VOLUME - 14, ISSUE - 04, APRIL - 2025 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Microbiology

DIAGNOSTIC UTILITY OF GENEXPERT MTB/RIF ASSAY IN THE DETECTION OF MYCOBACTERIUM TUBERCULOSIS FROM CLINICALLY SUSPECTED CASES OF TB MENINGITIS IN A TERTIARY CARE HOSPITAL

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ABSTRACT Tuberculous meningitis (TBM) is one of the most severe forms of Tuberculosis. The aim of the study was to evaluate sensitivity of GeneXpert MTB/RIF (CBNAAT) test in clinically suspected cases of TBM in comparison with MGIT culture, the gold standard test. This study was carried out in the TB Culture & DST Laboratory, Department of Microbiology of a tertiary care Hospital. A total of 741 CSF samples from clinically suspected cases of TBM were simultaneously subjected to CBNAAT and liquid culture using MGIT 960 system in which 46 (6.21%) tested positive and 695 (93.79%) tested negative on CBNAAT while in MGIT culture, 44 (5.94%) samples showed positive growth, 696 (93.93%) were negative and 1 (0.13%) was contaminant. Out of the 46 samples positive on CBNAAT, 7(15.22%) were RIF resistant, 37(80.44%) RIF sensitive and 2 (4.34%) were RIF indeterminate. Out of the total 741 samples tested on CBNAAT and MGIT culture, 24(3.24%) and 674 (90.96%) tested positive and negative by both tests respectively. However, in 22 (2.97%) samples, CBNAAT was positive while MGIT culture was negative and 20 (2.70%) samples showed vice versa results. Xpert MTB/RIF showed sensitivity of 54.54% and specificity of 97.11%. The positive and negative predictive value for Xpert MTB/RIF was 54.54%, and 97.11% respectively. Diagnostic accuracy of Xpert MTB/RIF in comparison to MGIT culture was 94.07%. Although, Gen IV Xpert MTB/RIF is a rapid method for diagnosing MTB, its limit of detection is 131 CFU/mL vis-a-vis Xpert MTB/RIF Ultra is 16 CFU/mL. As, TBM is a paucibacillary infection, the use of Xpert MTB/RIF Ultra in place of Gen IV Xpert MTB/RIF assay could substantially increase the chances of diagnosing TBM in an effective manner.

KEYWORDS : TBM, CBNAAT, Xpert MTB/RIF Ultra

INTRODUCTION

According to the Global Tuberculosis report 2024 of World Health Organization (WHO), TB is the world's leading cause of death from a single infectious agent and caused almost twice as many deaths as HIV/AIDS, although during the COVID-19 pandemic, it was replaced by coronavirus disease. More than 10 million people fall ill with TB every year and the numbers have been rising since 2021.Globally in the year 2023, TB caused an estimated 1.25 million deaths. Drug-resistant TB continues to be a public health threat. Resistance to rifampicin, the most effective first-line drug has been the greatest concern. In 2023, the estimated proportion of people with TB who had MDR/RR-TB amongst new cases was 3.2% and 16% amongst those previously treated. (1,2)

Tuberculous meningitis (TBM) is one of the most severe forms of Tuberculosis. TBM occurs when the membranes and fluid surrounding the brain and spinal cord are invaded by Mycobacterium tuberculosis. Without appropriate treatment, the disease invariably progresses, resulting in neurological impairment, CNS damage and often death. Globally, TBM represents approximately 5% of all extra-pulmonary TB (EPTB) cases. To diagnose TBM is more difficult than other forms of bacterial meningitis, as unlike TBM, symptoms with classic bacterial meningitis generally develop suddenly. Also, TB produces a paucibacillary infection that is difficult to detect in cerebrospinal fluid (CSF). (3)

Ziehl-Neelsen (ZN) microscopy staining of CSF is the most widely done rapid diagnostic technique with a low sensitivity of 20% for TBM. (4,5) Liquid culture methods, including the mycobacterial growth indicator tube (MGIT; BACTEC) and the mycobacterial observation drug susceptibility assay (MODS) culture offer improved sensitivity of almost 60%.(6) The clinical value of culture methods is limited as it takes 1 to 4 weeks for tests to turn positive, and negative results cannot be used to confirm an exclusion of TBM.(6) Amongst the wide array of nucleic acid amplification tests (NAAT), the GeneXpert MTB/RIF test (Cepheid), a closed-cartridge based system was approved by the WHO in 2010 for the diagnosis of pulmonary tuberculosis.(7,8)

The test is based on a real-time heminested PCR method which detects the presence of M. tuberculosis complex bacilli (9). By using 5 molecular beacons which span the rpoB gene 81-base pairs rifampicin resistance-determining region (RRDR), the test simultaneously determines susceptibility to Rifampicin, which can be used as a surrogate marker for multidrug resistance (MDR) (9). The closed-cartridge based system makes it possible for the test to be used outside the laboratory environment, and studies assessing biosafety have suggested that the use of Xpert MTB/RIF assay carries a smaller biohazard risk than smear microscopy (10). The risk of cross-contamination is also reduced with the closed cartridge-based system (10). The test has shown a sensitivity of above 90% for culture positive tuberculosis, with high specificity in sputum samples. (11,12,13)

Several studies have reported successful use of the Xpert MTB/ RIF test on extrapulmonary samples, with overall sensitivities of over 80% and specificity reaching up to 100% (14,15,16,17,18). As there is urgency of diagnosis in suspected cases of TBM because of rapid decrease in survival chances with the increase of severity (mortality for grade 1 patients is approximately 20%; for grade 3 it reaches 55% [19]), a rapid and accurate diagnostic test which is also able to identify Rifampicin resistance can have a great impact on survival.

