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CBNAAT: Advantage and Efficacy in Pulmonary Tuberculosis (PTB) atop on Traditional Methods for Diagnosis in a Tertiary Care Hospital in India

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: *Mycobacterium Tuberculosis* (MTB) is one of the most ancient diseases of mankind. Pulmonary tuberculosis (PTB) is the most common, despite the diagnosis and treatment of TB. Many studies reported, a collaboration between PTB susceptibility. In our research study, we report meantime findings after enrolling 732 of a planned 212 participants.
Study Design: A descriptive cross-sectional study.
Methods: The study conducted on patients with TB in west India was conducted in the Department of Microbiology, Index Medical College; Indore Madhya Pradesh. Patients suspected of PTB were qualified for screening if their age varied from 25 to 60 years and with both gender, signs and symptoms associated with PTB such as cough for more than 2 weeks, fever, weight loss, chest pain, and abnormal chest X-ray findings in results and cartridge-based nucleic acid amplification test (CBNAAT) positive. All Patients were monitored monthly while they visited in TB and chest clinic for TB treatment.

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Results: A total of 937 patients were selected for the study. Out of which only 732 patients were enrolled. About 212 patents were positive for CBNAAT and 520 were found negative. The confirmed positive CBNAAT patients do not have a history of tuberculosis. In this study about 21.72% were ZN stain positive, 33.46% were culture positive and 28.96% were CBNAAT positive.
Conclusion: The current scenario of traditionally AFB-negative PTB is not sensitive enough to establish the diagnosis of active tuberculosis without CBNAAT. They underdiagnose PTB and over-treat people without PTB.

Keywords: TB (Tuberculosis); PTB (Pulmonary Tuberculosis); MDR-TB (Multi drug-resistance tuberculosis); CBNAAT; GeneXpert; MDR.

ABBREVIATIONS AND THEIR EXPANSIONS

Abbreviations		*Expansions*
AFB	:	*Acid Fast Bacilli*
BAL	:	*Bronchoalveolar Lavage*
BSL	:	*Bio-Safety Level*
CBNAAT	:	*Cartridge-Based Nucleic Acid Amplification Test*
DM	:	*Diabetes Mellitus*
MCT	:	*Micro Centrifuge Tube*
MDR	:	*Multi-Drug Resistance*
MTB	:	*Mycobacterium Tuberculosis*
NaOH	:	*Sodium Hydroxide*
OADC	:	*Oleic Acid-Albumin-Dextrose-Catalase*
PANTA	:	*Polymyxin B, Amphotericin B, Nalidixic Acid, Trimethoprim, And Azlocillin*
PPE	:	*Personal Protective Equipment*
PTB	:	*Pulmonary Tuberculosis*
RIF	:	*Rifampicin*
Rt-PCR	:	*Reverse Transcription Polymerase Chain Reaction*
TB	:	*Tuberculosis*
WHO	:	*World Health Organization*
XDR	:	*Extensively Drug Resistance*
ZN	:	*Zeihl Neelsen*

1. INTRODUCTION

"Mycobacterium Tuberculosis (MTB) only the most prehistoric diseases of society, is one of the leading causes of mortality from a single infectious medium" [1,2]. The emergence of increasingly drug-resistant forms of tuberculosis (TB) is a considerable challenge to current and future TB prevention and care efforts. Despite recent progress in addressing the epidemic, TB persists as one of the major causes of mortality globally with an estimated 10.5 million new cases and 1.6 million deaths singly in 2016. Rifampicin and Isoniazid are the two anti-tuberculosis medications that work the best. It is projected that there are 580,000 new instances of rifampicin-resistant tuberculosis, which has a significant fatality rate [2].

MDR TB with supplementary Fluoroquinolones and Aminoglycosides resistance (i.e. extensively drug-resistant TB, XDR TB) many times results in even poorer treatment results. The action towards MDR and XDR TB although cost-effective leftovers overpriced with methodical costs 10-200 times that of DS TB and direct and indirect costs to patients often surpass ≥20% of their annual household earnings [3-7].

"MDR-TB, which results from inconsistent as well as incorrect TB treatment or direct person-to-person transmission, poses a global threat to tuberculosis control" [8]. "MDR-TB is far deadlier than drug-susceptible TB, and current treatments are expensive, time-consuming, and frequently cause severe side effects" [9]. "Patients face many financial, biological, and systemic barriers, psychosocial to treatment compliance, which constantly steer to poor results and elaboration of drug resistance" [10,11,12].

