Role of GeneXpert in the diagnosis of extrapulmonary tuberculosis

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Abstract

The World Health Organization endorsed the cartridge-based nucleic acid amplification test Xpert MTB/RIF (GXP) for the diagnosis of tuberculosis (TB). Studies about GXP efficiency in extrapulmonary TB (EPTB) are scarce. Hence, we decided to study the role of GXP in EPTB.

This prospective observational study, conducted in the pulmonary medicine department of a tertiary care hospital after ethics committee permission, recruited 200 EPTB patients. The diagnosis of TB was achieved with the help of clinico-radiological correlation with microbiological test positivity. Acid-fast bacilli (AFB) culture was treated as the comparative gold standard. Patients who had no or incomplete data were excluded from the study. Data were analyzed to calculate the sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of TB and the detection of rifampicin resistance.

The majority of cases were women (126 patients: 63%). The mean age was 23.71 years. On GXP, 130 (65%) had detected *Mycobacterium tuberculosis*, and 70 (35%) did not. Adding AFB culture data, 168 (81.5%) showed microbiological evidence of TB, and 32 (18.5%) were negative. On the drug susceptibility test, 131 cases were rifampicin-sensitive, 32 were rifampicin-resistant TB, and in 5 cases, data were unavailable. The most common extrapulmonary site of involvement was the lymph node, with 94 patients (47%). The most common lymph node involved was the cervical lymph node, with 70 patients (74.5%). The sensitivity, specificity, positive predictive value, and negative predictive value of GXP in EPTB collectively were 76.68%, 86.48%, 96%, and 45.7%, respectively.

GXP is useful for the rapid detection of EPTB and the identification of rifampicin resistance, especially in a high-prevalence country like India.

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Introduction

Tuberculosis (TB) remains a major health problem, accounting for millions of new cases and deaths every year worldwide. India is the highest burden country in the world, having an estimated incidence of 24.2 lakh cases in 2022 [1]. In 2022, with an increase in notification of over 13% as compared to 2021, the case notification rate was approximately 172 per lakh population [2]. Extrapulmonary TB (EPTB) is frequently a diagnostic and therapeutic challenge. It is a common opportunistic infection in people living with HIV/AIDS and other immunocompromised states such as diabetes mellitus and malnutrition [3]. EPTB encompasses the various conditions caused by *Mycobacterium tuberculosis* (MTB) infection of organs or tissues outside the lungs. For example: pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, or meninges. Symptoms and signs are specifically related to the affected organ system. There is a paucity of data from clinical trials in EPTB, and most of the information regarding diagnosis and management is extrapolated from pulmonary TB. Acid-fast bacilli (AFB) liquid culture is considered the gold standard test for the determination of TB, but the turnaround time is 2-8 weeks, and it requires trained personnel and expensive lab equipment [4]. Smear microscopy for AFB is one of the rapid and inexpensive tests available, but it has poor sensitivity and poor predictive value in the diag-

nosis of both pulmonary and EPTB. Xpert MTB/RIF (rifampicin) assay (GXP) is a novel, integrated, cartridge-based, nucleic acid amplification test for rapid diagnosis of MTB. It can be used for quick detection of rifampicin-resistant TB (RRTB), in both pulmonary TB and EPTB cases [5,6]. The GXP test was developed and launched by a foundation for innovative new diagnostics (FIND) and Cepheid Corporation in 2004. However, the development of the GXP was completed in 2008. The World Health Organization (WHO) endorsed the GXP for use in TB-endemic countries in December 2010, declaring it a major milestone for global diagnosis of TB [7]. GXP has a relatively high specificity in EPTB, while sensitivity is generally lower and highly variable among sample types and test methods [8]. Hence, we decided to study the role of GXP in the detection of EPTB in a tertiary care hospital. The objective was to evaluate the diagnostic accuracy of GXP for the detection of MTB in extrapulmonary samples by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and comparing it with conventional techniques like AFB smear microscopy and culture.

