity is lower than that for smear-positive pulmonary TB, which has a sensitivity of 98% and specificity of 98%.[8]

The sensitivity of CBNAAT for diagnosing smear-negative TB is also lower than that of Xpert MTB/RIF, which has an overall sensitivity of 83.7%.[9]

The study findings suggest that CBNAAT can be a useful tool for diagnosing extrapulmonary TB, especially in smear-negative cases, but it should be used in conjunction with other diagnostic methods to improve sensitivity. The results of this study are consistent with other studies that have shown that CBNAAT has high specificity but moderate sensitivity for diagnosing TB.[10,11]

Overall, the study findings suggest that CBNAAT can be a valuable tool for diagnosing extrapulmonary TB in (provided Minimum Biosafety level lab-2, Continuous Temperature of 2-28 degree Celusis, Negative Vacuum) but it should

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be used in conjunction with other diagnostic methods to improve sensitivity and accuracy.

Based on the results of this study, there are several recommendations for improving the use of the GeneXpert MTB/RIF assay in the diagnosis of extrapulmonary TB. Firstly, efforts should be made to address the factors contributing to false-negative and false-positive results, including the impact of genetic mutations and non-tuberculous mycobacterial cross-reactivity. Additional research is needed to better understand and mitigate these limitations.

Furthermore, expanding the sample size and conducting multicenter studies would provide more robust evidence regarding the diagnostic accuracy of the assay in diverse clinical settings and populations. Evaluating the assay's performance in specific subgroups, such as pediatric and immunocompromised patients, would help assess its utility in these vulnerable populations.

Additionally, incorporating other diagnostic modalities, such as imaging techniques and clinical algorithms, in conjunction with the GeneXpert MTB/RIF assay may further enhance the accuracy of TB diagnosis, especially in extrapulmonary cases. A multimodal approach could improve diagnostic sensitivity and specificity and aid in the timely initiation of appropriate treatment.

CONCLUSION

In this study, the GeneXpert MTB/RIF assay (CBNAAT) demonstrated moderate sensitivity and specificity for the diagnosis of extrapulmonary tuberculosis (TB). The overall sensitivity and specificity were found to be 63.3% and 76.9%, respectively. Notably, the assay performed better in smear-negative cases, with a sensitivity of 80% and specificity of 91%. These findings indicate the potential of the GeneXpert MTB/RIF assay in detecting TB cases that are missed by conventional smear microscopy, particularly in the context of extrapulmonary TB.

This study has certain limitations that should be considered. Firstly, the relatively small sample size and single-center design may restrict the generalizability of the findings. Further studies with larger sample sizes and multiple centers are needed to validate and reinforce the results.

Secondly, the reference standard used in this study, such as culture or a composite reference standard, may have its own limitations, which could impact the estimation of sensitivity and specificity. It is important to acknowledge that no diagnostic test is perfect, and there is inherent variability in the accuracy of different reference standards.

Finally, the study did not explore the impact of various confounding factors, such as HIV coinfection, comorbidities, or previous TB treatment, on the performance of the GeneXpert MTB/RIF assay. Future research should address these factors to better understand the assay's diagnostic accuracy in real-world clinical scenarios.

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