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Original Research Article

Study of Prevalence and Clinical Profile of Rifampicin Resistant Pulmonary Tuberculosis among Retreatment Patients by Expert MTB/RIF Technique

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Conflict of interest: Nil

Background: Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis due to organisms which show resistance to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs. Multidrug-resistant tuberculosis is more common in patients who have previously been treated for tuberculosis and public health efforts have typically focused on high-quality treatment of drug-susceptible tuberculosis to prevent acquisition of resistance while on therapy.

Objective: To determine prevalence of MDR-TB (multidrug resistant tuberculosis) among sputum positive re-treatment patients by CBNAAT (cartridge based nucleic acid amplification testing) method and to determine clinical profile of aforesaid patients.

Methodology: A prospective observational study was carried out at a tertiary care hospital in Ahmedabad from June 2016 to Feb 2018. All sputum positive pulmonary TB patients on retreatment were included and isolated extrapulmonary tuberculosis patients on retreatment were excluded. According to the NTEP (National TB Elimination Program) guidelines, their sputa were subjected to CBNAAT testing. The testing was done in Microbiology laboratory at AMC MET Medical College, Ahmedabad. Results thus obtained were analyzed.

Result: Out of total 1368 patients included in the study; the prevalence of MDR-TB patients was 13.8%(n=189). The mean age of patients in this study is 45.52 ± 7.38 yrs. MDR-TB was common in males (n= 130, 69%) than females (n=59, 31%). Mean body mass index (BMI) in the study is 19.98 kg/m^2 and median BMI is 20.02kg/m^2. Prevalence of MDR-TB is higher amongst lower socioeconomic status (n=100,53%). Risk factors to developing MDR-TB are diabetes mellitus (n=27, 14%), seropositivity (n=8,4%) and addiction (n=141, 75%) to smoking or alcohol or tobacco. Defaulter cases(n=101,53%) followed by relapsed cases(n=53,28%) and treatment failure cases(n=35,19%) suggested additional risk to develop MDR-TB. Chest x-ray findings and sputum grading suggested high infectivity amongst far advanced lung involvement(n=86,45%) and 3+ grading (n=67,35%) patients.

Conclusion: From our study we would like to be conclude that Molecular techniques have revolutionized the diagnosis of MDR-TB. In our study out of total 1368 patients, 189 had MDR-TB diagnosed through sputum CBNAAT. Males were more affected than females. Lower socioeconomic status, undernutrition, middle-aged, diabetics, HIV infected, alcoholics, smokers, tobacco addicts pose additional risk to develop MDR-TB. High infectivity was seen amongst far advanced lung lesions and 3+ sputum grading as per NTEP guidelines.

Keywords: MDR-TB, NTEP, CBNAAT, Retreatment, Sputum, Pulmonary TB

Introduction

The emergence and spread of multi-drug resistant tuberculosis (MDR-TB) is threatening to destabilize global tuberculosis control[1] The prevalence of MDR-TB is increasing throughout the world both among new cases as well as among previously treated ones. Although previous treatment for TB is the strongest risk factor for development of MDR-TB, [2,3,4] treatment-naïve

patients are also at risk due to either spontaneous mutations or transmission of drug-resistant strains[5]. The risk of transmission of resistant strains from close contacts is increasing day-by-day because of the growing burden of MDR-TB patients [5]. Therefore, in the present scenario, there is high likelihood that what initially seems to be drug-sensitive TB in a treatment-naïve patient might in fact be MDR-TB from the outset. Within the last ten years, advances in the molecular biology of Mycobacterium tuberculosis (Mtb) in conjunction with modern immunological methods have led to improvement in our ability to detect Mtb and to delineate the host's response to infection.

It is with these new tools that the WHO has proclaimed an ambitious target of detecting 70% of sputum smear positive cases and to successfully treat 85%.TB occurs in every part of the world. In 2016, the largest number of new TB cases occurred in Asia, with 45% of new cases, followed by Africa, with 25% of new cases. In 2016, 87% of new TB cases occurred in the 30 high TB burden countries. Seven countries accounted for 64% of the new TB cases: India, Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa. Global progress depends on advances in TB prevention and care in these countries [6,7].