Materials and Methods

A prospective observational study was conducted in the Pulmonary Medicine Department of a tertiary care hospital after institutional ethics committee permission (PG Academic Committee/Ecarp/2021/07). Sample size was calculated taking into consideration 15% [3,8], as the proportion of EPTB using the sample size calculator, which yielded 196, which was rounded off to 200. Diagnosed EPTB patients, referred to our Pulmonary Medicine Outpatient and Inpatient Department, whose GXP, AFB culture, and line probe assay (LPA) reports were available, were enrolled in the study. These EPTB cases mainly consisted of lymph node TB and TB pleural effusion, and some central nervous system (CNS) TB, TB spine, other bone TB, abdominal TB, TB pericardial effusion, and others referred for opinion to our department. Demographic data, clinical history, examination findings, and radiological tests of these patients were noted. Diagnosis of TB was achieved with the help of clinico-radiological correlation with microbiological test positivity. AFB culture (liquid culture method) was treated as the comparative gold standard. Patients who had no or incomplete data were excluded from the study. Invalid and erroneous GXP reports were repeated, and confirmed MTB detected or not detected reports were only included in the study.

Ultrasound guided lymph node biopsy and fine needle aspiration cytology samples in lymph node TB, pleural fluid and pleural biopsy samples in TB pleural effusion, cerebrospinal fluid studies in TB meningitis, computed tomography guided biopsy sample of vertebrae and paravertebral collections in TB spine, colonoscopy guided biopsy samples in abdominal TB cases; whose GXP, AFB smear and culture, LPA reports were recorded.

Qualitative data were represented in percentages and means. Data was analyzed to determine the performance (sensitivity, specificity, PPV, NPV) of GXP and compare it with conventional techniques like AFB smear and culture. The sensitivity, specificity, PPV, and NPV were calculated for the diagnosis of TB and the detection of rifampicin resistance using formulas. Chi-square test was used to study significance.

Results

In this study, 200 patients were included. The mean age was 23.71 years. The majority of the patients were in the age group 11-20 years, with 92 (46%) patients, and the second most common age group was 21-40 years, with 91 (45.5%) patients. The age groups of 0-10 years, 41-60 years, and 61-80 years consisted of 1(0.5%), 14 (7%), and 2 (1%) patients, respectively. Out of the 200 patients, 74 (37%) were men and 126 (63%) were women. The most common site of EPTB in this study was lymph nodes, with 94 patients (47%), and the second commonest was pleural effusion with 69 patients (34.5%). Table 1 summarizes the different sites of involvement in EPTB. A few patients had disseminated EPTB, wherein they had more than one site of involvement. Hence, the sum total of patients belonging to individual subtypes exceeded 200 due to the overlap. Cervical lymphadenopathy was the most common site of lymphadenopathy, with a total of 70 out of 94 patients (70%), and the second most common site was the mediastinum, with 22 patients (23.4%).

Out of the total 200 patients, 130 (65%) patients had a GXP report suggesting MTB was detected, and in 70 (35%) patients, MTB was not detected. Table 2 enlists the comparison of GXP at different EPTB sites. Out of the total, 60/94 (63.8%) of lymphadenopathy, 29/69 (42%) of pleural effusion, 22/33(66.6%) of bone TB, 12/20 (60%) of abdominal TB, and 3/5 (60%) of pericardial effusion, had detected MTB on GXP. In the small numbers of CNS, skin, breast, and retropharyngeal TB all (100%) were GXP MTB detected.

Of the 200 patients, 168 detected MTB by GXP and/or AFB culture methods, and 32 were negative microbiologically. Of the 168, 5 had only GXP evidence of TB, 38 were only AFB culture

Table 1. Different sites of extrapulmonary tuberculosis.

Sites	No. of cases (%)
Lymph nodes	94 (47)
Pleural effusion	69 (34.5)
Bone	33 (16.5)
Abdominal	20 (10)
Pericardium (heart)	5 (2.5)
CNS	3 (1.5)
Skin	1 (0.5)
Breast	1 (0.5)
Retropharyngeal abscess	1 (0.5)

CNS, central nervous system.

Table 2. Comparing GeneXpert in different sites.

Sites	Total no. of cases	GeneXpert MTB detected n (%)
Lymph nodes	94	60 (63.8)
Pleura	69	29 (42)
Bone	33	22 (66.6)
Abdomen	20	12 (60)
Heart	5	3 (60)
CNS	3	3 (100)
Skin	1	1 (100)
Breast	1	1 (100)
Retropharyngeal space	1	1 (100)

MTB, *Mycobacterium tuberculosis*; CNS, central nervous system.

positive, and 125 had both GXP and AFB culture evidence of TB. Table 3 enumerated the GXP and AFB culture reports. On drug susceptibility test, 131 were rifampicin sensitive, 32 were RRTB, and in 5, data were unavailable. Of the 32 RRTB, 23 were multidrug-resistant (MDR) TB, 7 were pre-extensively drug-resistant (XDR) with additional fluoroquinolone resistance TB, 1 was pre-XDR with additional second-line injectable resistance TB, and 1 was XDR TB.

