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COMPARATIVE EVALUATION OF CBNAAT WITH SMEAR MICROSCOPY, SYMPTOM SCREEN AND CHEST X-RAY FOR DIAGNOSIS OF PULMONARY TUBERCULOSIS

Pulmonary Medicine

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ABSTRACT

Context : CBNAAT-TB has emerged as an important diagnostic modality as more sensitive, rapid and accurate diagnostic modality for pulmonary Tuberculosis with fast detection of resistance.

Aim : Our Aim was to compare diagnostic accuracy of CBNAAT with commonly used modalities like smear microscopy, symptomatology and chest Xray for detection of pulmonary Tuberculosis and to enquire if it confers any diagnostic advantage in detection of smearnegative pulmonary TB.

Method. We screened all non –HIV patients present to TB- chest clinic for pulmonary TB.. We collected two sputum samples for microscopy using ZN stain , one sputum sample for CBNAAT and one sputum sample for BACTEC based culture in each patient . Using BACTEC culture positive as gold standard, we determined comparative sensitivity, specificity, Positive Predictive Value(PPV),Negative Predictive value(NPV), Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio(NLR) of CBNAAT and sputum microscopy using SPSS 15.0 software and Bayesian sensitivity analysis was done with WINBUGS 1.3

Results : 598 patients were included in study .131/598 (34.8 %) patients were sputum culture positive and 19/131 were Rifampicin resistant. Overall sensitivity , specificity, PLR, NLR,PPV,NPV of CBNAAT and smear microscopy were [82.44(74.8 – 88.53), 98.29(96.65 - 99.26), 48.13, 0.18, 84.95 %, 89.70 %] and[60.3 (51.39 – 68.74), 97% (95.02 – 98.3),20.12, 0.41,75%,87.5%] respectively . CBNAAT correctly picked up 29/52(55.76%) cases missed by smear microscopy. The Test accuracy as represented by AUROC (Area under receiver operator characteristics) was significantly higher for CBNAAT compared to Sputum microscopy[0.904vs0.793,p=0.003)

Conclusion : CBNAAT-TB is more accurate, rapidly performed ,valid and important adjunct to sputum microscopy for detection of pulmonary tuberculosis.

KEYWORDS

INTRODUCTION:

Mortality due to pulmonary tuberculosis [PTB] is increasing every year especially in developing counties. With the rise of multidrug resistant tuberculosis [MDR-TB] and extremely drug resistant tuberculosis [XDR-TB], the situation becomes only worse.

Various studies have showed that the sensitivity of sputum microscopy for detection of PTB is around 45-65% [1] thus leaving many cases of undiagnosed sputum negative PTB. The detection of MDR requires standard lab facilities which are well equipped for culture and sensitivity and it requires long time to diagnose.

World Health Organisation [WHO] has recommended a new diagnostic test Cartridge Based Nucleic Acid Amplification Test-Tuberculosis [CBNAAT-TB] which is a portable, rapid Reverse Transcriptase- Polymerase Chain Reaction [RT-PCR] based test for rapid diagnosis (<2hrs) of pulmonary TB with a sensitivity of 85 % and specificity of 97% established through a meta-analysis of various studies around the world. [2] It has been projected to save nearly 4 lakh lives yearly.[3] Thus it is currently recommended as a first line test for diagnosis of pulmonary TB in HIV [Human Immunodeficiency Virus] patients and as an add-on for diagnosis of MDR-TB and sputum negative TB. [2]

