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A comparative study of RIF resistance between newly diagnosed Pulmonary and Extra-pulmonary Tuberculosis patients in a tertiary care setting using Xpert MTB/ RIF Ultra

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ABSTRACT

Introduction: Mycobacterium tuberculosis remains one of the most significant causes of death from an infectious agent. The rapid diagnosis of tuberculosis and detection of rifampicin (RIF) resistance are 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 RIF resistance in clinical specimens.13 Rifampicin (RIF) resistance (RR) tuberculosis (TB) has posed a great challenge to TB control programs globally. Evidence of RIF-RR can help as a surrogate marker to find out multidrug-resistance cases. The study aimed to know the prevalence of Pulmonary and Extra-pulmonary tuberculosis cases and to detect Rifampicin resistance in newly diagnosed Pulmonary & Extra-pulmonary tuberculosis cases using Xpert MTB/RIF Ultra and to compare RIF resistance among Pulmonary & Extra-pulmonary tuberculosis cases.

Keywords: *RIF: Rifampicin, RR: Rifampicin resistance, MDR: Multi Drug Resistance*

INTRODUCTION

Tuberculosis is a contagious, airborne bacterial infectious disease caused by Mycobacterium tuberculosis. TB remains one of the world's deadliest infectious killers. Each day, close to 3425 people lose their lives to TB and close to 30,000 people fall ill with this preventable and curable disease. In 2023, 10.8 million people were diagnosed with TB and 1.25 million people died due to TB in the world.1 India accounts for about 25% of global TB burden, with an estimated TB incidence of 2.77 million in 2022.4 In 2023, Karnataka achieved 81% of its annual TB notification target, registering 81,331 TB notifications. It is estimated TB prevalence to notification (P: N) ratio is 4.08, which is higher than national average 2.84, indicating more cases might be missed.3Tuberculosis remains a major public health concern, exacerbated by emergence of drug-resistant strains of Mycobacterium tuberculosis. Despite ongoing efforts through global initiatives led by the world health organization (WHO) and National tuberculosis programs (NTPs), multidrug resistance (MDR) and extensive drug resistance (XDR)TB continue to threaten disease control strategies. The increasing prevalence of

these resistant strains poses significant challenges in achieving the End TB strategy goals by 2035. According to WHO, resistance to rifampicin is predictive of MDR-TB, and the patients should be given second line treatment.2The emergence and transmission of drug-resistant Mycobacterium tuberculosis have further complicated TB control. Rifampicin resistance (RIF-R) is particularly important because it is strongly associated with multidrug-resistant tuberculosis (MDR-TB) and serves as an important early marker of drug resistance. Prompt identification of RIF-R enables timely initiation of appropriate treatment and facilitates implementation of infection-control and public-health measures. Conventional drug susceptibility testing, although important for definitive resistance characterization, may require several weeks and may not be readily available in all clinical settings. Rapid molecular methods have therefore become integral to the early diagnosis of drug-resistant TB. The world health organization (WHO) has prequalified the Xpert® MTB/RIF Ultra, a molecular diagnostic test using GeneXpert for tuberculosis in which detection of genetic material of mycobacterium tuberculosis in sputum samples gives accurate results within hours. This is the first test to meet WHOs prequalification standards for both TB diagnosis and antibiotic resistance detection. Timely and accurate detection, especially of drug-resistant TB strains, is essential in controlling the disease and reducing its impact.1
The present study is taken up to diagnose tuberculosis and detect the RIF resistance between pulmonary TB and Extra-pulmonary TB for adequate and timely treatment.

Objectives

- To know the prevalence of Pulmonary and Extra-pulmonary tuberculosis cases using Xpert MTB/ RIF Ultra
- To detect Rifampicin resistance in newly diagnosed Pulmonary & Extra-pulmonary tuberculosis cases using Xpert MTB/RIF Ultra.
- To compare RIF resistance between Pulmonary & Extra-pulmonary tuberculosis cases.

Literature Review

Materials and Methods:

Study Design: An observational cross-sectional study.

Study Setting: Vydehi Institute of Medical Sciences & Research Centre, Bangalore

Study period: 1 year (1st April 2025– 31st March 2026)

Study Population: All patients tested positive for Pulmonary & extra-pulmonary tuberculosis during study period

Inclusion Criteria: Newly diagnosed pulmonary and extra-pulmonary patients who have tested positive for tuberculosis using Xpert MTB/RIF Ultra.

