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Original Research Article

Diagnostic accuracy of truenat MTB plus for the detection of pulmonary and extrapulmonary tuberculosis

Reena Anie Jose [a,*], Leeberk Raja Inbaraj [b], Ria Catherine Vincent [a], Adhin Baskar [c], Renu Mathew [a]

[a] Department of Microbiology, Believers Church Medical College Hospital, Thiruvalla, Kerala, India
[b] Department of Clnical Research, ICMR-National Institute for Research in Tuberculosis, Chennai, India
[c] Department of Statistics, ICMR-National Institute for Research in Tuberculosis, Chennai, India

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ABSTRACT

Background: The diagnosis of Tuberculosis (TB) has been a challenge till the advent of rapid molecular diagnostic tests. The traditional diagnostic tests have its own limitations with regard to its performance or the turnaround time. Truenat MTB Plus assay, a battery-operated molecular assay developed in India has been introduced for its use in pulmonary TB (PTB). However, the diagnostic accuracy of the assay is not well studied in comparison with Mycobacterial culture, especially for extrapulmonary TB (EPTB).

Aim: We aimed at evaluating the diagnostic accuracy of Truenat MTB Plus assay for both PTB and EPTB comparing with culture for adult population.

Methods: The specimens from presumptive PTB and EPTB patients were processed for Truenat MTB Plus assay, solid or liquid culture and AFB staining. The electronic data of all the specimen reports collected retrospectively were analysed for the sensitivity and specificity.

Results: Out of the 736 samples which had valid culture reports, 364 (49.4 %) were respiratory and 372 (50.6 %) were extrapulmonary specimens. The test positivity rate for smear microscopy, Truenat MTB Plus assay and culture was 3.7 % (27), 8.2 % (60), 7.1 % (52) respectively. Of the 60 Truenat MTB Plus positive patients with TB, 33 (55 %) were PTB and 27 (45 %) were EPTB. We estimated overall sensitivity and specificity of Truenat MTB Plus as 90 % (95 % CI: 73.4–97.8) and 98. 2 (95 % CI:96–99.3) respectively for the detection of PTB. The overall sensitivity and specificity for EPTB was 81.8 % (95 % CI: 59.7–94.8) and 97.4 % (95 % CI: 95.1–98.8) respectively.

Conclusions: Truenat MTB Plus assay has comparable diagnostic accuracy with other molecular assays. The Truenat MTB Plus assay can be used for the diagnosis of PTB and EPTB, especially in resource limited settings.

1. Introduction

The global aftermath of the COVID-19 pandemic has adversely affected efforts to combat TB, particularly in India, which bears the highest burden of the disease. The burden of TB and multidrug resistant/Rifampicin resistant TB (MDR/RR-TB) in the country, which in 2022 accounted for over a quarter (27 %) of global incidence [1]. The TB incidence is estimated to be 2.77 million in the year 2022 [2]. According to Global TB report 2020, Extrapulmonary TB (EPTB) constituted 16 % of the 7.1 million incident patients with TB globally and ranges from 20 to 29 % among new and relapse patients with TB in India [3].

Traditional smear microscopy using Ziehl-Neelsen (ZN) staining is a simple, cost-effective and quick method for detecting the acid-fast bacilli (AFB) in the smears of the clinical samples. However, it has limited sensitivity and it can be overcome by fluorescent staining methods, although it requires expertise and expensive equipment. Arora et al. in their study assessed the diagnostic usefulness of smear microscopy and observed that sensitivity and specificity was 65.7 % and 95.7 % respectively. A positive smear microscopy requires 5000 to 10000 bacilli/mL in the clinical sample [4]. The culture of *Mycobacterium tuberculosis (M. tuberculosis/MTB)* is considered as the gold standard for the diagnosis of TB, and includes conventional solid culture in Lowenstein Jensen (LJ) medium or MGIT (Mycobacteria Growth Indicator Tube) 960 system, for which the turnaround time (TAT) varies from four to eight weeks. The sensitivity and specificity of MGIT in detecting

* Corresponding author. Department of Microbiology, Believers Church Medical College Hospital, St. Thomas Nagar, Thiruvalla, Kerala, 689103, India.
E-mail address: reenakocherry@gmail.com (R.A. Jose).

