

# EPTB diagnosis by GeneXpert MTB/RIF test and its Clinical-epidemiological profile.

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Received: November 2018

Accepted: November 2018

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## ABSTRACT

**Background:** GeneXpert is a novel, automated diagnostic test that can identify Mycobacterium tuberculosis (MTB) DNA and resistance to rifampicin (RIF) rapidly for Extrapulmonary tuberculosis (EPTB). Incidence of EPTB is increasing in low burden settings in comparison to pulmonary tuberculosis (PTB) & EPTB is relatively neglected. Aim: This study is aimed at knowing the incidence of EPTB and rifampicin sensitivity using an automated rapid detection method, GeneXpert. **Methods:** 271 EPTB positive patients were included in this retrospective study during a period from January to July 2018. Details regarding TB diagnosis, rifampicin sensitivity, nature of the sample and patient details including age, sex, occupation, address, habits, past history of TB, HIV status and other clinically relevant information was obtained from hospital and laboratory registers. **Results:** Out of 1290 tuberculosis positive patients, 1019 were of pulmonary tuberculosis (PTB) i.e., 78.9% and remaining 271 were of extrapulmonary tuberculosis (EPTB) i.e., 21.1%. 42.4% (115 out of 271) patients were in the age group of 31-40 years. Female predominance was observed in EPTB patients. Among 271 EPTB patients, 122 (45%) were diagnosed as pleural TB, 95 (35%) patients affected by tuberculosis at lymphnodes, 3(1.1%) had meningeal TB, 9(3.3%) EPTB cases were diagnosed from pus samples of various clinical conditions and remaining 42(15.4%) EPTB cases identified from various samples including tissues, genitourinary, synovial fluid, bones & joints. 247 (91.1%) out of 271 EPTB patients clinical samples showed rifampicin sensitive. 12 (9.8%) out of 122 pleural tuberculosis cases and 5 (5.2%) out of 95 TB lymphadenitis cases showed resistant rifampicin. **Conclusion:** TB can be diagnosed by various methods, among which GeneXpert is a rapid, reliable, easy to operate, automated system. GeneXpert helps physicians by providing rapid diagnosis within 90 minutes, in turn aid to initiate prompt treatment at the earliest.

**Keywords:** Extrapulmonary Tuberculosis, GeneXpert, Rifampicin.

## INTRODUCTION

Extrapulmonary Tuberculosis (EPTB) involving organs other than lungs includes pleura, lymphnodes, abdomen, genitourinary tract, skin, joints and bones or meninges. EPTB is less common than Pulmonary tuberculosis (PTB).<sup>[1]</sup> EPTB usually occurs due to hematogenous dissemination from pulmonary tuberculosis or directly extends from adjacent organ.

Worldwide, TB is one of the top 10 causes of death. According to WHO, in 2017, 10 million people fell ill with TB & 1.6 million died from the disease (including 0.3 million among people with HIV) and also stated that largest number of new TB cases

occurred in the South-East Asia and western pacific regions (62% of new cases) followed by the African region (25% of new cases).<sup>[2]</sup>

EPTB incidence differs from region to region; cause may be no proper definition as few members consider pleural TB as a separate entity, difficulty in detection, poor diagnostic facilities in low resource healthcare settings. Incidence of EPTB is increasing in low burden settings in comparison to pulmonary tuberculosis (PTB) & EPTB is relatively neglected. It poses particular diagnostic and management challenges.<sup>[3]</sup>

Collection of samples from EPTB is difficult because of inaccessible sites, diagnosis is challenging, due to paucibacillary. The sensitivity of diagnostic tests needs to be increase by obtaining appropriate clinical samples. For diagnosis of EPTB, measurement of biochemical markers such as adenosine deaminase or gamma interferon and PCR are more useful adjuncts.<sup>[4]</sup>

Drug susceptibility testing plays a vital role in TB endemic countries like India. DST should be

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performed on the first isolate of Mycobacterium tuberculosis from all patients.