Exclusion Criteria: Pulmonary and extra-pulmonary TB positive patients who were already receiving treatment for the same

Sample size: All patients tested positive for Pulmonary & extra-pulmonary tuberculosis during study period using rapid diagnostic test and Xpert MTB / RIF Ultra were included. Sampling technique used was convenient sampling method

Data collection: After obtaining approval from Vydehi Research Committee and ethical clearance from VIEC, above study was conducted at VIMS & RC, Bangalore during study period. Data was collected using study instrument (Case proformas) of all patients with positive pulmonary and extra pulmonary TB who meets inclusion criteria.

Study instrument: CASE PROFORMAS
It includes 2 parts. Part I – Socio-demographic profile of patients with positive pulmonary & extra-pulmonary tuberculosis and part II - lab reports of confirmed diagnosis and RIF resistance among TB & extra-TB positive patients. Patient details will be kept confidential under laws and regulations.

Data collected was entered in Microsoft excel sheet and analyzed using SPSS version 23

Data analysis: Mean and SD was used for continuous data. Frequency and percentage was used for categorical data and to see the association between them, Chi-square test was used. $P<0.05$ was considered as statistically significant.

Result

Total number of 97 participants were included in the study who gave sample for tuberculosis testing from 1st April 2025–31st March 2026 from laboratory register of the institute.
The demographic profile of the participants is as shown in the table 1.

Table 1: Distribution of participants based on their demographic profile:

Sex	Number	Percentage (%)
Males	65	67
Females	32	33
Age:		
< 21 years	5	5.15
21 – 40 years	23	23.71
41 – 60 years	41	42.24
Above 60 years	28	28.9

Table 2 shows that pulmonary cases are more accounting 76.28 % than extra-pulmonary cases (23.72%)

Table 2: Distribution of types of tuberculosis (n=97)

Tuberculosis (Frequency)	Number	Percentage (%)
Pulmonary	74	76.28
Extra – pulmonary	23	23.72
Total	97	100

Table 3: Distribution of Rifampicin Resistant (RR) in Pulmonary Tuberculosis:

Pulmonary TB	Number	Percentage
RR present	3	4.05
RR absent	68	91.90
Indeterminate	3	4.05
Total	74	100

Table 3 & 4 shows Rif. Resistance among pulmonary and extra-pulmonary cases. Rifampicin resistance is seen among 3 in pulmonary whereas 1 in extra-pulmonary cases respectively. There were 3 and 12 indeterminate cases among pulmonary and extra-pulmonary cases respectively.

Table 4: Distribution of Rifampicin Resistant (RR) in Extra-Pulmonary Tuberculosis:

Extra Pulmonary TB	Number	Percentage
RR present	1	4.36
RR absent	10	43.47
Indeterminate	12	52.17
Total	23	100

Table 5 shows the types of sample collection to diagnose TB and MDR TB. Most were (37.11%) were sputum samples collected followed by tissue biopsy (23.72%), pus (18.55%), BAL (5.15%) and others.

Table 5: Distribution of types of samples collected:

Sample collected	Number	Percentage
Sputum	36	37.11
Oropharyngeal swab	2	2.06
BAL fluid	5	5.15
Pleural fluid	4	4.13
Tissue biopsy	23	23.72
Aspirate	2	2.06
Body fluid	2	2.06
Pus	18	18.55
CSF	2	2.06
Urine	2	2.06
Cervical swab	1	1.03
Total	97	100

Fisher's exact test

Pulmonary -Rifampicin resistance * Extrapulmonary -Rifampicin resistance Crosstabulation

			Extrapulmonary -Rifampicin resistance				Test statistics value	P value
			Absent	NA	Indeterminant	Total		
Pulmonary -Rifampicin resistance	Absent	No.	0	68	0	68		
		% of Total	0.0	91.9	0.0	2.4%		
	Not Applicable	No.	10	0	9	34		
		% of Total	49.0%	0.0%	17.6%	66.7%	54.397	0.000
	Indeterminant	Count	0	2	0	2		
		% of Total	0.0%	3.9%	0.0%	3.9%		
Total		Count	25	17	9	51		
		% of Total	49.0%	33.3%	17.6%	100.0%		

P<α considered as significant. P<α (0.000<0.05)

Discussion:

The present study evaluated the demographic characteristics, distribution of tuberculosis (TB), rifampicin resistance, and types of clinical specimens collected for the diagnosis of tuberculosis and drug-resistant tuberculosis among 97 participants. The findings provide an overview of the pattern of pulmonary and extra-pulmonary tuberculosis and the occurrence of rifampicin resistance in the study population.

In the present study, males constituted the majority of the study population, accounting for 67% of participants, while

females represented 33%. This male predominance may reflect differences in exposure, healthcare-seeking behaviour, occupational factors, or the distribution of tuberculosis in the population studied. The predominance of males in the present study indicates that TB surveillance and diagnostic services should continue to ensure adequate access to both sexes, particularly among individuals with clinical features suggestive of tuberculosis.