India is the country with the highest burden of TB. The World Health Organization (WHO) TB statistics for India in 2017 gives an estimated incidence of 279/lakh population for TB in India. The TB incidence is the number of new cases of active TB disease during a certain time period (usually a year). In 2021, the TB incidence was 210/lakh population and National TB Elimination programme (NTEP) had envisaged an incidence of only 77/lakh by 2023[6].

In India, there were 435/lakh population deaths due to TB in 2017. There were total 87,000 HIV TB cases in 2017 of which 12,000 died. Estimated MDR/RR cases recorded in 2017 is 147/lakh population. The incidence of TB has reduced from 289/lac/year in 2000 to 217/lac/year in 2015. The mortality due to TB has reduced from 56/lac/year in2000 to 36/lac/year in 2015. With the current rate of annual decline of TB cases globally being 1.5%, India is lagging behind in its National decline rate. NTEP aims to reduce the TB mortality to 3/lakh population and to eliminate TB by 2025. On World TB Day 2023, our Prime Minister had announced initiatives to help our country meet the 2025 target which is 10years ahead of WHO target to eliminate TB as a global threat by 2035. If India wants to end TB by 2025, rate of decline of TB incidence needs to be more than 10%-15% over next 8 years[8,9].WHO Global TB report 2022 suggested 21.4 lakh TB cases notified in 2021, 18% higher than 2020. Over 22crore people were screened for TB in 2021 across the country for early detection and treatment of TB. Under the new initiative Pradhan Mantri TB Mukt Bharat Abhiyan, more than 40,000 Nikshay Mitra supporting over 10.45lakh TB patients all over the country. Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat.

In India, the prevalence of MDR-TB among new and retreatment cases is 2.5%and 16% respectively. It is estimated that every year 130,000 cases of MDR-TB emerge, of which 79000 were notified cases in 2015. From these 79000, only 36%(28,876) were diagnosed, 34% (26,988)were started on treatment with success rate of 46%. Since 2011,there have been rising incidence of extensively drug resistant TB(XDR-TB) in India. Nearly 9.5% of MDR-TB cases were found to have XDR-TB. It is estimated that in India, about 8000 XDR-TB cases emerge every year. XDR-TB has raised the possibility that the current drug-susceptible TB will be replaced in the form of TB with severely restricted treatment options. This would halt the progress made in recent years to control TB[10].

Therefore the present study is done to find out the prevalence and clinical profile of rifampicin resistance pulmonary tuberculosis patients on retreatment by MTB/RiF technique at a tertiary care setup.

Materials and Method

This Prospective Observational Study was conducted at Department of Respiratory Medicine of Sheth LG Hospital and AMC MET Medical College, Maninagar, Ahmedabad from June 2016 to Feb 2018. All the patients who were sputum positive and were on retreatment regimen were included in the study. According to the new RNTCP guidelines, the sputum of each of these patients included in the study were sent for CBNAAT in falcon tube. The expert MTB/RIF technique is performed in the machine kept at Microbiology Department of AMC MET Medical College. Results regarding sensitivity of bacilli against rifampicin are produced using this technique within 2 hours. Results thus obtained, are analysed. All patients who are diagnosed sputum positive for tuberculosis and on retreatment at NTEP designated Directly Observed Treatment (DOTS) Centre in LG Hospital, Maninagar or to referral centre as prescribed by DOTS centre at LG hospital were included in study.

Inclusion criteria: All the sputum-positive pulmonary tuberculosis patients on retreatment as per NTEP guidelines.