Out of the 200 patients, 145 were Mantoux positive, 15 were Mantoux negative, and in 40 patients, the test was not done. Out of the 200 patients, 125 were true positives (both GXP MTB detected and AFB culture positive), 32 were true negatives (both GXP MTB not detected and AFB culture negative), 5 were false positives (only GXP MTB detected), and 38 were false negatives (GXP MTB not detected and AFB culture positive). Sensitivity, specificity, PPV, and NPV of GXP in EPTB were 76.68%, 86.48%, 96% and 45.71%, respectively. The sensitivity, specificity, PPV, and NPV of GXP for the diagnosis of TB at each extrapulmonary site are given in Table 4 and Figure 1.

Table 3. Comparing GeneXpert and acid-fast bacilli smear and culture.

No. of cases	GeneXpert only	AFB smear and culture only	Both GeneXpert and AFB culture
Positive	5	38	125
Negative	38	5	32

AFB, acid-fast bacilli; Chi-square test; p-value is <0.00001; the result is significant at p<0.05.

Table 4. Sensitivity, specificity, positive predictive value, and negative predictive value of GeneXpert for the diagnosis of tuberculosis at each extrapulmonary site.

Site	Sensitivity	Specificity	PPV	NPV
Abdomen	85.7	100	100	33.3
Bone	95.4	33.3	91.30	50
Breast	100	Could not be calculated	100	Could not be calculated
CNS	100	Could not be calculated	100	Could not be calculated
Heart	100	Could not be calculated	75	Could not be calculated
Lymph node	70.42	70.58	90.9	36.36
Pleura	63.8	73.3	88.2	39.2
Retropharyngeal space	100	Could not be calculated	100	Could not be calculated
Skin	100	Could not be calculated	100	Could not be calculated

PPV, positive predictive value; NPV, negative predictive value; CNS, central nervous system.

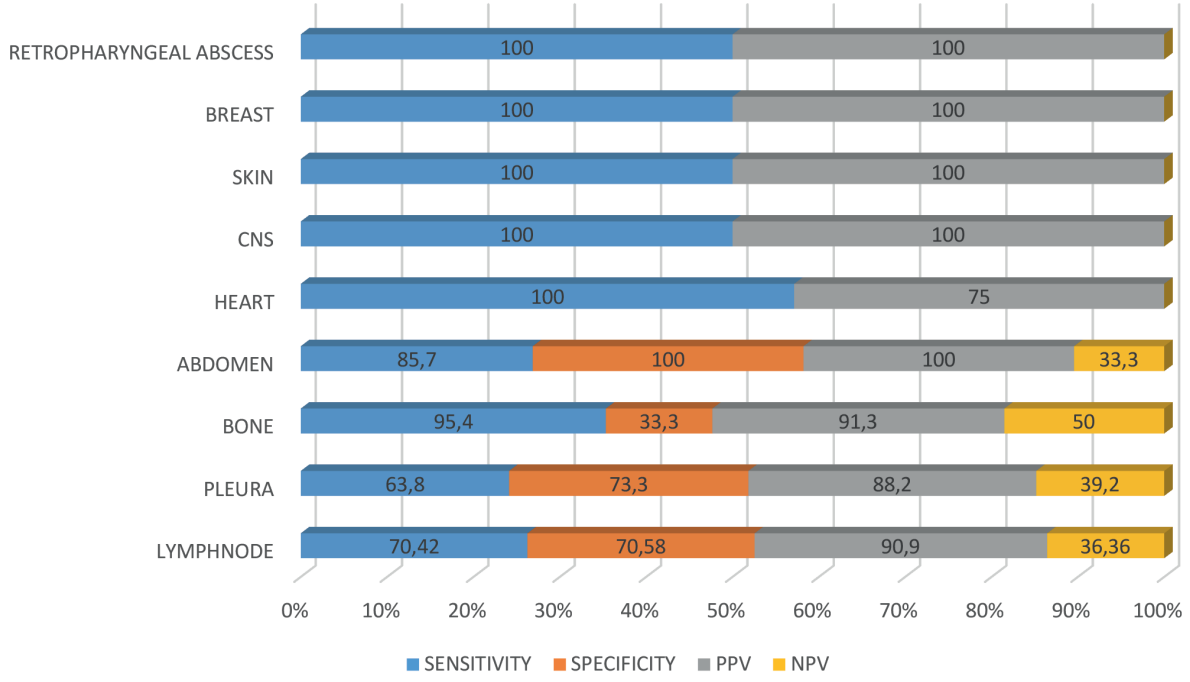

Figure 1. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of GeneXpert for the diagnosis of tuberculosis at each extrapulmonary site.

