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Rifampin Resistant Tuberculosis; Factors and Demo-Graphic Features

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ABSTRACT

Introduction: Pakistan has the highest burden of Tuberculosis (TB) worldwide and the 5th highest prevalence of multi-drug resistant (MDR) TB worldwide. There is scarce data on the socioeconomic characteristics and factors associated with the patients presenting with drug resistant-TB in Pakistani context.

Aims & Objectives: To determine the association of different variables with rifampin resistance (RR) in new and previously treated cases of pulmonary (PTB) and extra-pulmonary TB (EPTB)

Place and Duration of Study: It was a cross-sectional study conducted at Gulab Devi Hospital Lahore, a tertiary care trust hospital. Data was collected from Oct 2021 to December 31, 2021.

Material & Method: By applying convenient sampling technique, 202 individuals were interviewed, and data was recorded on a self-constructed questionnaire. Data was analyzed using SPSS version 24.0. Frequency tables were generated for sociodemographic variables as well as the site of TB and Chi square test was applied to find association between categorical variables. *P* value of <0.05 was considered significant. Patients who were categorized as having RR-TB based on detection of RR on Gene Xpert RIF/MTB assay were included.

Results: In this study the mean age of the patients was 31.46±14.67 years, 77 (38.1%) patients were males, and 125 (61.9%) patients were females. Statistically significant association was found between the site of RR-TB (PTB or EPTB) and history of repeated TB treatment ($p = 0.049$) as well as sex ($p = 0.019$). There were also statistically significant differences between new or previously treated RR-TB and patients' sex ($p = 0.019$), repeated treatment ($p = 0.049$) as well as treatment failure ($p < 0.001$).

Conclusion: More females compared to males suffered from both RR-EPTB and RR-PTB. Also, a higher number of patients with RR-PTB had a history of repeated TB treatments compared to those with RR-EPTB. In addition, significant association was found between sex, treatment failure and repeat anti-tuberculous therapy in previously treated RR-TB patients as compared to new RR-TB cases.

Keywords: Rifampin Resistance, Tuberculosis, DR-TB, Pakistan, High TB burden

INTRODUCTION

Tuberculosis (TB) is the 10th leading cause of death worldwide[1]. TB is a highly contagious disease, but it generally responds well to standard Anti-Tuberculosis Treatment (ATT). The first line or standard ATT used to treat drug sensitive TB are Rifampin (RIF), Isoniazid (INH), Ethambutol (E), Pyrazinamide (PZA) and Streptomycin (SM) [2]. RIF, which forms the mainstay of first-line ATT acts by interfering with transcription by the DNA-dependent RNA polymerase[3]. Antibiotic resistance in mycobacteria emerges from chromosomal mutations that reduce the bacterium's susceptibility to various drugs[4] .Resistance to RIF is rising globally with 580,000 cases of TB reported to have Rifampicin Resistance (RR) in 2015 out of which 480,000 were found to be resistant to both Rifampin and Isoniazid[5]. This figure rose to 600,000 reported cases of RR-TB in 2016 globally, 240,000 out of these died[4]. RR is considered a proxy marker for multi-drug resistant (MDR) TB as 90% of the patients diagnosed with RR also have resistance to INH[6]. DR-TB is a global issue of public health importance. Resistance to ATT is a major cause of mortality and morbidity in TB patients and it is estimated that 3.4% of new TB patients and 20% of previously treated TB patients have MDR-TB[1]. Drug Resistant TB (DR-TB) is disease caused by MTB resistant to at least 1 first line ATT[3]. MDR-TB is resistant to both Isoniazid and Rifampin, 2 of the first-line drugs against MTB. Treatment for DR-TB requires second line ATT drugs which are given for

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longer duration, are costly and may have higher adverse effects[7]. Approximately 9% of patients with DR-TB go on to have unsuccessful treatment outcomes and many them die[8]. Due to the higher morbidity, cost and length of treatment linked to DR-TB, controlling the transmission of DR-TB is a priority in public health[1].

Pakistan has a high burden of tuberculosis (TB) and is ranked fourth among the 30 high TB burden countries in the world. The emergence of drug-resistant TB is a growing concern in the country, Pakistan ranks 5th in the world in terms of MDR-TB burden with 4.2% new patients and 16% of previously treated patients presenting with MDR-TB, approximately 6100 patients in Pakistan in 2019 were reported to have RR or greater resistance[9]. WHO recommends that in high burden countries, RR-TB detected on Xpert MTB/RIF assay (Xpert) may be considered MDR-TB[10]. In Pakistan, the facilities for MTB culture are not widely available, therefore detection of RR on GeneXpert is considered as DR-TB and treated with second-line drugs where MTB culture is not possible.