The present study was thus aimed at evaluating the proportion of GeneXpert MTB/RIF test positivity in clinically suspected cases of TB Meningitis in comparison with MGIT, the gold standard diagnostic test.

MATERIALS AND METHODS

A total of 741 CSF samples were analysed for a period of 18 months from July, 2023 to December, 2024 in this cross-sectional, retrospective study carried out in the TB Culture & DST Laboratory, Department of Microbiology of a tertiary hospital.

Specimen

Cerebrospinal fluid

Inclusion Criteria

CSF (more than 0.1 ml) from clinically suspected cases of TBM

Specimen Collection And Processing

Aseptically collected CSF sample by lumbar puncture from clinically suspected cases of tuberculous meningitis were received at TB Culture & DST Laboratory. The sample was simultaneously subjected to Gen IV Genexpert MTB/RIF assay and liquid culture using MGIT 960 system.

RESULTS

A total of 741 clinically suspected cases of TBM were included in the study. The age group of the patients in the study ranged from 0 to 65 years and above. The most common age group affected was 0 to 14 years (18.08%) followed by 15 to 24 years (17.13%). (Table 1) Of the total cases, maximum were males, 391(52.76%) followed by females, 350(47.23%).

Table1: Age Wise Distribution Of Cases Of TBM (n=741):

Age group (years)	No. of cases	Percentage%
0-14	134	18.08
15-24	127	17.13
25-34	99	13.36
35-44	118	15.92
45-54	80	10.79
55-64	78	10.52
65 and above	105	14.17

Of the total 741 samples tested on Xpert MTB/RIF, 46(6.21%) samples tested positive and 695 (93.79%) tested negative. Amongst the 46 samples detected, maximum, 31 (67.39%) showed low bacillary load followed by 14 (30.43%) which showed very low bacillary load. (Table 2)

Table 2: Results of Xpert MTB RIF testing (n=741):

Results	Total no of samples			Percentage (%)
MTB detected	Very low	Low	Medium	6.21
	14	31	1	
MTB not detected	695			93.79

Out of the 46 samples detected on Xpert MTB/RIF assay, maximum, 31(67.39%) showed low bacillary load followed by very low bacillary load, 14(30.43%).

Amongst the samples with very low bacillary load, 7(50%) showed growth in MGIT culture and 7(50%) showed no growth while amongst the samples showing low bacillary load, 16(51.61%) and 15(48.39%) showed growth and no growth respectively in MGIT culture. (Table 3)

Table 3: Diagnostic performance of Xpert MTB/RIF based on Bacillary Load

	MGIT culture		
Xpert MTB/RIF	Bacillary load	MTB grown	MTB not grown
	Very Low	07	07
	Low	16	15
	Medium	01	00
	High	00	00

Similarly, out of the total 741 samples inoculated in MGIT culture, 44 (5.94%) samples showed positive growth, 696(93.93%) showed negative growth and 1 (0.13%) sample was contaminant. (Table 4)

Table 4: Results of MGIT culture testing (n=741):

Results	Total no of samples	Percentage (%)
MTB grown	44	5.94
MTB not grown	696	93.93
Contaminant grown	01	0.13

Of the 46 samples which tested positive on Xpert MTB/RIF assay, 7 (15.22%) showed Rifampicin resistance, 37 (80.44%) showed Rifampicin sensitive and 2 (4.34%) showed Rifampicin indeterminate results. (Table 5)

Table 5: Results of Rifampicin resistance on Xpert MTB/RIF testing (n=46):

Result of Rifampicin resistance	Total no. of samples	Percentage (%)
Detected	7	15.22
Not detected	37	80.44
Indeterminate	02	4.34

Of the total 741 samples tested on Xpert MTB/RIF and MGIT culture, 24(3.24%) tested positive by both tests. However, in 22 (2.97%) samples, Xpert MTB/RIF was positive while MGIT culture was negative. 674 (90.96%) samples were detected negative by both tests and 20 (2.70%) were negative on Xpert MTB/RIF but positive in MGIT culture. (Table 6)

Table 6: Comparison of Xpert MTB/RIF and MGIT culture results:

Xpert MTB/RIF	MGIT culture			
	MTB grown	MTB not grown	Contaminant	Total
MTB detected	24 (3.24%)	22 (2.97%)	00(0.00%)	46
MTB not detected	20 (2.70%)	674 (90.96%)	01 (0.13%)	695
Total	44	696	01	741

Table 7 shows the sensitivity and specificity of Xpert MTB/RIF as 54.54% and 97.11% respectively. The positive predictive value (PPV) for Xpert MTB/RIF was reported as 54.54%, and the negative predictive value (NPV) was 97.11%. Diagnostic accuracy of Xpert MTB/RIF in comparison to MGIT culture as the gold standard given was 94.07%.

