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Study of rapid detection of Mycobacterium Tuberculosis through GeneXpert MTB/RIF assay from acid fast bacilli smear-negative specimens in a Tertiary Care Hospital, Biratnagar Nepal.

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ABSTRACT

Introduction: Tuberculosis (TB) is an important public health concern around the world. It is well known that acid-fast bacilli (AFB) smear-negative TB cases are a major source of spreading TB to others when left untreated.

Objectives: Our study aim to detect Mycobacterium tuberculosis (MTB) in AFB smear-negative samples through GeneXpert MTB/RIF assay and also to evaluate the drug resistance patterns towards Mycobacterium tuberculosis in hospitals.

Methodology: This descriptive cross-sectional study was conducted among smear-negative presumptive TB patients at a tertiary care center with effect from September 2022 to September 2023 after approval from the Institutional Review Committee of the college. A convenience sampling method was used.

Results: Out of 653 smear-negative samples, 71 (10.9%) were positive for TB and 17 (2.6%) were rifampicin resistance cases detected by GeneXpert MTB/RIF assay. The cases of tuberculosis were more in age groups between 46->60 years and least in 17-30 years of age. Pulmonary samples yielded a higher number of MTB 66 (92.95%) as compared to extra-pulmonary samples 5 (7.04%). There is an almost equal proportion of mycobacterium infection in males 37(52.11%) and females 34(47.88%). All the rifampicin resistance cases detected in our study were from pulmonary samples.

Conclusion: Our study shows that the sensitivity of GeneXpert MTB/RIF assay is higher than AFB smear microscopy. We are missing actual TB cases while using AFB smear microscopy only. Hence the GeneXpert MTB/RIF assay is important for the rapid detection of MTB in smear-negative as well as smear-positive drug resistance MTB cases.

INTRODUCTION

The world's deadliest illness, tuberculosis (TB) is highly contagious, airborne, and a major public health threat caused by Mycobacterium tuberculosis. In Nepal, every day around 180 people become ill with this preventable and curable disease and 15 people lose their lives due to TB. Around the globe TB is an important public health issue causing chronic infectious disease due to a lack of inaccessible and advanced diagnostic techniques. [1] The most common ways that TB is spread are by sneezing and coughing, and it is one of the oldest illnesses that humans have been aware of. Although it mostly affects the lungs (pulmonary TB), extrapulmonary TB can also affect other parts of the body. Patients with TB who also have other diseases are more likely to die than those with just TB. The illness is chronic and patients present with persistent cough with or without expectoration, intermittent fever, loss of appetite, weight loss, chest pain,

and hemoptysis.[2] The epidemiological situation, risk factors, and other related abnormalities all have a role in TB death cases. Diabetes, cancer, heart disease, and bacterial infections are the most important factors that might cause TB sufferers to pass away. HIV/AIDS patients have been proven to present obstacles in the microscopic diagnosis of pulmonary TB (PTB), and the majority of the literature has revealed that HIV/AIDS is associated with low sputum smear positivity.[3] The health sectors in developing countries over-relying on clinical presentation, chest radiographs, and sputum smear microscopy for diagnosis of tuberculosis have only a sensitivity of 50%.[4] Nearly half of Nepal's population has TB, making it one of the top ten main causes of morbidity and mortality. Every year, 42000 Nepalese people contract a new case of TB and 5500 of them lose their life.[5] In Nepal, the prevalence of TB is estimated to be 241 per 100,000 people, with an incidence rate of 163 per 100,000. The Nepal Tuberculosis Programme (NTP) recorded 8,367 sputum smear-negative cases and 17,788 sputum smear-positive cases in 2012–2013. [6]

Smear microscopy is rapid but it is low sensitivity with a detection limit of 10,000 bacilli/ml of sputum. [7] GeneXpert MTB/RIF assay is one of the most advanced, reliable, and rapid methods and the sensitivity and specificity of GeneXpert MTB/RIF assay for the detection of TB bacilli are 88% and 99% respectively.[7,8] The detection limit of GeneXpert is about 131bacilli/ml of specimen. [7] But, still Mycobacterial culture is considered the gold standard.[9,10]

Hence, our study was aimed to detect MTB in AFB smear-negative samples through GeneXpert MTB/RIF assay and also to evaluate the drug resistance patterns of mycobacterium tuberculosis in hospitals.