In a developing country like India, sputum negative TB and MDR-TB pose significant health hazards. Chest x-ray and WHO symptom screen have modest sensitivity but poor specificity even when used as an addition to sputum microscopy. [4] Revised National Tuberculosis Control Program[RNTCP] aims to improve detection rate of PTB to 85% and detect MDR-TB. However it is not logistically feasible to establish so many labs with adequate culture facility which is the gold standard for diagnosis of PTB currently. Thus CBNAAT-TB has come out be a boon for developing countries like India where it can not only detect sputum negative PTB but also diagnose rifampicin resistant TB (a surrogate for MDR-TB) rapidly.[5] Thus CBNAAT-TB is a rapid, logistically viable and a cheaper Rs. 750 alternative to Mycobacterium tuberculosis [MTB] culture especially in sputum negative, HIV positive and resistance prone cases. [6] RNTCP in its phase three has started a project for CBNAAT-TB where it planned to extend to 1000 centres by 2019. [7] Though CBNAAT-TB has been validated across multiple centres around the world. [8-17] there is a paucity of validation studies for CBNAAT-TB in Indian population. In a pilot study done by us, we found that CBNAAT-TB was significantly superior for diagnosis of PTB than sputum microscopy, chest x-ray and symptom screen in HIV positive cases. [18]

The goal of this study was to evaluate diagnostic efficacy of CBNAAT-TB in non-HIV infected TB suspects presenting at our chest clinic. We also aimed to calculated prevalence of rifampicin resistance in these patients and comparatively evaluate the role of CBNAAT-TB, chest x-ray and symptom screen in diagnosis of PTB in sputum negative cases.

MATERIALS AND METHODS:

The study was carried out in Directly Observed Treatment Short-course [DOTS] Centre and sputum collection centre of Rajendra Institute of Medical Sciences, Ranchi .

Inclusion criteria : All patients suspected of pulmonary TB.
Exclusion criteria : 1. Patients on any ATT (Anti-tubercular therapy)
2. HIV positive patients.

The study was cleared by Institutional ethical committee and informed consent was taken from all study participants.

A relevant history of cough, night sweats, fever, weight loss, haemoptysis and history of previous tuberculosis was taken along with physical examination and chest x ray in all study subjects. All patients were enrolled consecutively. Patients were asked to submit 4 sputum samples: a raw sputum sample was sent for performing CB-NAAT-TB to a specialised tuberculosis diagnostic lab at Sadar Hospital, Ranchi and 3 samples were concentrated out of which two were sent for sputum microscopy by Ziehl-Neelsen [ZN] stain at DOTS Centre while one was sent for and sputum culture of MTB by using MGIT [Mycobacterium growth in tube] and read on BACTEC-960 at

Department of Microbiology. The standard procedures for CBNAAT, culture and microscopy were performed on all the specimens as laid out in guidelines.[19,20] The results of CBNAAT-TB, sputum microscopy and Mycobacterial culture were interpreted separately by trained technicians blinded to the results of each other. Similarly, rifampicin sensitivity testing on culture was interpreted without knowledge of results of CBNAAT-TB.

2.1 Performance of test

CBNAAT-TB test was done using a 4 cartridge module (GeneXpert Cepheid Inc. Technology) by trained health workers at District Hospital. Three laboratory technicians were trained for four days and obtained proficiency testing after ten runs per person. Sample reagent was added in a 2:1 ratio to untreated sputum. The closed sputum container was manually agitated twice during a 15-minute period at room temperature before 2 ml of the inactivated material was transferred to the test cartridge. Four Cartridges were inserted into a four cartridge module machine. After two hours, electronic test results were generated on the computer and sent directly from the CBNAAT-TB test system to the central database. The assay generated results within 2 hours with only fifteen minutes of hands on time.

M. tuberculosis was identified when at least two of the five overlapping molecular beacons which were complementary to 81 bp rpoB gene probes gave positive signals with a cycle threshold (C_T) of ≤38 cycles and that differed by no more than a pre-specified number of cycles. The *B. globigii* was used as internal control. The user interface indicated the presence or absence of *M. tuberculosis* and a semi-quantitative estimate of the bacilli as defined by the C_T range (very low: >28, low: 22–28, medium: 16–21, high: ≤ 15). The difference between the first (early C_T) and the last (late C_T) *M. tuberculosis*-specific beacon (ΔC_T) was observed. Rifampicin resistance was reported when ΔC_T was >3.5 cycles and rifampicin sensitivity if ≤3.5 cycles.