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Abbreviations

COVID-19	Coronavirus disease-19
TB	Tuberculosis
CI	Confidence Interval
CSF	Cerebrospinal fluid
PPV	positive predictive value
NPV	negative predictive value
SD	standard deviation
NE	not estimable
PCR	polymerase chain reaction

mycobacteria is estimated to be 81 % and 99.6 % respectively. Currently, a combination of conventional solid media with liquid media is recommended as the reference standard for the diagnosis of TB [5]. Hillemann et al. investigated the performance of mycobacterial culture in EPTB specimens and observed sensitivity of 88.8 % and 69.3 % for MGIT and solid culture respectively [6]. The disadvantages of culture are the high frequency of breakthrough contamination, higher TAT and the requirement of a well-equipped laboratory.

In order to overcome the barriers of smear microscopy and increase the case detection rate, the World Health Organisation (WHO) approved a few molecular-based rapid diagnostic tests (mWRD) such as, Xpert MTB/RIF assay (GeneXpert) and Truenat assays including Truenat MTB (quantitative assay), MTB Plus (semi-quantitative assay) for the initial diagnosis of TB [7]. The main advantage of Truenat assay is that it's a battery-operated, portable device that can be used in resource limited settings. The diagnosis of EPTB is even more challenging due to paucibacillary nature of the disease and difficulty in obtaining the appropriate specimens. The diagnostic accuracy for EPTB specimens are relatively lower compared to PTB even with molecular tests. The diagnostic performance of Xpert assay for tuberculous meningitis (60 %) was inferior to pulmonary TB (PTB) (88 %–95 %), as well as bone and joint infections (95 %), but both maintained high specificity [8]. The line probe assay (LPA) had high diagnostic performance with sensitivity of 89–96 % and specificity of 94–99 % for the diagnosis of MTB and drug resistant TB [9]. The limitations of the use of these highly-priced imported test in resource-limited settings and the increasing incidence of MDR/RR-TB contributes to the main challenges for TB control in Indian healthcare system.

Truenat assay, being manufactured within the country, most of the validation was performed in comparison with Xpert MTB. More-over, there is scarcity of data with regard to the diagnostic accuracy of Truenat MTB Plus in the diagnosis of EPTB. The Truenat MTB Plus assay was introduced for its better diagnostic performance when compared to Truenat MTB assay and WHO recommends research priorities on the evaluation of the diagnostic performance of the assay [7]. On the background, we aimed at studying the diagnostic accuracy of Truenat MTB Plus assay for both EPTB and PTB in comparison with culture for adult population.

2. Materials & methods

2.1. Study setting

This retrospective cross-sectional study was done during the period of January 2020 to June 2023 in the Department of Microbiology in a private medical college hospital in Kerala, India. The study was approved by the Institutional Ethics Committee (IEC Study No. IEC/2023/13/379) dated December 06, 2023.

2.2. Specimens

The clinical specimens of those patients (age more than 10 years) with presumptive PTB and EPTB were collected across various department of the medical college from January 1st, 2020 to June 29, 2023. They were processed for Truenat MTB Plus assay, Mycobacterial culture and AFB staining. All the clinical specimens were collected as per standard procedures and transported in two sterile screw capped containers to the Microbiology laboratory.

2.3. Truenat MTB plus assay

This is a semiquantitative chip based real time polymerase chain reaction (PCR) which detects *M. tuberculosis* by the amplification of *nrdz* and *IS6110* gene sequence. The limit of detection (LoD) for this assay is 29.0 cells/mL.

The body fluids were centrifuged and the sediment was considered as specimen. The tissue sample is homogenised using a Microcentrifuge tube after the addition of liquefaction buffer. The pretreated samples (using MTB lysis buffer) were transferred to the sample chamber of the universal cartridge using a Pasteur pipette. The cartridge was loaded into the TruePrep Auto and after the extraction process, after which the elute was pipetted from the elution chamber to the Elute collection tube and then loaded in TrueLab Uno Dx/Quattro real time micro PCR analyzer for amplification process.

2.4. Mycobacterial culture

Mycobacterial culture was performed either by conventional solid culture or by liquid culture using BACTEC MGIT 320 system. All the specimens received from January 1, 2020 to May 10, 2022 were processed by solid culture and the remaining in MGIT system.