Exclusion criteria: Isolated extrapulmonary tuberculosis on retreatment regimen as per NTEP guidelines

Statistical Analysis: Inferential statistics

Results

The study involved subjects from all age groups. The minimum age was 14 and maximum age was 73. The highest incidence of rifampicin resistant was seen in the age group 21-30 yrs(40%) followed by age group 31-40 yrs(17%), 41-50yrs(16%), 51-60yrs(14%), 11-20 yrs(11%), 61-70yrs(4%) and only 1 patient was found in the age group 71-80yrs. The mean age in this study is 45.52 ± 7.38. Mean age of males (n=130) is 38.25yrs with standard deviation 14.1yrs while mean age of females (n=59) is 30.29yrs with standard deviation 13yrs.(Table 1)

Table 1: Age & Gender wise distribution of participants

Age Group (Years)	Rifampicin Resistance (RR) Patients
11-20	21(11%)
21-30	68(40%)
31-40	33(17%)
41-50	31(16%)
51-60	27(14%)
61-70	8(4%)
71-80	1(0.5%)
Total	189
Mean age of males (n=130)	38.25±14.1
Mean age of females (n=59)	30.29±13

Prevalence of rifampicin resistance in sputum positive retreatment cases in this study is 13.8% using MTB/RiF technique. In this study out of total 1368 sputum positive retreatment cases, 1179(86%) are rifampicin sensitive cases and 189(13.8%) are rifampicin resistant cases diagnosed by CBNAAT method. Further analysis is based on 189 rifampicin resistant patients who were sputum positive and on retreatment regimen under NTEP.(Table 2)

Table 2: Showing Prevalence of Rifampicin Resistance

No of sputum positive retreatment patients	1368
Rifampicin resistance	189(13.8%)
Rifampicin sensitive	1179(86.18%)

Table 3: BMI Distribution of Rifampicin Resistant Patients Based on their Gender

BMI(Kg/M^2)	Males	Females
Underweight (<18.5) N=54	26(48%)	28(52%)
Normal (18.5-24.9) N=133	103(77.4%)	30(22.6%)
Overweight (>25) N=2	1(50%)	1(50%)
Total	130	59
Mean BMI (P Value=0.00)	20.44±2.4	19±2.4

In this study majority of the patients with MDR-TB were in the normal range of BMI that is 18.5-24.9kg/m^2 (69.3%) and majority of these patients had BMI more than 18.5kg/m^2 but less than 20kg/m^2 because the mean BMI in this study is 19.98kg/m^2 with standard deviation 2.5kg/m^2. The median BMI is 20.02kg/m^2.So we can draw an inference from this study that low BMI patients are more prone to develop DR-TB. About 29.6% patients were underweight (BMI range: <18.5kg/m^2). There were 2(1%) patients who were overweight (BMI range: 25-29.9kg/m^2). None of the patients were obese (BMI range: >30kg/m^2). The mean BMI of males (n=130) in this study is 20.44kg/m^2 with standard deviation 2.4 and the mean BMI of females (n=59) in this study is 19kg/m^2 with standard deviation 2.4. (p value=0.00 which means this study is significant)(Table 3.)