The sputum samples of CBNAAT-TB positive but rifampicin resistant pattern on CB-NAAT were sent to an approved lab for detection of MDR-TB based on Line Probe Assay (LPA) and Solid Culture technique.

2.2 Interpretation of Test

Patients were classified as bacteriologically confirmed (culture-positive) TB, clinical TB (culture-negative patients with clinical features suggesting TB and responding to ATT), no TB and indeterminate (invalid CBNAAT and contaminated culture). All indeterminate tests were excluded from final analysis.

2.3 Statistical analysis

A 2x2 table and Receiver Operator Characteristic curves [ROC] were constructed. The sensitivity, specificity, positive and negative predictive values, and likelihood ratios (PPV, NPV, PLR, NLR) and Area under ROC (AUROC) of sputum microscopy, CB NAAT-TB, chest x-ray, chronic cough, WHO symptom screen (any symptom out of weight loss, fever, current cough and night sweats)[21] were determined against the bacteriologically confirmed culture positive gold standard using SPSS 15.0. A Bayesian sensitivity analysis of the data using informed prior from a large meta-analysis[2] and a uniform prior was done using WINBUGS 1.3 software. The convergence diagnostics were calculated as appropriate.

RESULTS:

Out of 700 pulmonary TB suspected patients screened at TB/Chest clinic, 22 patients did not meet inclusion criteria(10 could not generate sputum samples, 4 already on ATT (Anti- tubercular therapy, 8 HIV positive), while 80 were not eligible (36 had contaminated culture, 20 had invalid CBNAAT, 24 patients did not give 4 sputum samples). Thus in final analysis 598 patients were included out which 131 were culture-positive and 467 were culture negative. Patient flow is represented in the figure below. [Figure 1]

The demographic profile of the patients is summarized in Table 1.

3.1 Performance of Smear microscopy

The performance of smear microscopy with culture positive TB as Gold standard, was as follows: sensitivity 60.3% (95% CI 51.39–68.74), specificity 97% (95% CI 95.02–98.3), PLR 20.12, NLR 0.41 and AUROC-0.793.

The kappa value of agreement between smear microscopy and culture was 0.666

3.2 Performance of CBNAAT/RIF

On using culture-positive TB as gold standard, the overall performance of CBNAAT was as follows: sensitivity 82.44% (95% C.I. 74.8-88.53), specificity 98.3% (95%C.I. 96.65-99.26), PLR 48.13, NLR 0.18, PPV 93.1 %, NPV 95.23 % and AUROC-0.904. CBNAAT was significantly superior to sputum microscopy with higher sensitivity, specificity and AUROC (mean difference= 0.111 (p=0.0003). (Figure 2) Only 1 test of CBNAAT was performed as opposed to 2 sputum smears due to financial constraints CBNAAT.

Out of smear-negative cases, CBNAAT correctly picked up 29 out of 52 cases missed by smear microscopy, having sensitivity of 55.76% and specificity of 98% in these cases.

3.3 Performance of Chest x-ray

On using culture-positive TB as gold standard, the overall performance of chest x-ray was as follows: sensitivity 70.23% (61.62-77.90), specificity 74.95% (70.76 – 78.81), PLR 2.8, NLR 0.40, PPV 21.91%, NPV 89.97 % and AUROC 0.726(0.688-0.761)

The kappa value of agreement between chest x-ray and culture was 0.372 while inter-observer agreement for chest x-ray between two experts was 40 % In the smear-negative group, even chest x-ray picked up 26 of the 52 culture-positive cases (50 % sensitive) but had a modest specificity of 75%

3.4 Performance of Prolonged/ Chronic Cough (Cough > 2 weeks)

On using culture positive TB as gold standard, the overall performance of chronic cough was as follows: sensitivity 45.80% (37.07- 54.73), specificity 85.01% (81.45 – 88.12), PLR 3.06, NLR 0.64, PPV 46.15 %, NPV 84.83% and AUROC 0.654(0.614-0.692)

