Original Research Article

CBNAAT: ADVANTAGE AND EFFICACY IN PULMONARY TUBERCULOSIS (PTB) ATOP ON TRADITIONAL METHODS FOR DIAGNOSIS IN A TERTIARY CARE HOSPITAL OF INDIA

ABSTRACT

Background: *Mycobacterium Tuberculosis* (MTB) is one of the most ancient diseases of mankind. Pulmonary tuberculosis (PTB) is the most common, in spite of 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 subjects.

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 varies from 25 to 60 years and with both gender, signs and symptoms associated with PTB such as coughofmore than 2 weeks, fever, weight loss, chest pain, and abnormal chest X-ray findings in end results and CBNAAT positive. All Patients were monitored monthly while they visited in TB and chest clinic for TB treatment.

Results: The 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 on the basis of age criterion and out of 732 only 212 were entitled and found verifiable positive in our research study after confirmed through CBNAAT.

Conclusion: The current scenario of traditionally AFB negative Pulmonary Tuberculosis (PTB) is not sensitive enough to establish the diagnosis of active tuberculosis without CBNAAT. They under diagnose PTB and over-treat people without PTB.

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Comment [BAR1]: Better use word "participants" or "patients" instead of "subjects".

Comment [BAR2]: Use past tense "varied". Do this in the other parts of the manuscript too.

Comment [BAR3]: "For", not "of".

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Comment [BAR5]: This sentence is very long. Make the sentence shorter and divide into more than one small sentences. Also, this sentence is incorrect grammatically. Revise it and make easily understandable sentences.

Comment [BAR6]: Just use PTB only, as this abbreviation is already mentioned in 2nd sentence of the Abstract.

KEYWORDS: *TB (Tuberculosis), PTB (Pulmonary Tuberculosis), MDR-TB (Multi drug-resistance tuberculosis), CBNAAT, GeneXpert, MDR*

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. In spite of recent progress in addressing the epidemic, TB persist one of the major causes of mortality globally with an estimated 10.5 million new cases and 1.6 million deaths singly in 2016. Multi-drug resistant TB (MDR TB) resistant to at least the two most effective first-line anti-TB drugs (Rifampicin and Isoniazid), and Rifampicin-resistant TB (RR TB) were estimated to have caused 580,000 of these new cases and an excessive in high number of deaths[2].

MDR TB with supplementary Fluoroquinolones and Aminoglycosides resistance (i.e. extensively drug resistant TB, XDR TB) many times results in even poorer treatment end result. The action towards of 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 earning[3,4,5,6,7].

Multidrug-resistant tuberculosis (MDR-TB) bully TB control global, it results from incompatible with or mistaken TB treatment or direct person-to-person transferral[8]. Differentiate to drug-susceptible TB, MDR-TB is far mortal and current treatments are overpriced, prolonged, and often cause acute side-effects[9]. Patients faces many financial, biological, systemic barriers and psychosocial to treatment compliance, which constantly steer to poor end result and elaboration of drug-resistance[10,11,12].

The National Strategic Plan (2017–25) of India suggests 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 TB free India. The goal is to attain a quick diminish in burden of TB, morbidity and mortality while working towards exclusion of TB in India by 2025[13].Whereas WHO with its “STOP TB” strategy has given a 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 generally, the focus of TB treatment has been on attain microbiological cure with less significance on morbidity and patient-reported end result, similarly quality of life (QOL). Health-related quality of life is a multi-dimensional construct that point up the patient’s viewpoint and defines health as physical, mental and social welfare rather than rigidly the truancy of illness[15].

As patient standard of life and treatment authority are key drivers of treatment beneficial end result and dropping to gape within an opportunity for arbitration. Some socioeconomic convincing also connected with lack of success of MDR-TB treatment such as lack of education, small income alcohol misuse, joblessness and be lacking of health insurance[16,17].

As studies that assess the merger of extended authority have not been smoothly directed in countries with an elevated burden of TB without proper and facts related studies that impact the victory of MDR-TB make use of prolonged treatment authority[18]. Hence in this research

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study, we sight to pinpoint the elements, particularly connected with favorable outcome treatment in high burden MDR-TB setting in India.

2. MATERIALS AND METHODS

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

2.1SAMPLE SIZE

A total number of 732 samples were collected which includes sputum, bronchoalveolar lavage and gastric aspirate.

2.2 STUDY DURATION

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

2.3 STUDY POPULATION

Patients visited in TB and chest clinic and diagnosed for pulmonary tuberculosis (PTB). We included all the age groups and gender after taking written informed consent in our study.