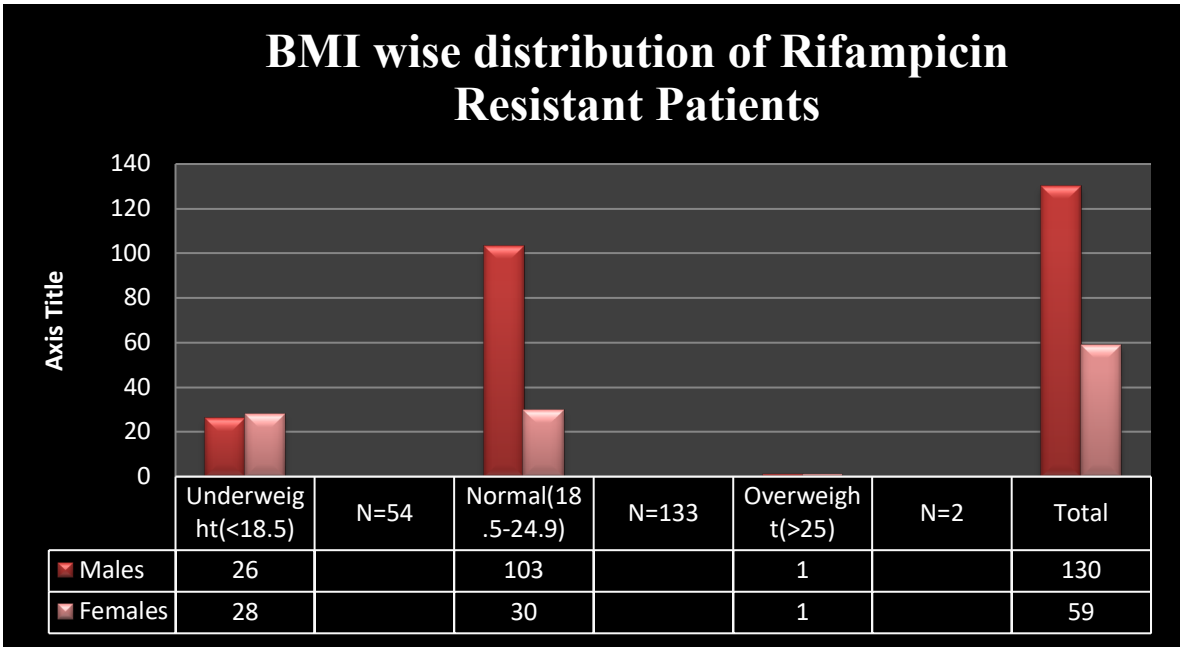

Figure 1: Showing Graphical Presentation of BMI Distribution of Rifampicin Resistant Patients

In this study, 100(53%) patients belonged to lower socioeconomic class followed by 71(38%) patients in middle socioeconomic class and only 18(9%) belonged to upper socioeconomic class. This shows that patients who belong to lower socioeconomic class are more prone to develop DR-TB. (Table 4.)

Table 4: Socioeconomic Status Wise Distribution of Participants

Social Class	No. of Rifampicin resistant patients
LSES(lower socioeconomic status)	100(53%)
MSES(middle socioeconomic status)	71(38%)
USES(upper socioeconomic status)	18(9%)
Total	189

In this study out of 189 MDR-TB patients, 27(14%) had diabetes mellitus and 8(4%) had seropositive HIV status. There were 16(59.25%) males and 11(40.74%) females who had diabetes. All the HIV seropositive patients were males. . Both diabetics and HIV seropositive patients were on regular treatment for their disease.(Table 5)

Table 5: Distribution of Participants according to co morbidity

	Males	Females	Total
Diabetes Mellitus	16(59.3%)	11(40.7%)	27
PLHA	8(100%)	0	8

In this study out of total 189 MDR-TB patients, 48(25%) were non-addicts and 141(75%) were addicts to tobacco, smoking nicotine or alcohol. Of the 141 addicts there were 62(43%) alcoholics, 51(36%) tobacco chewers and 28(19%) smokers. None of the patients showed addictions to more than one habit. Further the study showed that there were 47(92.15%) males and 4(7.8%) females who consumed tobacco. There were 59(95.16%) males and 3(4.8%) females who drank alcohol and there were 24(85.71%) males and 4(14.2%) females who smoked. All males were addicted to tobacco, alcohol or smoking. About 48(81.35%) females were non-addicts.(Table 6)

Table 6: Distribution Of Participants according to Addiction habit

Addictions	Male	Female	Total
Tobacco Addicts	47(92%)	4(8%)	51
Alcoholics	59(95%)	3(5%)	62
Smokers	24(85%)	4(15%)	28
Non-Addicts	0	48(100%)	48