"The National Strategic Plan (2017–25) of India suggests a strong master plan with equivalent resources to rapidly diminish TB in the country by 2030. This is in pipeline with the worldwide end TB targets and defensive development goals to achieve the innovation of a TB-free India. The goal is to attain a quick diminish in the burden of TB, morbidity, and mortality while working towards the exclusion of TB in India by 2025" [13]. "Whereas WHO with its "STOP TB" strategy has given the vision to eliminate TB as a public health problem from the face of this earth by 2050" [14].

"Health-related quality of life during MDR TB treatment traditionally, the goal of tuberculosis treatment has been microbiological cure, with less emphasis on morbidity and patient-reported outcomes such as quality of life (QOL). Health-related quality of life is a multidimensional concept that emphasises the patient's point of view and defines health as physical, mental, and social well-being rather than simply the absence of illness" [15].

Patient quality of life and treatment retention are important factors in treatment success, and failure to follow-up represents an opportunity for intervention. Some socioeconomic factors, such as a lack of education, a low income, alcohol abuse, joblessness, and a lack of health insurance, are also linked to the failure of MDR-TB treatment [16,17].

Without proper and fact-based studies that impact the victory of MDR-TB, studies that assess the merger of extended authority have not been smoothly directed in countries with a high TB burden [18]. Hence in this research study, we sight to pinpoint the elements, particularly connected with favorable outcome treatment in high-burden MDR-TB settings in India.

2. MATERIALS AND METHODS

The study was conducted in the Department of Microbiology at Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh (M.P.).

2.1 Sample Size

A total number of 732 samples were collected which includes sputum, bronchoalveolar lavage (BAL), and gastric aspirate. After dividing the patient base into pre-diabetic and diabetic groups, the sample size was chosen.

2.2 Study Duration

Two years (July 2019 – July 2021) including 2 years of data analysis.

2.3 Study Population

Patients visited the TB & chest clinic and were diagnosed with PTB.

2.4 Inclusion Criterion

Patients were qualified for screening if their age varied from 25 to 60 years and with both genders, signs and symptoms associated with PTB. Symptoms such as cough of more than 2 weeks, fever, weight loss, chest pain, and abnormal chest X-ray findings (patchy consolidation, poorly- defined nodules) in results and CBNAAT positive.

2.5 Exclusion Criterion

Patients were disqualified for screening if they were below 25 years and more than 60 years of age. Patients with a pre-diabetic history were also excluded from the study because their levels were not high enough to be classified as Type 2 diabetes.

2.6 Specimen Collection (PTB)

Two consecutive morning speck sputum samples will be collected from suspected PTB cases in a sterile, wide-mouthed, triple layer-leak proof plastic container according to RNTCP protocol. All patients were instructed to cough vigorously in order to produce sputum specimens that could be collected without contaminating the sample collection container. If a patient is unable to produce sputum, such as a child or the elderly, gastric aspirate and bronchoalveolar lavage fluid will be accepted for further processing.

2.7 Transport

The specimens were transported from the concerned departments to the central laboratory by maintaining a cold chain with triple-layer packaging.

2.8 Sample Processing

I. All specimens were processed by taking aseptic precautions and personal

protective equipment (PPE) properly in the BSL-II laboratory.

II. Visually, the grade of the sputum specimen will be judged for consistency and if it carries more saliva then the specimen will be rejected and asked for a new specimen.

2.9 Smear Microscopy

All smears were prepared directly from the specimens and stained with Z-N staining. Specimens with two negative smears were documented. These patients engaged in conversation. Research Study Performa was being filled up for those with clinical-radiological suspicions of PTB & who are willing to agree to participate in the research study. The enrolled patient's specimen was further processed. A minimum of 100 fields for acid-fast bacilli in a smear indicated the severity of PTB infection in patients. In grading, positive AFB smears were reported. as shown in Table 1 [19].

2.10. Middlebrook7h9 Broth Culture

2.10.1 Decontamination procedure

1. 4% NaOH, 2-3 times the volume of solution will be added to an allowable specimen and left there at 37ºC for 30 minutes until the sample is completely liquidized.
2. Another part of liquidize specimen is separated into 1.5ml Micro Centrifuge Tube (MCT) additionally for processing of liquid culture medium.
3. Liquidize samples of 900µl alongside 500µl Negative Control and 500µl Positive Control will be dispensed into 1.5ml MCT tubes separately.
4. Centrifuged to all MCT tubes for 10 minutes at 13,000rpm.
5. Discard the upper liquid phase and add 1ml sterile physiological saline to the precipitate and vortex it, to put it back into suspension.
6. Centrifuged all tubes for 10 minutes at 13,000rpm and discard the upper liquid phase.