With regard to age distribution, the largest proportion of participants belonged to the 41–60-year age group (42.24%), followed by those aged above 60 years (28.9%). Participants aged 21–40 years accounted for 23.71%, whereas those below 21 years constituted only 5.15% of the study population. Thus, the majority of patients in the present study were adults aged above 40 years. The higher representation of older adults may be associated with the cumulative risk of TB exposure and the presence of age-related vulnerabilities; however, these factors were not specifically evaluated in the present study.

Pulmonary tuberculosis was the predominant form of disease, accounting for 74 (76.28%) of the 97 cases, whereas extra-pulmonary tuberculosis accounted for 23 (23.72%) cases. The predominance of pulmonary TB is clinically relevant because pulmonary disease constitutes an important source of transmission and is generally more readily accessible for microbiological sampling. Nevertheless, the proportion of extra-pulmonary cases in this study highlights the importance of maintaining a high index of suspicion for TB at sites other than the lungs and of using appropriate specimens for microbiological diagnosis.

Rifampicin resistance was assessed separately among pulmonary and extra-pulmonary TB cases. Among the 74 pulmonary TB cases, rifampicin resistance was detected in 3 cases (4.05%), while 68 cases (91.90%) were reported as rifampicin resistant negative/absent and 3 cases (4.05%) had an indeterminate result. Among the 23 extra-pulmonary TB cases, rifampicin resistance was detected in 1 case (4.36%), while 10 cases (43.47%) were negative/absent for resistance and 12 cases (52.17%) had indeterminate results.

The occurrence of rifampicin resistance in both pulmonary and extra-pulmonary TB cases is an important finding because rifampicin resistance serves as a critical marker for suspected drug-resistant tuberculosis and has implications for subsequent diagnostic and therapeutic management. Although the proportion of confirmed rifampicin-resistant cases was similar in the pulmonary and extra-pulmonary groups, the small number of resistant cases limits meaningful comparison between the two groups.

A notable finding was the relatively high proportion of indeterminate rifampicin-resistance results among extra-pulmonary TB cases. More than half of the extra-pulmonary specimens (52.17%) had an indeterminate result, compared with 4.05% among pulmonary cases. This difference may be related to the nature and characteristics of extra-pulmonary specimens, including variations in specimen type, bacillary load, and adequacy of the clinical sample. However, these factors were not directly investigated in the present study. The high proportion of indeterminate results emphasizes the importance of appropriate specimen collection, adequate sample volume, proper transportation and processing, and repeat or supplementary testing where clinically indicated.

The distribution of clinical specimens further demonstrates the heterogeneity of samples required for TB diagnosis. Sputum was the most frequently collected specimen, comprising 36 (37.11%) of all samples, which corresponds with the predominance of pulmonary TB in the study population. Tissue biopsy was the second most common specimen, accounting for 23 (23.72%), followed by pus at 18 (18.55%). Other specimens included bronchoalveolar lavage (BAL) fluid (5.15%), pleural fluid (4.13%), oropharyngeal swabs, aspirates, body fluids, cerebrospinal fluid (CSF), and urine. Cervical swab accounted for the smallest proportion of specimens (1.03%).

The wide range of specimens collected reflects the diverse clinical presentations of tuberculosis and the diagnostic challenges associated with extra-pulmonary disease. While sputum remains an important specimen for pulmonary TB, diagnosis of extra-pulmonary TB frequently requires sampling from the affected anatomical site. The substantial contribution of tissue biopsies and pus specimens in the present study reinforces the importance of specimen-specific molecular and microbiological approaches for detecting TB and assessing drug resistance.

Statistical analysis using Fisher's exact test demonstrated a statistically significant association between the pulmonary and extra-pulmonary rifampicin-resistance categories, with a test statistic of 54.397 and a reported p-value of <0.001. However, the interpretation of this association should be made cautiously because the contingency table contains small cell counts and a substantial number of indeterminate/not-applicable observations. In addition, the statistical association does not by itself establish a causal relationship between the site of TB and rifampicin resistance.

Overall, the findings of this study demonstrate that pulmonary TB was substantially more common than extra-pulmonary TB, with males and individuals aged 41–60 years forming the largest demographic groups. Rifampicin resistance was identified in both pulmonary and extra-pulmonary disease, although the absolute number of resistant cases was small. The relatively high frequency of indeterminate results, particularly among extra-pulmonary specimens, represents an important diagnostic consideration. The findings emphasize the need for timely microbiological testing, appropriate specimen selection, and reliable molecular detection of rifampicin resistance in both pulmonary and extra-pulmonary TB.