Nucleic acid Amplification Test (NAAT) is a most advanced and reliable test for rapid detection of pathogen and its antibiotic sensitivity. The Xpert MTB/RIF is a cartridge based NAAT for simultaneous rapid tuberculosis diagnosis and rapid antibiotic susceptibility test. It is a novel, automated diagnostic test that can identify Mycobacterium tuberculosis (MTB) DNA and resistance to rifampicin (RIF) rapidly for EPTB.<sup>[5]</sup>

Even in the era of DOTS, MDR TB, EPTB, HIV-TB coinfection continues to be in major public health concern. Scarcity of data and also lack of knowledge on latest tuberculosis technologies gave an impulse to do this study in this tertiary care hospital. This study is aimed at knowing the incidence of EPTB and rifampicin sensitivity using an automated rapid detection method, GeneXpert.

## MATERIALS AND METHODS

A Retrospective study was conducted on EPTB patients during a period from January to July 2018 at RNTCP (Revised National Tuberculosis Control Program) center, Department of Microbiology, Kurnool Medical College, Kurnool.

All Suspected Tuberculosis patient clinical samples were collected from various departments including respiratory and TB Medicine, General Medicine etcetera at Kurnool Medical College, were sent to RNTCP center for diagnosis. All clinical samples were processed by Ziehl-Neelsen stain and GeneXpert for Tuberculosis diagnosis and also for assessment of rifampicin sensitivity.

All clinical samples were processed in GeneXpert according to manufacturer's instructions (Cepheid). A total of 2538 suspected TB samples received during the study period. 271 EPTB positive patients were included in this study.

Details regarding TB diagnosis, rifampicin sensitivity, nature of the sample and patient details including age, sex, occupation, address, habits, past history of TB, HIV status and other clinically relevant information was obtained from hospital and laboratory registers.

Data was entered into spread excel sheet and analyzed. Statistical analysis was done in the form of diagram, numbers and percentages.

## RESULTS

A total of 1290 Tuberculosis positive patients were included in this study. Out of 1290 patients, 1019 were of pulmonary tuberculosis (PTB) i.e., 78.9% and remaining 271 were of extrapulmonary tuberculosis (EPTB) i.e., 21.1%.

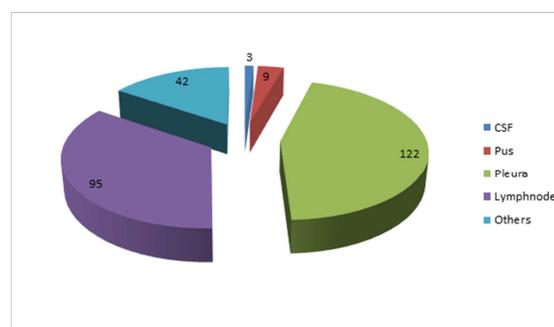
EPTB patients were commonly observed in the age group of 31-40 years. 42.4% (115 out of 271) patients were in the age group of 31-40 years, 211

(77.8%) EPTB patients out of 271 were aged between 20-50 years. Female predominance was observed in EPTB patients. There is no much difference observed in EPTB prevalence among patients hailing from rural & urban areas [Table 1].

**Table 1: Demographic characteristics of Extrapulmonary tuberculosis patients**

Parameters	No. of patients	Percentage (%)
<b>Age in Years</b>		
<20 years	28	10.3
21-30 years	52	19.1
31-40 years	115	42.4
41-50 years	44	16.2
>50 years	32	11.8
<b>Sex</b>		
Male	108	39.8
Female	163	60.1
<b>Community</b>		
Rural	161	59.4
Urban	110	40.5

EPTB refers to tuberculosis involving organs other than lungs. Here in this study, pleura is the most common site affected followed by lymphnode. Among 271 EPTB patients, 122 (45%) were diagnosed as pleural TB, 95 (35%) patients affected by tuberculosis at lymphnodes, 3(1.1%) had meningeal TB, 9(3.3%) EPTB cases were diagnosed from pus samples of various clinical conditions and remaining 42(15.4%) EPTB cases identified from various samples including tissues, genitourinary, synovial fluid, bones & joints [Figure 1].



**Figure 1: Prevalence of various types of Extrapulmonary tuberculosis**

Tubercular meningitis, pleural tuberculosis was predominantly observed in female patients. Mycobacterium tuberculosis isolated from lymphnode sites almost equally distributed in male and female patients [Table 2].