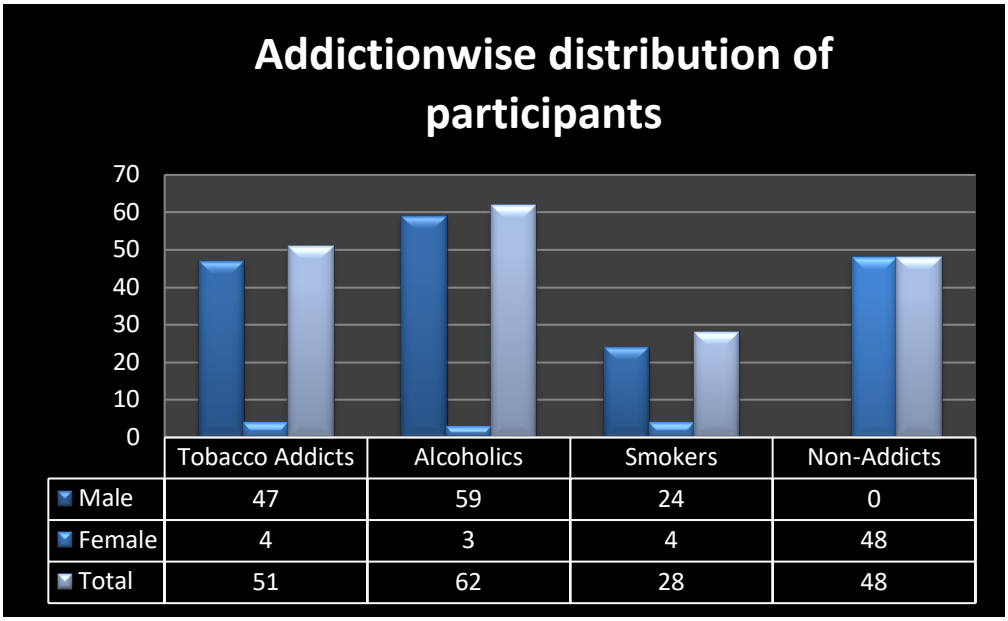

Figure 2: Graphical presentation of Participants according to Addiction habit

Out of 189 rifampicin resistance cases in this study, 101(53%, p value=0.041 which is significant) were defaulter cases followed by 53(28%, p value=0.052) relapse cases and 35(19%, p value=0.711) treatment failure cases. This study shows that patients who default their treatment and those who relapse after treatment completion are more prone to develop DR-TB as compared to treatment failure cases.

Out of 35 treatment failure cases, there were 25(71%) males and 10(29%) females. There were 63(62%) males and 38(38%) females who were defaulters and 42(79%) males and 11(21%) females were relapse cases.(Table 7)

Table 7: MDR-TB In Various Subcategories of Retreatment Pulmonary Tb Patients

	Males	Females	Z Test (P Value)	Total
Relapse	42(79%)	11(21%)	0.052	53
Defaulter	63(62%)	38(38%)	0.041	101
Failure	25(71%)	10(29%)	0711	35

Out of 189 MDR-TB patients, there were 86(45%) patients with far advanced radiological lesion followed by 76(40%) with moderately advanced lesions and 27(15%) patients with minimal involvement of their lungs as shown in their chest X-rays. In this study there were 12(44.44%) males and 15(55.55%) females with minimal lesion on CXR (PA), 59(77.63%) males and 17(22.36%) females had moderately advanced lesions on CXR (PA) while 59(68.6%) males and 27(31.39%) females had far advanced lesions on CXR (PA). p values for minimal and moderately advanced lesions in both genders is <0.05 so, inference from this study is that patients with far advanced lesions on CXR (PA) are less likely to develop MDR-TB than those with moderately advanced or minimal lesions.(Table 8)

Table 8: Chest X- ray (PA) finding of participants according to Gender

CXR(PA) Grading	Males	Females	Z Test (P Value)	No Of RR Patients
A (minimal)	12(44%)	15(56%)	0.003	27
B (moderately advanced)	59(78%)	17(22%)	0.031	76
C (far advanced)	59(69%)	27(31%)	0.96	86
Total	130	59		