2.4 INCLUSION CRITERION

Patients were qualified for screening if their age varies from 25 to 60 years and with both gender, signs and symptoms associated with PTB such as cough more than 2 weeks, fever, weight loss, chest pain and abnormal chest X-ray findings in end results and CBNAAT positive.

2.5 EXCLUSION CRITERION

Patients were dis-qualified for screening if they were below than 25 years and more than 60 years of age. Patients with pre diabetic history were also excluded from the study.

2.6Specimen Collection (PTB)

Two consecutive morning speck sputum samples will be collected from suspected cases of PTB as per RNTCP protocol in a sterile, wide mouthed, triple layer-leak proof plastic container. All the patients were directed to cough deeply to produce sputum specimen and to collect without contaminating the sample collection container. If the patient is unable to produce sputum as in the case of children or elderly patients, gastric aspirate and bronchoalveolar lavage fluid (BAL) will be accepted for further processing.

2.7Transport

The specimens transported from concern departments to central laboratory by maintaining cold chain with triple layer packaging.

2.8 Sample processing:

I. All specimens processed by taking aseptic precautions and personal protective equipment(PPE) properly in BSL-II laboratory.

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Comment [BAR14]: Please explain the reason why these patients were excluded?

II. Visually, the grade of 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.

2.9Smear Microscopy: All smears will be prepared directly from the specimens and stained with Z-N staining.Specimen with two negative smears will be documented. These patients will be engage in conversation. Research Study Performa will be filled up for those with clinico-radiological suspicious of pulmonary tuberculosis (PT) & are willing to agree for participation in the research study. Enrolled patient's specimen will be further processed. After observing minimum 100 fields for acid-fast bacilli in a smear was an indication of the PT infection severity in patients. AFBsmears which were positive, reported in grading as shown in **Table 1**[19].

Comment [BAR15]: Use Past tense, not Future tense.

TABLE1:GRADINGOFAFBSMEARS

Noofacid-fast Bacilli (AFB)	**Fields**	**Report**
NoAFB	In100immersionfields	Negative
1-9AFB	In100immersionfields	Positive scantyRecordexact figure
10to99AFB	In100 immersion fields	1+
1to 10AFB	Perfield(examine 50fields)	2+
Morethan10AFB	Perfield(examine 20fields)	3+

2.10. MIDDLEBROOK7H9 BROTH CULTURE

2.10.1. DECONTAMINATION PROCEDURE

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

2.10.2.PROCEDURE

One MCT tube pallet cultured into Middlebrook7H9 broth. One smear will be checked by Z-N staining. 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 manufacturer's

instruction Hi Media (Hi Media Pvt Ltd, Mumbai, India). 0.5 ml of processed sample will be inoculated and tubes will be incubated at 37 +/- 1°C. Readings will be taken visually twice weekly up to 6 weeks. Positive culture with 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 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 conical tube containing 1ml of a sample (Sputum, BAL, and gastric aspirate), 2 ml of sample reagent added and mixed vigorously. This mixture Incubated at room temperature for 10 to 15 minutes and treated sample transferred into the sample cartridge chamber by using a sterile graduated or ungraduated pipette and then cartridge loaded into the GeneXpert machine. Result Interpretation done by using GeneXpert Dx System software, which measured fluorescent signals algorithm[16].

3. RESULT

The total 937 patients were registered in TB and chest clinic which were as have a suspicion of TB but at most 732 patients were enrolled on the basis of 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 sampleswhichwere suspected for MTB,212(28.96%) sampleswereconfirmedpositiveforMTBbyCBNAAT (GeneXpert) comparatively with smear and culture assummarizedin**Table2**.

Outof212 positive TB cases, most of the patient do not had past history oftuberculosis but positivity were high as compare to patients with family history of TB. Suspected male patients also show high positivity rate as compare to suspected female patients with include alcohol consumption and smokingas shown in socio-economic demographic **Table 3**.

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
SEDANTARY	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

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Among which distribution of clinical samples were (546/74.53% sputum, 140/19.18% gastric aspirate and 46/6.27% broncho-alveolar lavage: BAL) as shown in **Table 4**. Clinical data at the time demonstration of patient enrollment and radiological peculiarity found in chest X-ray of positive CBNAAT cases is outline in **Table 5**.