The digestion and decontamination procedure for sputum samples were performed by modified Petroff's method using 4 % NaOH (sodium hydroxide) followed by centrifugation. Other body fluids were centrifuged and the tissue specimen was homogenised in a homogeniser tube. The sediment was inoculated to readymade Lowenstein Jensen (LJ) media and incubated at 37^0C for 8 weeks for a final negative report. The typical colonies were further confirmed by AFB staining and reported as positive.

The digestion and decontamination procedure for sputum and other specimens which were thick in consistency were performed by NaOH-NALC (N-acetyl L-cysteine) method. The sediment was added to MGIT tubes containing MGIT medium, MGIT growth supplement and MGIT PANTA (Polymixin B, Amphotericin B, Nalidixic acid, Trimethoprim and Azlocillin). Decontamination procedure was not generally performed for other samples. The tubes were loaded into the BACTEC MGIT system and incubated for 6 weeks. A positive tube was confirmed by performing AFB staining and rapid card test for MPT 64 antigen (Bioline™ TB Ag MPT64 by Abbott Diagnostics), which is specific for *M. tuberculosis*.

2.5. Data collection

The clinical details and the laboratory reports of Truenat MTB Plus, AFB culture and AFB staining were retrieved from the electronic medical record. The retrospective data was filtered and the clinical samples from those patients who were on Anti-tubercular treatment (ATT) and those infected with Non-Tuberculous Mycobacteria (NTM) were excluded from analysis.

2.6. Statistical analysis

Mycobacterial culture was considered as a reference standard and diagnostic accuracy estimates such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of Truenat MTB Plus were calculated and presented with 95 % confidence interval (CI).

3. Results

A total of 1580 clinical specimens were tested with Truenat MTB Plus assay during the study period, out of which only 736 samples had valid culture reports. We analysed specimens from 736 patients, out of which 364 (49.4 %) consists of respiratory specimens for the detection of PTB and the remaining (372, 50.6 %)) were extrapulmonary specimens for the diagnosis of EPTB. Our population consisted of predominantly males (55.6 %) and with age group ranging from 11 to 90 years. The mean age of the study population was 52.3 years (SD ± 19.1). The test positivity rate for smear microscopy, Truenat MTB Plus assay and culture was 3.7 % (27), 8.2 % (60), 7.1 % (52) respectively.

There were 60 positives for MTB. Of the 60 Truenat MTB Plus positive patients with TB, 33 (55 %) were PTB and 27 (45 %) were EPTB. Males were the predominant group among the patients with PTB (22, 66.7 %) and EPTB (15, 55.6 %). The mean age of the patients with PTB and EPTB were 58 years and 46.4 years respectively.

3.1. Diagnostic accuracy of truenat MTB plus for PTB

Among the respiratory specimens, sensitivity and specificity of the sputum was 94.7 % (95 % CI:73.9–99.8) and 98.3 % (95 % CI: 95.3–99.6) respectively (Table .1). Gastric lavage had 100 % specificity and sensitivity. However, the sample size was too less. Among the smear positive individuals, all respiratory specimens were culture and Truenat MTB Plus positive indicating 100 % sensitivity. The sensitivity and specificity were 81.2 % (95 % CI: 54.3–95.9) and 98.2 % (95 % CI: 96.1–99.3) respectively among smear negative specimens for PTB.

3.2. Diagnostic accuracy of truenat MTB plus for EPTB

Among the different specimens for EPTB, the sensitivity of the lymph node was 85.7 % (95 % CI: 42.1–99.6). Specimens such as CSF, pleural fluid, pus aspirate and synovial fluid had 100 % sensitivity. The specificity of EPTB specimens across different EPTB sites ranged from 85.7 % to 100 %. Among the EPTB specimens, 13 (3.4 %) were positive in smear microscopy. Of 13 specimens, 8 (6.1 %) were culture positive and Truenat MTB Plus positive and 2 (1.5 %) were false positives. Similarly, 359 (96.5 %) were smear negative of which 10 (2.7 %) were true positives and 7 (1.9 %) were false positives.

We estimated overall sensitivity and specificity of Truenat MTB Plus for the detection of pulmonary TB as 90 % (95 % CI: 73.4–97.8) and 98.2 (95 % CI:96–99.3) respectively. Overall sensitivity and specificity for EPTB was 81.8 % (95 % CI: 59.7–94.8) and 97.4 % (95 % CI: 95.1–98.8) respectively (Table 2).