Table 9: Sputum Grading of MDR TB patients

AFB Grading (Z N Staining)	No of RR patients
SC+	15(10%)
1+	64(33%)
2+	43(22%)
3+	67(35%)
Total	189

MDR-TB patients were divided on the basis of sputum AFB grading which depicted their infectivity. Out of 189 MDR-TB patients in this study, there were 67(35%) patients with AFB grading 3+ followed by 64 (33%) patients having AFB grading 1+, 43(22%) patients having AFB grading 2+ and 15(10%) patients having AFB grading as SC+(scanty). These AFB grading of sputum sample is based on RNTCP guidelines on sputum microscopy.(Table 9).

Discussion

A study was undertaken to determine the prevalence of MDR TB patients visiting tertiary care hospital in Ahmedabad and to study risk factors. The patients were analyzed on basis of their age, gender, clinical features, habits, treatment history, drug susceptibility and chest x-ray findings.

The present study is comparable to other studies [11-21] which took place in India and also with the national survey done by WHO in 2016 which tells that the incidence of MDR TB in new cases is 4.1% and in retreatment cases its 19%.

The mean age and maximum age in our study was found to be higher but the minimum age was lower than other studies(11,22-25) and standard deviation in our study is 7.38. In this study mean age is higher because 1 patient in this study was in the age group 71-80 years. MDR-TB is more predominantly seen in males as compared to females. This can be seen in previous studies[11,24-26] done and present study also justifies it. In this study it is seen that defaulters are more prone to develop DR-TB as compared to those who completed their treatment while other studies[11,24,26-7] show that DR-TB is more prevalent in relapse cases.

This study showed more number of patients having BMI in the normal range. However, majority of them had their BMI more than 18.5kg/m2 but less than 20kg/m2. So we can draw the inference that underweight patients are more prone to develop DR-TB which was also stated in the previous study done by Agarwal et al [27].

In this study patients belonging to lower socioeconomic class were seen more prone to develop DR-TB and this is comparable to the study by Rajesh et al [26].In the present study, alcoholics are more prone to develop DR-TB and this is comparable to the study done by Harrison MG et al [23]. In the study by Rajesh et al [26] smoking is the higher risk factor than alcoholism in the development of DR-TB.

Diabetes is an important risk factor in the development of DR-TB and diabetics who are on retreatment more likely to have been infected with the resistant strain of MTB and this is comparable to other studies [26,28-29]. In this study it can be seen that those patients with higher bacterial load are more prone to develop DR-TB which can be comparable to other studies [24,26] also. It can be seen from the present study that more extensive the lesions seen on CXR (PA), higher the chances of developing MDR-TB. This can be compared to the study by MA Nawas et al [25]. Another study done by Rajesh et al [26] showed that there is no significance of CXR(PA) findings and risk to develop MDR-TB.

The emergence of MDR-TB is a global problem which is threatening to destabilize the best efforts of TB control. It has been attributed to factors such as non-adherence to treatment, inappropriate treatment regimens, drug malabsorption, poor drug quality, lack of health education and a poor health infrastructure for effective delivery of treatment. However, even if good drugs are available without a properly functioning DOTS plus programme, it may not show good results. To manage MDR-TB in poor economic settings, the WHO and its partners launched the DOT- Plus initiative to develop a global policy to provide technical assistance to DOTS programme and also to enable access to second-line drugs under rational use.

Conclusion

From our study we would like to be conclude that Molecular techniques have revolutionized the diagnosis of MDR-TB. In our study out of total 1368 patients, 189 had MDR-TB diagnosed through sputum CBNAAT. Males were more affected than females. Lower socioeconomic status, undernutrition, middle-aged, diabetics, HIV infected, alcoholics, smokers, tobacco addicts pose additional risk to develop MDR-TB. High infectivity was seen amongst far advanced lung lesions and 3+ sputum grading as per NTEP guidelines.

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