The study should be interpreted in light of certain limitations. The sample size was relatively small, particularly for the extra-pulmonary and rifampicin-resistant subgroups, which limits the precision and generalizability of the findings. The study also did not evaluate potential risk factors for TB or rifampicin resistance, such as previous anti-tubercular treatment, treatment adherence, HIV status, comorbidities, or socioeconomic and epidemiological factors. Furthermore, the high proportion of indeterminate results, especially among extra-pulmonary specimens, may influence comparisons between the two groups. Future studies involving larger sample sizes and detailed clinical, microbiological, and epidemiological variables would be useful to better characterize rifampicin resistance and diagnostic outcomes in

pulmonary and extra-pulmonary tuberculosis.

S. Atashi, et al., conducted research on "Evaluation of GeneXpert MTB/RIF for determination of rifampicin resistance among new tuberculosis cases in west and northwest Iran" in 2017. The study was conducted to detect rifampicin resistance in new cases of tuberculosis using GeneXpert MTB/RIF. In a total of 400 new cases of suspected tuberculosis, 162(40.5%) of the cases were smear- and culture- positive for Mycobacterium tuberculosis. These samples were tested for detection of antibiotic susceptibility using proportional method and GeneXpert MTB/RIF assay. Overall, both tests were positive in five individuals.5

Guesh Gebremariam, et al., conducted research on "Trend of pulmonary tuberculosis and rifampicin-resistance among tuberculosis presumptive patients in Central Tigray, Ethiopia; 2018 -2023: a six-year retrospective study" in 2024. In this study, overall pulmonary tuberculosis and rifampicin resistant tuberculosis detection rates were found to be 11.7% and 8.1% respectively. It was observed that there was an increasing trend of pulmonary tuberculosis especially in the years 2020-2023.6

Bekele Sharew, et al., conducted a study on "Detection of Rifampicin Resistance rpoB Gene Using GeneXpert MTB/RIF Assay in Pulmonary Tuberculosis Cases at Debre Tabor Comprehensive Specialized Hospital, Northwest Ethiopia" in 2024. A retrospective analysis from 2017 to 2024 was done on a total of 12,981 patients. In these patients, 8.9% (1160/12.981) were Mycobacterium tuberculosis-positive and 7.1% (82/1160) were rifampicin resistant.7

Alain Farra, et al., conducted research on "Surveillance of Rifampicin Resistance with GeneXpert MTB/RIF in the National Reference Laboratory for Tuberculosis at the Institute Pasteur in Bangui, 2015-2017" in 2019. The study showed that in 617 registered cases, GeneXpert MTB/RIF tests were positive in 79.1% (488/617), and rifampicin resistance was positive in 42.2% (206/488).8

Conclusion: The present study demonstrates that pulmonary tuberculosis was more common than extra-pulmonary tuberculosis, accounting for 76.28% and 23.72% of cases, respectively. The study population showed a male predominance, with the 41–60-year age group representing the largest proportion of participants. Rifampicin resistance was detected in both pulmonary and extra-pulmonary tuberculosis, although the number of confirmed resistant cases was relatively small. A considerable proportion of extra-pulmonary specimens showed indeterminate rifampicin-resistance results, highlighting the diagnostic challenges associated with extra-pulmonary tuberculosis.

Sputum was the most frequently collected specimen, followed by tissue biopsy and pus, reflecting the predominance of pulmonary disease and the diversity of clinical presentations requiring specimen-specific investigation. The findings emphasize the importance of appropriate specimen collection and timely molecular testing for the detection of tuberculosis and rifampicin resistance. Larger studies with detailed clinical and epidemiological data are recommended to further characterize drug resistance patterns and improve the diagnosis and management of tuberculosis, particularly extra-pulmonary disease.

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ANNEXURE

CASE PROFORMA

[A] Patients details;

1. Name:
2. Hospital Number:
3. Gender: a) Male b) Female c) Other
4. Age: a) Below 21 years b) 21-30 years c) 31-40 years d) 41-50 years e) 51-60 years f) Above 60 years

[B] Laboratory findings;

5. Sample Number:

Based on the reports received, the following were the findings in the patient;

6. Test result for tuberculosis:
   a) Positive b) Negative
7. Type of tuberculosis:
   a) Pulmonary b) Extrapulmonary
8. If pulmonary, rifampicin resistance:
   a) Present b) Absent c) Not applicable
9. If extrapulmonary, rifampicin resistance:
   a) Present b) Absent c) Not applicable
10. The specimen type:
    a) Sputum b) Pus c) Tissue/biopsy d) Other
11. Extrapulmonary site affected:
    a) Lymph nodes b) pleura c) genitourinary tract d) bones and joints e) others