4. Discussion

Despite constant efforts of TB control and management, TB continues to be a global health issue, especially in developing country like India. In the present study, the sensitivity of Truenat MTB Plus was 94.7 % and 80 % for sputum and bronchial wash respectively. This is comparable with a large multicentric study performed in 19 clinical sites and seven reference laboratories across four countries, including India. Penn-Nicholson in their study have compared the two Truenat assays with culture for PTB and observed that the pooled sensitivity of Truenat MTB was lower (73 %) as against 80 % for Truenat MTB Plus for smear negative specimens [10]. In the present study, we observed sensitivity and specificity of 81.2 % and 98.2 % respectively among smear negative specimens for PTB, which was higher when compared with Penn-Nicholson study.

Nikam C et al. evaluated the clinical performance, a validation study in 2013 and found sensitivity greater than 99 % in smear positive and culture positive samples for TB [11]. In another study by Nikam C et al., where they evaluated the performance of Truenat MTB with GeneXpert and MGIT, and reported an overall sensitivity of 94.7 % and 99 % for smear positive sputum samples [12]. The diagnostic accuracy of Truenat MTB Plus for PTB specimens was assessed in Ethiopia by Meaza et al. with culture as reference standard and observed a sensitivity of 91.7 % [13]. In the present study, we observed an overall sensitivity of 90 % for PTB detection by Truenat MTB Plus when compared with culture. Ngangue et al. in their study on the diagnostic accuracy of Truenat MTB Plus assay for PTB in HIV infected patients observed a similar sensitivity of 91 %. However, the study included only sputum specimens and had excluded the people with paucibacillary disease who are unable to expectorate a relatively large amount of sputum [14]. Gomathi et al. in their study compared Truenat MTB assay with culture on pulmonary samples, noted a sensitivity of 88.3 % when compared with culture. They observed a sensitivity of 91.2 % and specificity of 90.5 % when compared with the comprehensive reference standard (smear, culture, Xpert and TRC_4 PCR), similar to the study done by Nikam C et al. [11, 15]. Akhtar et al. analysed the performance of Truenat MTB with Xpert assay, and the sensitivity was 94 % [16]. In their study, the reference standard for comparison was not Mycobacterial culture. Singh UB et al. in their study in pediatric PTB (age less than 18 years), observed sensitivity and specificity of 58.7 % and 87.5 %, respectively for Truenat

Table 1
Diagnostic accuracy of Truenat MTB Plus assay across different respiratory and extrapulmonary specimens[a].

Pulmonary TB (Respiratory specimens)					
Specimens	N	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)
Sputum	203	94.7 (73.9–99.8)	98.3 (95.3–99.6)	85.7 (66–94.8)	99.4 (96.4–99.9)
Bronchial wash	149	80 (44.3–97.4)	97. 8 (93.8–99.5)	72.7 (45.5–89.4)	98.5 (95.1–99.5)
Gastric lavage/aspirate	3	100 (2.5–100)	100 (15.8–100)	100 (2.5–100)	100 (15.8–100)
Lung biopsy	9	Not estimable (NE)	100 (66.3–100)	NE	100 (66.3–100)
Extra pulmonary specimens					
CSF	46	100 (2.5–100)	100 (92.3–100)	100 (2.5–100)	100 (92.3–100)
Urine	10	NE	90 (55.5–99.7)	NE	100 (66.37–100)
Pleural fluid	78	100 (2.5–100)	100 (95.3–100)	100 (2.5–100)	100 (95.32–100)
Peritoneal fluid	16	0 (0–97.5)	93.3 (68–99.8)	NE	93.3 (92.4–94.13)
Synovial fluid	7	NE	100 (59–100)	NE	100 (59–100)
Pus aspirate	39	100 (59.0–100)	87.5 (71–96.4)	63.6 (41.1–81.4)	100 (87.6–100)
Bone marrow	8	NE	100 (63.06–100)	NE	100 (63.06–100)
Lymph node	69	85.7 (42.1–99.6)	98.3 (91.3–99.6)	85.7 (45.6–97.7)	98.3 (90.8–99.7)
Intestinal biopsy	35	0 (0–97.5)	97 (84.6–99.3)	97 (96.8–97.22)	94.2(80.8–99.3)
Omentum	7	NE	85.7 (42.3–99.6)	NE	100 (54.0–100)
Synovial tissue or bone biopsy	32	100 (29.2–100)	100 (88–100)	100 (29.2–100)	100 (88–100)
Skin	15	NE	100 (78.2–100)	NE	100 (78.2–100)
Peritoneal tissue	5	0 (0–97.5)	100 (39.7–100)	NE	80 (80–80)
Mesh	5	NE	100 (39.7–100)	NE	100 (39.7–100)

[a] Low sample size with wide 95 % CIs to be noted for diagnostic accuracy measures of non-sputum and extra-pulmonary specimens.