Discussion and Conclusions

Rapid identification of TB is essential for early treatment and to improve patient outcomes. GXP helps to achieve the same. We discuss results from our study in relation to our study objectives and other similar studies.

In the study by Chander *et al.*, the mean age of patients was 26.67±11.72 years, and most of the patients were in the age group of 15-34 years [9], which was almost similar to our study. In the study by Sankar *et al.* [10], the most common forms were lymph node TB (35%), followed by pleural (20%), bone (10%), and genitourinary (9%). Cerebrospinal, abdominal, skin sites, etc., accounted for the remaining 26% of cases. Similar distribution was observed in our study, with the most common site being the lymph node, followed by the pleura. Cervical lymph nodes were the most common site of involvement and were reported in 60% to 90% patients with or without involvement of other lymphoid tissue, as stated by Mohapatra *et al.* [11], which concurred with our study results.

The GXP is believed to be a "game-changer" in the field of TB diagnostics. In most of the studies, it has been documented that less than 50% compared were diagnostic on GXP where whereas our study documented a higher diagnostic yield of 65% on the GXP test. Ahmed *et al.* in 2014 did a similar study with a total of 100 extrapulmonary samples processed (60 pus, 19 pleural fluids, 16 ascitic fluids, and 5 CSF). Out of these, 37% had MTB detected on the GXP test, 17% were AFB culture positive, and 12 % were AFB smear positive [12]. Avashia *et al.*, in 2016, in their study on comparison of conventional methods with GXP in EPTB, found a diagnostic yield of 37% [13]. The study by Uppe *et al.*, a comparison study of GXP vs. AFB culture in EPTB in 2019, showed that 39.33% of all extrapulmonary samples detected MTB [14]. The most probable reason for this increase in positivity in our study may be due to an increase in the availability of GXP as an upfront test for diagnosis in the current era. In our study sensitivity of GXP was 76.68%, the specificity was 86.48%, the PPV was 96% and the NPV was 45.71%, with respect to culture as a reference standard in EPTB. The results are similar to other studies. In 2019, Mechal *et al.* showed the sensitivity and specificity of GXP to be 79.3% and 90.3% respectively, in EPTB [15]. In the study conducted by Sasikumar *et al.*, the PPV and NPV were 96% and 47% [16]. In a study by Habous *et al.*, of 168 non-respiratory samples, 52 were positive by both culture and GXP, and 9 were detected positive only by culture [17]. In our study, GXP was a false positive in 5 cases. False positivity of GXP results has been reported previously and occurs because of the presence of dead MTB in the test samples, particularly among previously treated patients. There are highly likely chances for such patients to receive avoidable anti-TB therapy. Hence, careful history taking with emphasis on previous treatment with anti-TB drugs is essential to prevent unnecessary treatment of such false positive cases.

Worldwide, TB resistance to anti-bacillary treatments was estimated by WHO in 2017 at 18% in treated cases and 3.5% in new cases. The national anti-TB drug resistance survey from India 2014-2016 showed that RRTB was estimated in 6.19% among all TB patients, with 2.84% among new and 11.60% among previously treated TB patients [18]. The WHO recommended GXP in 2010 for the diagnosis of pulmonary TB and subsequently in 2013 for the diagnosis of EPTB [1]. WHO recommendations for the integration of GXP in the process of TB diagnosis are linked to its short time to results and demonstrated performance (sensitivity and specificity) for both pulmonary TB and EPTB diagnosis. In our study, out of 200 patients, 32 (16%) were rifampicin-resistant. This increased estimate could be due to referral bias to a tertiary care center of majorly difficult-to-treat TB cases. In Sasikumar's study, the sensitivity, specificity, PPV, and NPV of GXP in the diagnosis and detection of rifampicin resistance in EPTB cases were 97%, 95%, 97%, 95%, respectively [16]. In our study, the sensitivity, specificity, PPV, and NPV of GXP in the diagnosis and detection of rifampicin resistance in EPTB cases were 90.32%, 99.24%, 96.55%, and 98.49% respectively, which is similar to the above study. In our study, out of 32 drug-resistant cases, 23 were MDR, 7 were pre-XDR with fluoroquinolone resistance, 1 was pre-XDR with second-line injectable resistance (as per old programmatic management of drug-resistant tuberculosis guidelines), and 1 was XDR TB.