The kappa value of agreement between chronic cough and culture was 0.309

3.5 Performance of WHO symptom screen (any out of these five symptoms: current cough, fever, night sweats, haemoptysis, and weight loss)

On using culture-positive TB as gold standard, the overall performance of WHO symptom screen was as follows: sensitivity 75.57% (67.73- 82.65), specificity 70.02% (65.64 – 74.15), PLR 2.52, NLR 0.35, PPV 41.42 %, NPV 91.09% and AUROC 0.728(0.690-0.763)

In the smear-negative group, WHO symptom screen picked up 27 of the 52 cases (51.92 % sensitive) but had a modest specificity of 66%.

3.6 Rifampicin Resistance and MDR

19 Out of 131 [14.5% (8.47 – 20.5)] CBNAAT positive cases came out to be Rifampicin resistant as indicated by signal delay exceeding a ΔC_T value (>3.5), between the earliest and latest cycle threshold values [26] . Eighteen of these Nineteen Rifampicin resistant cases (94.7%) turned out to be resistant to both Rifampicin and Isoniazid [INH], thus being true MDR cases. All the MDR TB cases were sent to a specialised MDR –TB unit for treatment.

3.7 Indeterminate tests

Twenty patients had invalid CBNAAT (5 bad sample processing, 10 RT- PCR inhibited, 5 susceptible power supply) and were excluded from analysis. Thirty-six patients had contaminated culture and were excluded from analysis.

3.8 Discordant cases analysis

23 patients were CBNAAT-negative but culture-positive (false negatives). 21 of these patients were smear-negative, while 2 were smear positive. Eight cases were CBNAAT positive but culture negative (false positive). However, three out of these eight cases had clinical evidence of TB and they responded well to ATT. Two cases were negative on CBNAAT but positive on smear microscopy. One of these showed rapid growth of mycobacteria and resistance to Para nitro benzoic acid and was classified as NTM (Non-tuberculous Mycobacteria).

3.9 Comparison with other symptoms and diagnostic algorithms

The comparative sensitivity and specificity of chronic cough, the WHO symptoms screen, abnormal chest X-ray, and CBNAAT and smear microscopy is described in Table 2. CBNAAT test is significantly better than all other tests. (Figure 3) Sputum microscopy

outperforms all other test except CBNAAT justifying its position as standard diagnostic modality. Chest x-ray has higher specificity but lower sensitivity than WHO symptom screen for detection of TB. Chronic cough, which is the first step in the diagnostic algorithm espoused by the WHO, unfortunately is inferior to all these diagnostic modalities.

3.10 Sensitivity Analysis

We carried out a Bayesian Sensitivity Analysis of sensitivity and specificity of CBNAAT as first line test and in smear negative cases, using a uniform prior from beta distribution and informed prior from results of a large meta analysis. [2] The 95% credible intervals for sensitivity of CBNAAT as first line test were 82% (75.7-88.7) and 86.9% (83.9-90) for uniform and informed prior respectively. The 95% credible intervals for specificity of CBNAAT as first line test were 98.1% (96.7-99.2) and 98.5% (98-98.9) for uniform and informed prior respectively.

As an add on to smear-negative cases, The 95% credible intervals for sensitivity of CBNAAT as first line test were 55.6 % (43.3-69.8) and 64.6% (58.4-70.9) for uniform and informed prior respectively. The 95% credible intervals for specificity of CBNAAT as first line test were 97.8% (96.4-99) and 98.5% (98-98.9) for uniform and informed prior respectively.

DISCUSSION

Our study detected that CBNAAT had high sensitivity (82.44%) and specificity (98.3%) as compared to sputum microscopy (60.3%, 97%) for detecting culture-positive tuberculosis even in non-HIV infected individuals.