METHODOLOGY

This descriptive cross-sectional study was conducted among smear-negative but presumptive TB patients based on signs and symptoms of tuberculosis given by patients in the Department of Microbiology at Nobel Medical CollegeTeaching Hospital, Biratnagar, Nepal with effect from September 2022 to September 2023 after approval from the Institutional Review Committee(Ref:IRC-NMCTH651/2022) of the college. Convenient sampling was done and sample size (n) was calculated as:

$n = z^2pq/e2$

$n = (1.96)^2 \times 0.416 \times 0.584/(0.05)^2 = 374$

Where, Z = 1.96 at a 95% confidence interval

n = sample size

p = prevalence [11], 416/100,000 = 0.416

q = 1-p= 0.584

e = margin error, 5%= 0.05

The sample size was calculated to be 374. However, a total of 653 patients were enrolled. Inclusion criteria for this study were suspected cases of pulmonary and extrapulmonary tuberculosis of ≥ 15 years population based on signs and symptoms suggestive of TB or with a chest X-ray showing abnormalities suggestive of TB.[5] Smear-positive samples, samples received without clinical history, sputum mixed with saliva and patients with a history of HIV were excluded from our study. For pulmonary TB two sputum specimens- spot and early morning sputum and extrapulmonary sample like pleural, ascetic, synovial fluid and CSF collected were submitted to the microbiology laboratory. Spot sample (collected on the same day under supervision) and early morning sample (collected on the next day).[7] Both male and female patients aged >15 years suspected to have tuberculosis having at least 2 samples negative for AFB underwent same-day for GeneXpert MTB/RIF assay according to manufacturer's instruction of GeneXpert MTB/RIF assay.[12,13] If failed to give an early morning sample then a spot sample was used. The volume of the specimen not less than 2 ml was considered optimum for processing, else rejected.

The collected data were analyzed using a statistical package for the social science for Windows(SPSS) version 20.

RESULTS

The study included 653 smear-negative samples that were subjected to the GeneXpert MTB/RIF testing. Among the included smear-negative cases, 71 (10.9%) were positive for MTB, of which 17 (2.6%) had rifampicin resistance. (Fig-1, 2)

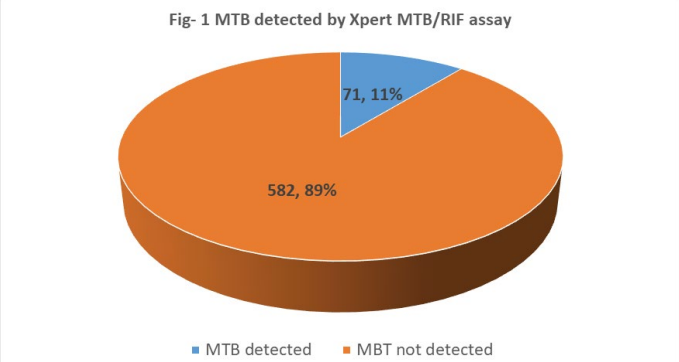

Fig 1: MTB detected by Xpert MTB/RIF assay

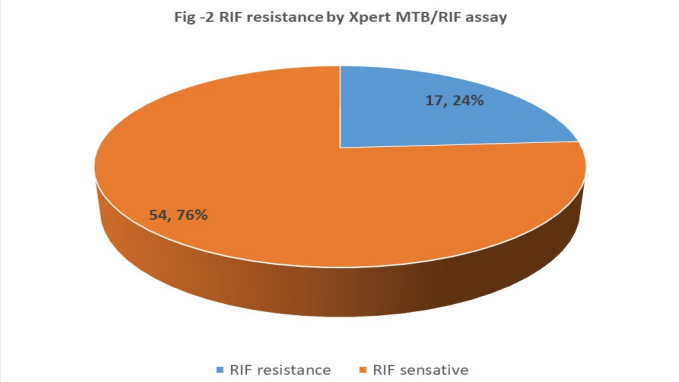

Fig 2: RIF resistance by Xpert MTB/RIF assay

The cases of tuberculosis were more in age groups between 46->60 years and least in 17-30 years of age. (Table 1)