**Table 2: Sex distribution of EPTB patients**

Type of Sample	No. of TB positives	Male	%	Female	%
CSF	3	0	0	3	1.1
Pus	9	6	2.2	3	1.1
Pleura	122	43	15.8	79	29.1
Lymphnode	95	44	16.2	51	18.8
Others	42	15	5.5	27	9.9
Total	271	108	39.8	163	60.1

247 (91.1%) out of 271 EPTB patients clinical samples showed rifampicin sensitive. 12 (9.8%) out of 122 pleural tuberculosis cases and 5 (5.2%) out of

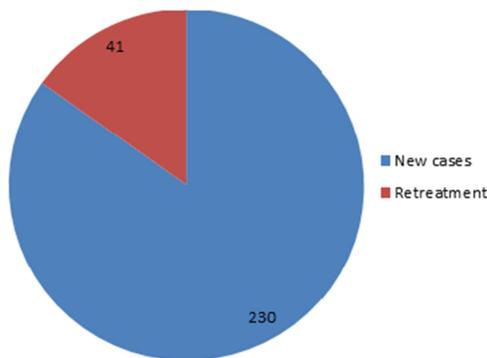
95 TB lymphadenitis cases showed resistant rifampicin [Table 3].

**Table 3: Showing Rifampicin sensitivity among EPTB patients**

Type of Sample	No. of positives	Rifampicin Sensitive		Rifampicin resistance		Rifampicin Intermediate	
		No. of samples	%	No. of samples	%	No. of samples	%
CSF	3	3	100	0	0	0	0
Pus	9	9	100	0	0	0	0
Pleura	122	107	87.7	12	9.8	3	2.4
Lymph Node	95	87	91.5	5	5.2	3	3.1
Others	42	41	97.6	1	2.3	0	0
Total	271	247	91.1	18	6.6	6	2.2

**CSF – Cerebrospinal fluid**

Among 30 out of 271 EPTB patients had HIV infection. 11% HIV-TB coinfection observed among EPTB patients. 84.8% EPTB patients were diagnosed as new cases and 15.1% patients were under retreatment [Figure 2].



**Figure 2: Showing number of new cases and retreatment of EPTB patients**

**DISCUSSION**

NAAT is a most specific and rapid diagnostic test, very useful in special clinical aspects like life threatening condition such as tubercular meningitis, paucibacillary condition. It can detect as few as 10 mycobacteria.<sup>[6]</sup> NAAT is a highly specific, low sensitive test; sensitivity is highly variable among sample type and test methods.<sup>[7]</sup> In India, this test is widely used, commonly known as the CB-NAAT (Cartridge Based Nucleic Acid Amplification Test). The World Health Organization (WHO) in December 2010, endorsed the use of Xpert MTB/RIF for use in TB endemic countries.<sup>[8]</sup> Benefits of Xpert MTB/RIF are reliability, results can be obtained in 90 minutes, minimal biohazard and very little technical training require for operating.<sup>[9]</sup> Disadvantages of this test are shelf life of cartridges is only 18 months, a very stable electricity supply is required, the cost of the test, temperature ceiling is critical.<sup>[10]</sup> EPTB diagnosis is based on identification of bacilli in infected fluid or tissue by microscopic

examination; or culture; or nucleic acid amplification tests; or histopathological evidence; or strong clinical evidence. EPTB diagnosis by Xpert MTB/RIF has an overall sensitivity of 83.1% and a pooled specificity of 98.7%.<sup>[11]</sup> EPTB patients should be evaluated for concomitant PTB, as about 10-50% of EPTB patients have concomitant pulmonary involvement.<sup>[12]</sup>

Conventional smear microscopy is not a reliable test for EPTB samples, as negative results cannot exclude the presence of TB, has a low sensitivity of 0-40% mycobacterial culture is a slow diagnostic test usually takes 2-8 weeks and the yield may vary from 30% up to 80%.<sup>[13]</sup>

In the present study, out of 1290 tuberculosis patients, 1019 were of pulmonary tuberculosis (PTB) i.e., 78.9% and remaining 271 were of extrapulmonary tuberculosis (EPTB) i.e., 21.1%. The incidence of EPTB varies from one place to another; maybe due to poor clinical assessment, inaccessible site, no proper diagnostic facilities. In India, at tertiary care centers it varies between 30% and 53%.<sup>[14]</sup>

As per this study, 42.4% (115 out of 271) patients were in the age group of 31-40 years, 211 (77.8%) EPTB patients out of 271 were aged between 20-50 years. Female predominance was observed in EPTB patients. In similar to the present study, EPTB most commonly noticed between 20-40 years by another study.<sup>[15]</sup> Chang-Yeung M et al,<sup>[16]</sup> did a study in Hong Kong on sex differences in tuberculosis stated that female preponderance among EPTB cases. Pooja Singh Gaur et al,<sup>[17]</sup> also observed more number of EPTB positives among females when compared to males.