Table 7: Diagnostic accuracy of Xpert MTB/RIF in comparison to MGIT Culture:

Characteristic	Value
Sensitivity	54.54%
Specificity	97.11%
Positive predictive value	54.54%
Negative predictive value	97.11%
Accuracy	94.07%

DISCUSSION

Tuberculous meningitis is a type of extra-pulmonary TB and has the potential to be lethal and it is the most devastating consequence of infection with Mycobacterium tuberculosis. Approximately a third of patients die soon after presenting to hospital, and many of those surviving are left with severe neurological sequelae. (22, 23, 24) TBM progresses quite rapidly, leading to severe complications like hydrocephalus, cerebral infarction, and cranial nerve palsies. Improved patient outcomes and efficient management depend on early and accurate diagnosis. Detecting meningitis in clinically suspected cases of TBM is a challenge due to the paucibacillary nature of this disease presentation in patients and the availability of minimal sample volumes of CSF. (25)

In this study, we observed a total positivity of 6.21% using the GeneXpert MTB/RIF assay. A study conducted by Sharma et al (25) showed 10.3 % positivity on CBNAAT. While Iqbal et al reported 9.78% of positivity of clinically presumed TBM cases for MTB by Gene Xpert MTB/RIF assay. (26)

In this study, MGIT culture positivity was 5.94 % which is similar to a study reported by Sharma et al which showed 6.98% culture positivity. (25) However, it is lower than a study from Varanasi, India, by Rai et al. which showed 27.3% culture positivity. (27)

Maximum numbers of patients were in 0-14 years of age group i.e. 134 (18.08%) which is comparable with a study conducted by Guneet et al, while Shetty et al reported maximum patients in 41-60 years of age group. (28,29)

In our study slightly more than half, 52.76% were male and 47.23% were female patients which is similar to a study done by Iqbal et al in which 51% were male and 49% were female patients. (26) While a study conducted by Sundar et al showed 64% patients were males while females comprised of 36%. (30) In this study, 15.90% (7) Rifampicin resistance was detected by GeneXpert MTB/RIF assay, which is comparable with another Indian study from Rajasthan which showed 13% resistance to rifampicin. (25) Detection of presence of antibiotic resistance is important to start the treatment for the management of disease. In a study by Kamboj et al (2023) on CSF samples in 132 participants, out of 63 confirmed TB cases, only 7(11.11) cases exhibited rifampicin resistance. (31) This is crucial for understanding the prevalence of drug resistance, which can help in selecting the most appropriate treatment strategy for managing the condition effectively.

Sensitivity of CBNAAT in CSF has been variable among various studies. The pooled sensitivity of CBNAAT in CSF in a meta-analysis was 80.9%. (32) Other studies showed sensitivity ranging from 38.6 % to 68.42%. The sensitivity of CBNAAT in our study was 54.54.% which is comparable with results of other studies depicted in the following table.

Table 8: CSF CBNAAT for diagnosis of Tuberculous meningitis:

Name of study	Sensitivity %	Specificity %	PPV %	NPV %
Present study	54.54	97.11	54.54	97.11
Rai et al (27)	40	92.5	66.78	80.4
Iqbal et al (26)	63	100	100	93.6
Rathod et al (33)	68.42	97.6	92.85	87.23
Singh et al (34)	38.6	100	-	-
Shetty et al (29)	27.90	-	-	-
Sundar et al (30)	14%	-	-	-

In 22 (2.97%) samples, Xpert MTB/RIF was positive while MGIT culture was negative. This may occur due to loss of viability of MTB in patients under treatment. Out of 44 cases detected by MGIT culture, 20 isolates were not detected by GeneXpert MTB/RIF assay may be due to the low sensitivity of Gen IV Xpert MTB/RIF assay (Limit of detection is 131 CFU/mL) as compared to liquid culture (Limit of detection is 60 CFU/mL). A study conducted by Shao et al to evaluate the performance of Xpert ultra for detection of tubercle bacilli in CSF reported that the sensitivity of Xpert Ultra for CSF sample is more than that of MGIT culture. (35)

CONCLUSION

Definitive diagnosis by culture and demonstration of organisms takes weeks to months but Gene Xpert MTB/RIF assay is an effective, simple and rapid method which gives results in hours to diagnose MTB and detection of rifampicin is an added advantage. TB Meningitis requires rapid diagnosis. Although, Gen IV Xpert MTB/RIF is a rapid method for diagnosing MTB, its limit of detection is 131CFU/mL vis-a-vis Xpert MTB/RIF Ultra is 16 CFU/mL. As, TBM is a paucibacillary infection, the use of Xpert MTB/RIF Ultra in place of Gen IV Xpert MTB/RIF assay could substantially increase the chances of diagnosing Tuberculous meningitis in an effective manner.

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