TABLE4:SAMPLEWISEDIFFERENTIATION OFRESULTINGENEXPERTWITHAFBSMEARANDCULTURE

Specimens	Distribution	Middlebrook7H9 Broth Culture		AFBsmear		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

TABLE5:CLINICALANDRADIOLOGICALCHARACTERISATION BETWEEN TOTAL SUSPECTED /CONFIRMEDTBCASES

Dispensationofdifferentclinicalpresentation(n=732)		
Symptoms	Numbers	Percentage(%)
Cough	502	68.71
Hemoptysis	84	11.43
Lossofappetite	402	54.98

Weightloss	289	39.48
Fever	513	70.19
Breathlessness	322	44.01
Nightsweat	159	21.67
Dispensation ofdifferentradiologicalfindingsinpositive TBcases(n=212)		
Characters	Numbers	Percentage(%)
Thickwall	26	12.01
Infiltration	152	71.90
Consolidation	64	30.19
Single/multiplenodules	11	5.19
Bronchiectasis	19	8.93
Otheropacities	70	32.86

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 which were established with drug susceptibility **Fig. 1**

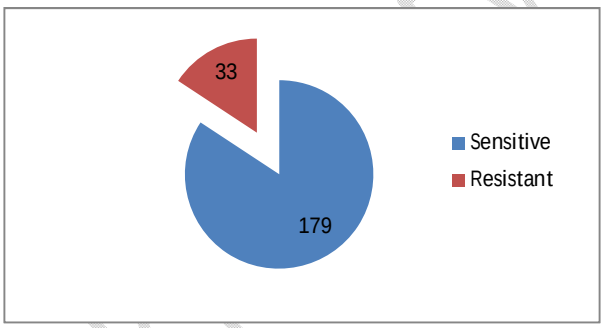

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FIG. 1: RIFAMPICIN SENSITIVITY AND RESISTANCE AMONG TB CASES (n=212)

4. DISCUSSION

In this research study, we have evaluate 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 for mortality and morbidity in India. In our research study MTB was generally high in urban community in comparison with rural community and that is alike with the study at Madurai, India in 2015 and Madhya Pradesh in 2016 [20,21,22]. The most important and regular indicator in our research study were fever (70.19%) and cough (68.71%). In a corresponding research study from Avashia*et al.,* in 2016, as they base fever (69.4%) and cough (72.2%) as the main indicator. One of radiological finding infiltration was most familiar (71.90%) followed by consolidation (30.19%) in positive PTB cases in our research study, which was almost alike with the study done by Avashia*et al.,* in 2016 and Ganesh CM *et al.,* in 2018 bases consolidation in 33.3% and infiltration in 79% of sufferer correspondingly[21,23]. In our research study, 73% of patients who were newly

exposed of PTB in the number of all positive cases for MTB, which was compatible (71%) with other research study shore up by Subbarao *et al.,* in 2018[24].

Besides using CBNAAT, so far a extended span of Rifampicin resistance was clock in [25]. In a research study by Ikuabe*et al.,* in 2018[25, 26]. Some of CBNAAT positive samples had Rifampicin resistance in 14.7%, whichever was nearly comparable to our research study (15.42%), but in a divergent research work by Lee *et al.,* 2013 reported 5.7% resistance. RIF's resistance by CBNAAT is considered to be a substitute indicator of MDR-TB[27, 28].

Barely 212 CBNAAT positive samples were Rifampicin resistant, that was relatively towering as relate with other research work study specify multidrug-resistant tuberculosis (MDR-TB) since commonness of MDR-TB is changeable in literary texts and it is assorted and be contingent next to numerous element; distinct quantity of resistance may be attributable to discrepancy in mutation, co-infected with HIV and scanty or unsuitable dosage of anti-TB therapy[26]. Resistance through these medications in mycobacterium strain was considering not long in the rear of clinical presentation. To this extent the evolution of newly discovered chemical amalgamation to act towards MTB, few newly medications in the channel, yet these are up to this time in introductory clinical phase[29].

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5. CONCLUSION

The current scenario of traditionally AFB negative Pulmonary Tuberculosis (PTB) is not sensitive enough to establish the diagnosis of active tuberculosis without CBNAAT. They under-diagnose PTB and over treat people without PTB. PTB add up to a uttermost of all tuberculosis which is surrounded by more than half to bear a resemblance as negative-smear and it is very arduous to compel a bacteriological identification for negative TB specimen[23]. Detection by CBNAAT for PTB with high specificity and sensitivity rather than liquid culture medium and microscopy of sputum samples that is why CBNAAT detects MTB rapidly and correctly in less than 2 hours. At the same time CBNAAT additionally discover RIF's for MDR-TB screening and patient prompt treatment perhaps decline the new victim graph prevalence[30].

ETHICAL APPROVAL

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

SOURCE OF SUPPORT

Revised national tuberculosis control program (RNTCP), Govt. of India, State TB cells, Bhopal, Madhya Pradesh and District health society (DHS), Indore, Madhya Pradesh.

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