Among 271 EPTB patients, 122 (45%) were diagnosed as pleural TB, 95 (35%) patients affected by tuberculosis at lymphnodes, 3(1.1%) had meningeal TB, 9(3.3%) EPTB cases were diagnosed from pus samples of various clinical conditions and remaining 42(15.4%) EPTB cases identified from various samples including tissues, genitourinary, synovial fluid, bones & joints in this study.

In Similar to this study, Pooja Singh Gaur et al,<sup>[17]</sup> documented that pleural tuberculosis was the most common presentation (54.7%) followed by

lymphnodes (34.9%), genitourinary (5.55%), abdominal (3.6%) and CNS (1.1%). Chander vishav et al,<sup>[18]</sup> and Prakash SR et al,<sup>[14]</sup> also observed pleural tuberculosis is the most common type of EPTB [Table 4].

**Table 4: Comparison of EPTB prevalence among various studies**

Site	Present study	Pooja Singh Gaur et al, <sup>[17]</sup>	Chander vishav et al, <sup>[18]</sup>	Prakash SR et al, <sup>[14]</sup>
Pleura	45	54.7	61.6	28.03
Lymphnode	35	34.9	23.2	24.81
CNS	1.1	1.1	-	12.5
Abdomen	-	3.6	9.3	9.6
Genitourinary	-	5.5	-	-
Pus	3.3	-	-	-
Others	15.4	-	-	12.69
Bones & Joints	-	-	-	12.31

A Study from south India, Cailhol J et al observed there is an increase in EPTB prevalence among HIV-infected patients.<sup>[19]</sup> In HIV-Positive patients, EPTB accounts for more than 50 percent of all cases of Tuberculosis. The risk of tuberculosis increases as immunosuppressive progresses.<sup>[20,21]</sup> HIV infected persons are at increased risk for primary or reactivation tuberculosis and for second episodes of tuberculosis from exogenous reinfection.<sup>[22,23]</sup> For Pulmonary tuberculosis and Extrapulmonary tuberculosis mainstay of management is Antituberculous treatment. Under RNTCP according to DOTS (Directly Observed treatment Short course) approach, management of EPTB patients under category I & III. Category I for severe form of EPTB cases and less severe forms of EPTB are considered under Category III.<sup>[24]</sup> Paradoxical reactions are more common in EPTB when compared to PTB. To exclude paradoxical reactions, there is a great need to know Drug Resistant EPTB prior to start Antituberculosis treatment.

247 (91.1%) out of 271 EPTB patients clinical samples showed rifampicin sensitive. 12 (9.8%) out of 122 pleural tuberculosis cases and 5 (5.2%) out of 95 TB lymphadenitis cases showed resistant rifampicin as per this study. Boonsarngsuk V et al,<sup>[25]</sup> documented prevalence of Isoniazid, Rifampicin and Multidrug resistant EPTB (MDR EPTB) were 7.8%, 0.5% & 0.5% respectively. They also stated that DR is lower than those of PTB and previous history of Tuberculosis and use of steroids or immunosuppressive drugs were also associated with Rifampicin and MDR TB in multivariate analysis.

## CONCLUSION

Pleura, the most common organ affected by Tuberculosis followed by lymphnodes. EPTB was

predominantly observed among middle aged persons and females. 6.6% of EPTB patients had rifampicin resistant bacilli. TB can be diagnosed by various methods, among which GeneXpert is a rapid, reliable, easy to operate, automated system. GeneXpert helps physicians by providing rapid diagnosis within 90 minutes, in turn aid to initiate prompt treatment at the earliest.

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**How to cite this article:** Devi AR, Kumari SS, Surekha A. EPTB diagnosis by GeneXpert MTB/RIF test and its Clinical-epidemiological profile. *Ann. Int. Med. Den. Res.* 2019; 5(1): MB01-MB05.

**Source of Support:** Nil, **Conflict of Interest:** None declared