2.10.2 Procedure

One MCT tube pallet was cultured into Middlebrook7H9 broth. One smear will be checked by Z-N staining. The result will be recorded. Middlebrook7H9 broth supplemented with 0.8 ml OADC and PANTA will be used for liquid culture. It will be prepared as per the manufacturer's instruction Hi Media (Hi Media Pvt Ltd, Mumbai, India). 0.5 ml of the processed sample will be inoculated and tubes will be incubated at 37 +/- 1°C. Readings will be taken visually twice weekly for up to 6 weeks. Positive culture with a granular appearance without significant turbidity will be noted. If growth is observed, Z-N staining will be done to confirm the presence of AFB.

2.11 CBNAAT

It is a novel rapid automated machine for the rapid diagnosis of TB. This is the cartridge-based nucleic acid amplification test (CBNAAT) that can detect TB within 2 h of the collection along with RIF's resistance directly from the pulmonary samples. Detection based on the target sequences and nucleic acid amplification by RT-PCR and reverse transcriptase. In a conical tube containing 1ml of a sample (Sputum, BAL, and gastric aspirate), 2 ml of sample reagent was added and mixed vigorously. This mixture was incubated at room temperature for 10 to 15 minutes and the treated sample was transferred into the sample cartridge chamber by using a sterile graduated or ungraduated pipette and then cartridge loaded into the GeneXpert machine. Result Interpretation is done by using GeneXpert Dx System software, which measured fluorescent signals algorithm [16].

Table 1. Grading of AFB smears

No of acid-fast Bacilli (AFB)	Fields	Report
No AFB	In 100 immersion fields	Negative
1-9 AFB	In 100 immersion fields	Positive scanty Record exact figure
10 to 99 AFB	In 100 immersion fields	1+
1 to 10 AFB	Per field (examine 50 fields)	2+
More than 10 AFB	Per field (examine 20 fields)	3+

3. RESULTS

A total of 937 patients were registered in the TB and chest clinic which were as have a suspicion of TB but at most 732 patients were enrolled based on age criterion and out of 732 only 212 were entitled and found verifiable positive in our research study after confirmed through CBNAAT as shown in table-2. The rest (520 patients) were found negative. In the number of 732 samples which were suspected of MTB, 212 (28.96%) samples were confirmed positive for MTB by CBNAAT (GeneXpert) comparatively with smear and culture as summarized in Table 2.

Out of 212 positive TB cases, most of the patient do not have a history of tuberculosis but positivity were high as compared to patients with a family history of TB. Suspected male patients also show a high positivity rate as compared to suspected female patients with include alcohol consumption and smoking as shown in the socio-economic demographic Table 3.

Among this, the distribution of clinical samples was (546/74.53% sputum, 140/19.18% gastric aspirate, and 46/6.27% BAL) as shown in Table 4. Clinical data at the time of demonstration of patient enrollment and radiological peculiarity found in chest X-rays of positive CBNAAT cases are outlined in Table 5.

Table 2. Comparison of result of genexpert with AFB smear and culture

Variables (n=732)	Smear	%	Culture	%	CBNAAT	%
Positive	159	21.72	245	33.46	212	28.96
Negative	573	78.27	453	61.94	509	69.53
Contamination/Invalid Result	0	0	34	4.6	11	1.51

Table 3. suspected TB patient's demographic, lifestyle, and anthropometric details at enrollment (in %)

Variable	Sputum	Gastric Aspirate	BAL
Age	46.6 ± 10.6	42.2 ± 8.7	38.7 ± 11.3
Male	76	84.5	86
Female	24	15.5	14
Educated	74	54	65
Uneducated	26	42	35
Rural	45	41	44
Urban	55	59	46
Sedentary	34	26	16
Non- sedentary	66	74	84
Smoking current	18	27	29
Smoking former	24	29	32
Smoking never	58	44	39
Alcohol yes	32	29	54
Alcohol no	68	71	46
Family history of TB (Yes)	30.13	17.64	23.8
Family history of TB (No)	58	79	83.4
Family history of DM (Yes)	42	21	16.6

DM- Diabetes Mellitus

Table 4. Sample-wise differentiation of result in genexpert with AFB smear and culture

Specimens	Distribution	Middlebrook7H9 Broth Culture		AFB smear		GeneXpert	
		+ve	-ve	+ve	-ve	+ve	-ve
Sputum	546	224	223	141	359	189	309
Gastric aspirate	140	09	169	07	157	10	141
BAL	46	12	61	11	57	13	59

BAL- Bronchoalveolar Lavage

Table 5. Clinical and radiological characterisation between total suspected / confirmed TB cases