Table 2
Diagnostic accuracy of Truenat MTB Plus assay for PTB and EPTB.

Truenat MTB Plus assay	Culture		Sensitivity	Specificity	PPV	NPV
	Positive	Negative				
PTB						
Positive	27	6	90 (73.4–97.8)	98. 2 (96–99.3)	81.8 (66.8–90.9)	99.(97.3–99.6)
Negative	3	328				
EPTB						
Positive	18	9	81.8 (59.7–94.8)	97.4 (95.1–98.8)	66.6 (50.4–79.7)	98.8 (97.2–99.5)
Negative	4	341				

MTB detection assay [17]. It has been observed that the performance characteristics depends on the study population, comparator and the type of assay.

The confirmatory diagnostic tests for EPTB are culture and molecular techniques to differentiate Mycobacterium tuberculosis complex organisms and NTM species [18]. Tuberculous lymphadenitis is the most common form of EPTB. The sensitivity of Truenat MTB Plus ranged from 66.6 % to 85.7 % for various EPTB specimens [19–22]. The lower sensitivity as observed in the studies could be due to the paucibacillary nature of EPTB disease which is one of the greatest challenges in its early diagnosis and management. Appropriate and adequate clinical material from the right site is required for a better diagnostic yield of EPTB. In the current study, the EPTB positive samples were low EPTB (27/372) for a proper specimen wise analysis.

The overall sensitivity and specificity of Truenat MTB Plus for the diagnosis of EPTB specimens was 81.8 % and 97.4 %, respectively in our study. A recent study in Kerala, India evaluated the performance of Truenat MTB for EPTB samples, and the sensitivity and specificity was 65 % and 70 % respectively. However, they observed that the sensitivity and specificity for PTB samples, were 90 % and 96 %, respectively [23]. In another evaluation with Truenat MTB conducted in the same study setting during one-year duration, observed sensitivity and specificity of 100 % and 96 %, for EPTB specimens [24].

In various studies, the diagnostic accuracy (sensitivity, specificity) of Xpert MTB/RIF Ultra assay for the diagnosis of PTB were 90 % and 96 % respectively [25]. For various EPTB specimens, the sensitivity and specificity of Xpert MTB/RIF Ultra assay was 38–100 %. Sensitivity was lowest with pleural fluid specimens and specificity was lowest with lymph node biopsy samples [26]. In our study, Truenat MTB Plus assay had a comparable diagnostic accuracy for PTB, with sensitivity of 90 % and specificity of 98 %. The overall sensitivity of EPTB specimens was 81.8 % and specificity of 97.4 % in the present study. Truenat MTB Plus assay has added advantage of being a battery-operated device, cost-effective and comparable performance characteristics could be a better option for resource limited country like India when compared to Xpert MTB assay [27].

The present study has evaluated the diagnostic accuracy of Truenat MTB Plus assay for both PTB and EPTB. The main limitation of the present study was that the diagnostic accuracy could not be analysed separately for all the TB positive specimens due to the low sample size. The sensitivity and specificity for specific EPTB specimens could not be assessed due to the low sample size. The pediatric specimens were not included in the study, due to the low number.

5. Conclusion

Truenat MTB Plus assay has good sensitivity and specificity for pulmonary and exrapulmonary tuberculosis. We recommend Truenat MTB Plus assay for the diagnosis of tuberculosis in limited resource settings.

Ethical approval

The study was duly approved by the Institutional Ethics Committee (IEC Study No. IEC/2023/13/379) dated December 06, 2023.

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None.

CRediT authorship contribution statement

Reena Anie Jose: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Leeberk Raja Inbaraj:** Writing – review & editing, Validation, Supervision, Formal analysis, Conceptualization. **Ria Catherine Vincent:** Writing – review & editing, Data curation. **Adhin Baskar:** Validation, Formal analysis. **Renu Mathew:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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