In sputum smear negative individuals, CBNAAT picked up almost three-fifth of cases[sensitivity 56%] at high specificity of 98%. [Table 3] Chest x-ray and WHO symptom screen also diagnosed almost half of sputum negative culture positive cases but had relatively poor specificity of 75% and 66% respectively, implying that using these diagnostic adjuncts in almost one-fourth and one-third non-TB cases would be wrong respectively and would be diagnosed as TB, and hence over treated. These findings are also confirmed by a meta-analysis exploring role of symptoms and chest x-ray in diagnosis of TB. [4] Further, the inter-observer agreement for chest x-ray was moderate at 40%, as is seen in other studies.[4,23] This limits the role of chest x-ray as a reliable diagnostic modality in diagnosis of pulmonary TB Thus CBNAAT-TB emerged as a highly sensitive and specific test as a first line test and even as an add-on to sputum-negative cases where it accurately diagnosed almost three-fifth of cases with minimal false positives.

The sensitivity of CBNAAT-TB in sputum-positive cases was 98%, while it fell down to 56% in sputum-negative cases. In meta-analysis of CBNAAT-TB, the sensitivity of CBNAAT was found to around 60-65% in sputum-negative cases, so it is consistent with results of our study. [2] The lower sensitivity of CBNAAT in sputum-negative cases is explained by decreased bacillary load in these cases. WHO also recommends use of CBNAAT-TB as a diagnostic modality in sputum negative and retreatment cases.[22] Out of 23 false negative cases in our study, 21 were smear negative, indicating low bacillary load, which lead to both smear and CBNAAT negatives. One case of CBNAAT negative and smear positive rapidly grew within 3 days on MGIT culture and was PNBA resistant and later diagnosed as atypical mycobacteria. This also indicates relatively high specificity of CBNAAT-TB in detecting MTB specific sequences only. Thus it can also be of help in differentiating atypical mycobacteria from MTB. Out of 8 false positive cases, three cases responded to ATT and were classified as clinical culture negative TB. This may be due to detection of unviable bacilli by CBNAAT-TB which could not be cultured by MGIT. These results are consistent with multi-centre analysis of CBNAAT. [8]

Rifampicin resistance was found in 19 out of 131 CBNAAT-positive cases. 18 out of 19 rifampicin resistant cases were found out to be rifampicin-resistant by phenotypic sensitivity as well. One case of false positive resistance could not be genotyped because of lack of resources at our centre. Out of 18 remaining true positive cases, 17 were resistant to INH as well, indicating that Rifampicin resistance can be used as surrogate for MDR. This is consistent with results of other studies where rifampicin resistance is commonly associated with INH resistance as well. [24] The relatively high prevalence of rifampicin resistance is explained by high prevalence of retreatment cases in our study group (40%). It has been hypothesized that CBNAAT has high positive predictive value for predicting rifampicin resistance in population with high prevalence of MDR (>15%) [25] However as of now, WHO recommends testing for phenotypic drug sensitivity in CBNAAT-positive but rifampicin resistant cases before starting treatment for MDR-TB, to rule out false positive rifampicin resistance and to check for coexisting INH resistance as well. A recent study has raised concern about poor sensitivity (65%) of CBNAAT-TB to detect rifampicin resistance in susceptible patients.[26] However in our study CBNAAT picked up all cases of rifampicin resistance with culture as gold standard. Limiting our study was that we had only 19 cases of rifampicin resistance and thus was inadequately powered to deal with detection of drug resistance. Hence, larger studies should be carried out for prospective validation.

The strength of our study is that we included all patients presenting to DOTS clinic without selective screening and sent the sample for processing without delay to a quality assured lab. We also compared it with commonly used symptom screen, chest x-ray, sputum microscopy and generated test characteristics for each one of them. The limitation of our study is that we could use only one sputum sample for CBNAAT processing due to financial constraints and the number of rifampicin resistant patients was too small to generalize its prevalence to a larger population.

Thus CBNAAT-TB has high sensitivity and specificity for diagnosing TB and can be used as an add-on in diagnosing sputum-negative pulmonary tuberculosis. It can also prove helpful in rapid diagnosis of rifampicin resistance as was seen in our study.