Table 1: MTB detected according to age groups

Age groups(years)	Xpert MTB/RIF assay		Total
	MTB detected	MTB not detected	
17-30	11	68	79
31-45	14	121	135
46-60	23	137	160
>60	23	255	278
Total	71	582	653

Among the various clinical samples,pulmonary samples(Sputum 65, BAL1) yielded a higher number of MTB 66(92.95%)as compared to extra-pulmonary samples (pleural fluids 2, ascetic fluids 1, synovial fluid 1, CSF 1) 5 (7.04%) (Table 2)

Table 2: MTB detected from various clinical samples

Types of samples	Xpert MTB/RIF assay		Total
	MTB detected	MTB not detected	
Extra-pulmonary sample	5(7.04%)	26	31
Pulmonary samples	66(92.95%0	556	622
Total	71	582	653

Table 3 showed an almost equal proportion of mycobacterium infection in males 37 (52.11%) and females 34 (47.88%). Rifampicin resistance cases were detected from pulmonary samples only i.e. 17 (23.94%) and not from extra-pulmonary samples.

Table 3: Gender-wise cases of tuberculosis and RIF resistance cases

Gender	Xpert MTB/RIF assay		Total
	MTB detected	MTB not detected	
F	34(47.8%)	298	332
M	37(52.1%)	284	321
Total	71	582	653

The higher number of TB cases were from the Morang district 27 followed by Sunsari 14, Jhapa 11 ascompared to other districts. Table 4

Table 4: District-wise cases of tuberculosis

Address	Xpert MTB/RIF assay		Total
	MTB detected	MTB not detected	
Bhaktapur	0	2	2
Bhojpur	1	7	8
Dhankuta	1	12	13
Dhanusha	1	2	3
Ilam	0	19	19
India	1	2	3
Jhapa	11	76	87
Khotang	1	6	7
Lalitpur	0	2	2
Makwanpur	0	2	2
Morang	27	256	283
Panchthar	3	3	6
Sankhuwasabha	3	2	5
Saptari	3	21	24
Sindhuli	0	1	1
Siraha	4	25	29
Solukhumbu	0	2	2
Sunsari	14	104	118
Taplejung	0	1	1
Taplejung	0	4	4
Tehrathum	0	13	13
Udaipur	1	19	20
Total	71	582	653

DISCUSSION

In order to break the TB disease transmission chain, early TB diagnosis is crucial. Untreated AFB smear microscopy-positive TB patients are well recognized as the main source of TB transmission to healthy people. Our investigation revealed that roughly 11% of TB disease transmission is caused by TB suspects with negative AFB smear microscopy results, hence the risk of disease transmission by AFB-negative patients to healthy individuals could not be ignored.

The rapid diagnosis of tuberculosis and detection of rifampin (RIF) resistance is essential for early disease management. The GeneXpert MTB/RIF assay is a novel integrated diagnostic device for the diagnosis of tuberculosis and rapid detection of rifampin resistance in clinical specimens. So the main aim of this study was to perform the GeneXpert MTB/RIF assay to diagnose the tuberculosis cases and also detect the rifampin resistance in smear-negative pulmonary and extrapulmonary samples taken from suspected cases of tuberculosis.

Among the enrolled total of 653 smear-negative cases, 71

(10.9%) were positive for MTB, and 17 (2.6%) were rifampicin resistance cases detected by GeneXpert MTB/RIF assay. This result is much lower ascompared to the study conducted by Moure R et al.and Lama C et al. [13,14] The present study shows the cases of tuberculosis were maximum from age of more than 46 years of age. This was similar to the study done by Lama C in Thimi Bhaktapur Nepal.[14] This age group is more active and mobility is more common and chances of exposure to infection are high. Which supports the evidence of acquiring infection in this age group.

The present study showed that the sensitivity of Xpert MTB/RIF for diagnosis of pulmonary tuberculosis is lower as compared to other studies, while the sensitivity was higher in other in other study from smear-negative cases for diagnosis of pulmonary tuberculosis.[15] In our study the cases of tuberculosis were all most same in both males 52.11% and females 47.8% which is not similar to the study done by Khadka P et al in Nepal and Kabir S et al in Malaysia. [1,16] It was found that both males and females were equally exposed to cases of tuberculosis. In a study conducted by Boehme CC et al.[17] the prevalence of tuberculosis from smear-negative was 90.2% which was much higher as compared to our study with prevalence of 11% only.