Dispensation of different clinical presentations (n=732)		
Symptoms	**Numbers**	**Percentage (%)**
Cough	502	68.71
Hemoptysis	84	11.43
Loss of appetite	402	54.98
Weight loss	289	39.48
Fever	513	70.19
Breathlessness	322	44.01
Night sweat	159	21.67
Dispensation of different radiological findings in positive TB cases (n=212)		
Characters	**Numbers**	**Percentage (%)**
Thick wall	26	12.01
Infiltration	152	71.90
Consolidation	64	30.19
Single/multiple nodules	11	5.19
Bronchiectasis	19	8.93
Other opacities	70	32.86

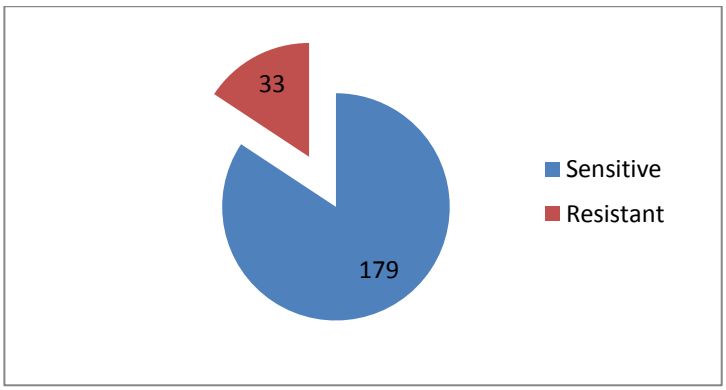

Fig. 1. Rifampicin sensitivity and resistance among TB cases (n=212)

Out of 212 positive TB cases through GeneXpert, only 33(15.42%) patients were resistant against Rifampicin and diagnosed as drug resistance tuberculosis (DR-TB) as a representative marker for MDR-TB, while 179 (84.58%) cases were established with drug susceptibility Fig. 1.

4. DISCUSSION

In this research study, we have evaluated the role of GeneXpert over regular methods for MTB and Rifampicin-resistant detection in pulmonary specimens (sputum, gastric aspirate, and BAL) since PT is the foremost cause of mortality and morbidity in India. In our research study, “MTB was generally high in urban communities in comparison with the rural community, and that is similar to the study in Madurai, India in 2015 and Madhya Pradesh in 2016”; [20,21,22]. The most important and regular indicators in our research study were fever (70.19%) and cough (68.71%).

“In a related research study published in 2016, Avashia et al. identified fever (69.4%) and cough (72.2%) as the primary indicators. In our study,one of the most common radiological findings was infiltration (71.90%), followed by consolidation (30.19%) in positive PTB cases, which was almost identical to the studies done by Avashia et al., in 2016 and Ganesh CM et al, in 2018, which based consolidation in 33.3% and infiltration in 79% of sufferers, respectively” [21,23]. In our research study, “73% of patients who were newly exposed to PTB in the number of all positive cases for MTB”, which was compatible (71%) with other research studies shore up by Subbarao *et al.,* in 2018 [24].

Aside from the use of CBNAAT, an extended span of Rifampicin resistance was a clock in [25]. Some of the CBNAAT positive samples in a research study by Ikuabe et al., in 2018 [25,26] had Rifampicin resistance of 14.7%, which was nearly comparable to our research study (15.42%). However, a divergent study by Lee et al., 2013 found 5.7% resistance. Resistance to RIF in CBNAAT is thought to be a substitute indicator of MDR-TB [27,28].

Rifampicin resistance affects a specific quantity of resistance, such as mutation, co-infection with HIV, and insufficient or inappropriate anti-TB medication, as only 212 CBNAAT-positive samples were [26]. Resistance to these medications in mycobacterium strains was discovered not long after their clinical appearance. In terms of developing new chemical combinations to treat MTB, some new medications are in the works, but they are still in the preliminary clinical phase [29].

5. CONCLUSION

The current scenario of traditionally AFB negative PTB is insufficiently sensitive to establish the diagnosis of active tuberculosis without CBNAAT. They underdiagnose PTB and overtreat those who do not have it. PTB accounts for nearly half of all tuberculosis, and it is extremely difficult to obtain a bacteriological identification for negative TB specimens [23]. CBNAAT detects PTB with high specificity and sensitivity rather than liquid culture medium and sputum microscopy, which is why CBNAAT detects MTB quickly and correctly in less than 2 hours. Simultaneously, CBNAAT identifies RIFs for MDR-TB screening and patient prompt treatment, potentially lowering the new victim graph prevalence [30].

CONSENT

We included all the age groups and gender after taking written informed consent in our study.

ETHICAL APPROVAL

This study was approved by Independent Ethics Committees (IEC), Index Medical College Hospital & Research Center (Malwanchal University) vide- MU/ Research/ EC/Ph.D/ 2019/51.

SOURCE OF SUPPORT

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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