Table 1: Demographic profile of Patients.

	Mean	CI SD	95%
AGE	39.074	38.08 - 40.06	12.30
SEX (male) %	51	46.7 - 55.0	50.03
WEIGHT (kg)	49.3	48.7 - 49.9	7.49
Chronic cough (%)	21.7	18.4 - 25.5	41.28
Abnormal chest x-ray (%)	34.9	31.1 - 38.8	47.72
Positive smear (%)	14.5	11.7 - 17.4	35.29
Positive CBNAAT (%)	19.4	16.2 - 22.6	39.57
WHO symptom screen (%)	40	36 - 43.9	49.02
Culture-positive TB (%)	21.9	18.6 - 25.2	41.4

Table 2: Comparative test characteristics of various symptoms and tests with sputum culture positive as Gold standard.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR (%)	NLR (%)	AUROC
CBNAAT-TB	82.44	98.29	93.1	95.23	48.13	0.18	0.904
Smear microscopy	60.31	97	84.95	89.70	20.12	0.41	0.793
Chest x-ray	70.23	74.95	44.02	89.97	2.80	0.40	0.726
Chronic cough	45.80	85.01	46.15	84.83	3.06	0.64	0.654
WHO symptom screen	75.57	70.02	41.42	91.09	2.52	0.35	0.728

(PPV-positive predictive value, NPV-negative predictive value, PLR-Positive likelihood ratio, NLR-Negative likelihood ratio

Table 3 . Comparative test characteristics of various symptoms and tests in smear negative patients with culture positive as Gold standard.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
CBNAAT-TB	55.77	98.26	78.4	95.1	32	0.45
Chest x-ray	50	74.94	18.44	92.97	2.00	0.67
WHO symptom screen	51.92	66.01	14.75	92.38	1.53	0.73

(PPV-positive predictive value, NPV-negative predictive value, PLR-Positive likelihood ratio, NLR-Negative likelihood ratio)

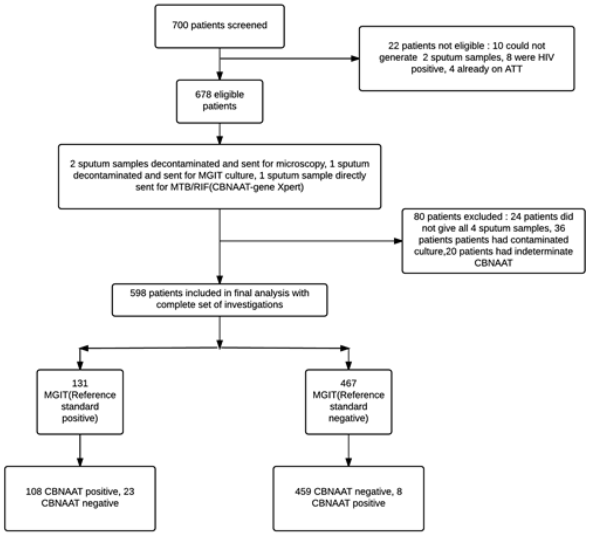

Figure 1. Patient Flow Diagram

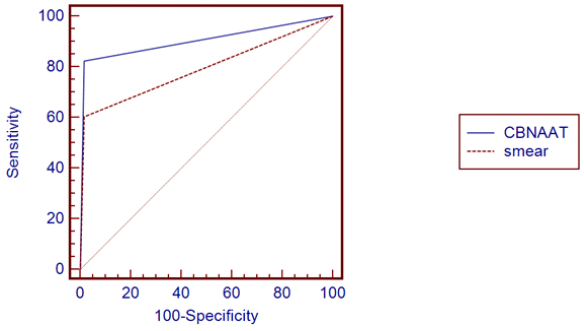

Figure 2. Comparative diagnostic performance of CBNAAT and Smear microscopy in detection of Tuberculosis.

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