The rifampicin-resistant Mycobacterium tuberculosis was 17 (23.94%) in pulmonary and not from extra-pulmonary infections. This result was higher as compared to the study done by Shrestha P et al in Nepal 2018.[18] The GeneXpert MTB/RIF assay can improve diagnosis without a doubt, but it cannot replace clinical judgment, mycobacterial culture, and AFB smear microscopy.[19,20] We found relatively fewer cases of RIF resistance 17(23.94%) as compared to the study conducted by Iran ullah et al where 72 (72%) specimens were susceptible to RIF while 28 (28%) were resistant as per the Xpert MTB/RIF assay. Possible reasons for these differences could be sample size, methodology for selection of suspected DR-TB patients, and geographical location.[21] The study by Rimal Raksha et al in Bhaktapur Nepal in 2016 by showed 162 smear-negative samples, 35 (21.6%) were confirmed to have MTB by culture, and 31 (19.1%) by GeneXpert MTB/RIF assay. Of 31 GeneXpert-positive samples, 25 (80.6%) were susceptible, 4 (12.9%) were resistant. But this finding was not similar to our study finding. [22] The current study showed 10.9% were positive forMTB which was less as compare to study done by Shrestha P et al in Lalitpur area of the Kathmandu valley showed 55 (21.32%) were positive for MTB 21.32% (n=55/258).[23] The study done by Subedi S et al in Sitapaila Kathmandu Nepal showed that among the total of 208 patients, 60 (28.85%) were MTB positive of which 2 (3.33%) were MDR-TB which was higher to our result.[24] Ghulam R et al. demonstrated significantly higher sensitivity of GeneXpert assay for the detection of MTB (28.57%). This was not comparable to our study, where MTB was detected (11%) using the gene Xpert MTB/RIF assay. Whereas the culture technique (34.52%) which is regarded as the gold standard for MTB diagnosis—takes a longer time to develop MTB growth colonies and cannot simultaneously detect RIF/DR. The Xpert MTB/RIF assay will unquestionably increase the rate of MTB bacterium detection when used in conjunction with rapid MTB culture.[25] Our study supports previous research that found gene Xpert MTB/RIF assay to be beneficial for smear-negative patients in underdeveloped nations.[26,27] The study done by Agrawal M et al showed that the smear-negative sample's sensitivity and specificity of GeneXpert MTB/RIF assay is 79.1% and 93.1% that do not correlate with our finding. [20] GeneXpert does not replace the requirement for standard microscopy, culture, and anti-tubercular drug sensitivity, which are necessary to track the course of treatment and identify drug resistance to substances other than rifampicin.

CONCLUSIONS

The sensitivity and specificity of GeneXpert MTB/RIF assay for diagnosis of TB is much higher as compared to AFB smear microscopy. We are missing actual TB cases while using AFB smear microscopy only. Hence the GeneXpert MTB/RIF assay should be considered as important technique for the rapid detection of MTB in smear-negative cases and also detects rifampicin resistance in patients with MDR. But still, mycobacterial culture is considered a gold standard for the diagnosis of TB.

RECOMMENDATIONS

By relying solely on AFB smear microscopy, we are failing to detect real TB patients. Therefore, it is recommended to perform the GeneXpert MTB/RIF assay to quickly identify MTB in smear-negative cases and to assess the drug resistance profile of Mycobacterium tuberculosis. We recommend starting TB treatment based on the results of the Xpert MTB/RIF assay in Nepal.

LIMITATION

The result could not be generalized to another area because the study was conducted in an urban population and therefore, it may not apply to the whole population of Morang. We could not perform the phenotypic DST and line probe assay for all gene Xpert MTB/RIF positive samples. If achievable, it might be possible to detect a clear MDR status that would otherwise go undetected by the Xpert MTB/RIF assay. Although we are unable to use mycobacterial culture in our investigation, it is still regarded as the gold standard for diagnosing MTB. The fact that the pediatric population was not investigated is another drawback of our study.

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CONFLICT OF INTERESTS None

FINANCIAL DISCLOSURE None

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