In our study, 60/94 (63.8%) of lymphadenopathy, 29/69 (42%) of pleural effusion, 22/33 (66.6%) of bone TB, 12/20 (60%) of abdominal TB, and 3/5 (60%) of pericardial effusion had MTB detected. But the sites of CNS, cutaneous, breast, and retropharyngeal abscess were fewer in number, as compared to lymph node and pleural TB cases. CNS, cutaneous, various site abscess TB cases need supportive medical and surgical management beyond the conventional therapy for TB, and are usually referred cases. All three cases of CNS TB were GXP MTB detected (100%). This data cannot possibly be analyzed due to the bias of confirmed CNS TB cases only being referred to the Pulmonary Medicine Department, usually for suggestions on the TB treatment regimens. The scenario with skin, breast, and retropharyngeal space TB cases is similar; hence, the analysis of these small numbers of system-wise cases was not done.

The comparison and discussion related to statistics for GXP diagnosis at various other sites are as follows. The study conducted by Sasikumar had sensitivity, specificity, PPV, and NPV of GXP in the diagnosis of lymph node TB cases as 77%, 80%, 95%, 42%, respectively [16]. As per studies by Boehme *et al.*, Armand *et al.*, Causse *et al.*, Tortoli et al, GXP sensitivity in lymph node samples using AFB culture as a reference standard ranged from 50% to 100% [19-22]. In our study, sensitivity, specificity, PPV, and NPV of GXP in the diagnosis of lymph node TB cases were 70.42%, 70.52%, 90.9%, and 36.36% which is similar to the above study. In the study by Meldau *et al.*, GXP in pleural TB showed sensitivity from 58-100% and specificity from 87-100% [23]. However, in our study sensitivity, specificity, PPV, and NPV of GXP in the diagnosis of pleural TB cases were 63.8%, 73.3%, 88.2%, and 39.2%. In the study by Massi *et al.* [24], for bone TB and GXP, the sensitivity value was 100%, the specificity value of 16.6%, the PPV of 35.48%, and the NPV of 100%. In the study conducted by Held *et al.*, the sensitivity of the GXP was 95.6%, the specificity 96.2%, the PPV 97.7% and the NPV 92.6% in spinal TB [25]. However, the sensitivity, specificity, PPV, and NPV of GXP in the diagnosis of bone TB cases in our study were 95.4%, 33.3%, 91.30%, and 50%. In a meta-analysis of 12 studies (699 samples) that tested GXP in abdominal TB and compared the results against culture as a reference standard (10 studies had more than 10 samples), the estimates of sensitivity varied widely and ranged from 42% to 100%. The pooled estimate of sensitivity was calculated as 81.2% [95% confidence interval (CI) 67.7-89.9%]. The pooled specificity was 98.1% (95% CI, 87.0-99.8%) [26]. In our study, the sensitivity, specificity, PPV, and NPV of GXP in the diagnosis of abdominal TB cases were 85.7%, 100%, 100%, and 33.3%. In a study by Saeed *et al.*, pericardial fluid GXP showed high sensitivity (84.3%), specificity (100%), with PPV (100%), and NPV (96.7%) [27]. However, the sensitivity, specificity, PPV, and NPV of GXP in the diagnosis of pericardial TB cases in our study were 100%, 0.00%, 75%, and 0.00%. Studies regarding the above extrapulmonary sites are limited, and the speci-

ficity and NPV could not able to calculated due to the small sample size for the above cases, as there were only true positives.

Our study is an addition to the available literature and calls for data from the WHO on TB. GXP has always been useful for rapid detection of TB and identification of rifampicin resistance, especially in a high-prevalence country like India. Our study reiterates the same. GXP should be used in routine TB diagnosis due to the rapid turnaround time, early diagnosis, and the management of patients with presumptive TB. The test results must always be confirmed by AFB culture and further drug susceptibility tests in clinically discordant and drug-resistant TB cases.

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