Drug resistance can be present in new TB cases as well as previously treated patients[4]. The treatment success rate for DR-TB in Pakistan is below the 75% success rate target set out by WHO. Globally, poor treatment outcomes are linked to HIV-DRTB coinfection in patients[11], some other factors are delayed diagnosis and incomplete or inadequate treatment[10]. Direct transmission of the DR resistant strain from family members and close contacts with DR TB accounts for a significant number of cases of DR TB[12]. While the factors associated with DR-TB have been studied worldwide, there is scarce data on the socioeconomic characteristics and factors associated with the patients presenting with DR-TB in Pakistani context.

The National TB Program Pakistan, in keeping with WHO guidelines on diagnosis and treatment of TB, advise testing all newly diagnosed and suspected cases of TB for drug resistance by Xpert, however due to resource limitation at the study site at the time of data collection, testing for RR by Xpert was recommended for all DR-TB presumptive cases[2].

MATERIAL AND METHODS

This study aims to understand the factors associated with the various forms of RR-TB. Understanding the factors and behaviors associated with RR-TB leads to better understanding of the factors that lead to poor treatment outcomes. This cross-sectional study was conducted at the Pulmonology Department, Gulab Devi Hospital, Lahore. Gulab Devi Hospital is a tertiary care, trust hospital with fully equipped TB diagnostic and treatment services. Data was collected from October 2021 to December 31, 202, after approval from the IPH ethical review board (No. 44/N&D/IPH) dated 23-09-2021. All TB patients who had been taking first-line ATT regimen for a minimum of two months and were still positive for MTB, either on sputum smears or cultures, were further evaluated for RR-TB by Xpert as per the 2015 Revised National TB Program Pakistan guidelines[2]. Those found to have RR-TB on Xpert testing were included in the study. Sample size was calculated using WHO sample size calculator, considering that 5% of total TB cases in Pakistan were reported to have RR-TB in 2018[4], a minimum sample size of 73 was calculated with 5% margin of error. A total of 202 patients were included in the study using convenient sampling technique.

Informed consent was provided by all patients. The study was approved by the institutional review board. Data was entered on self-developed questionnaire via interview with patients as well as reviewing the information on patients TB card.

Data was analyzed using SPSS version 24.0. Frequency tables were generated for all possible variables and the Chi square test was applied to find association between categorical variables. P value of <0.05 was considered significant.

The variables of interest included sociodemographic variables such as age, gender, marital status, education level, monthly income and living conditions as well as lifestyle and medical history related variables such as co morbidities, smoking and drug use.

Treatment Failure is defined as a sputum smear positive patient who becomes positive or remains positive after 5 months of treatment[2].

Repeat TB treatment means history of TB treatment more than once4. A new TB case is defined as a patient who has never been treated for TB or has taken anti-TB medicines for less than 1 month, whereas a previously treated patient is one who has received 1 month or more of anti-TB medicines in the past[4]. Pulmonary TB(PTB) is a bacteriologically confirmed or clinically diagnosed case of TB limited to the lung parenchyma or the tracheobronchial tree while Extra Pulmonary TB (EPTB) is a bacteriologically confirmed or clinically diagnosed case of TB involving sites other than lungs[2].

RESULTS

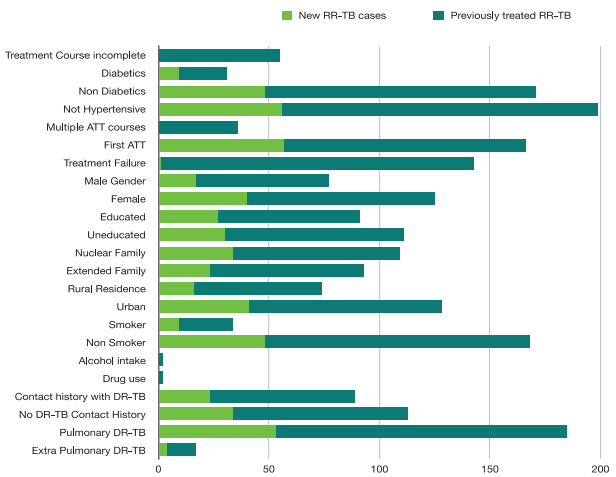
During the study period a total of 202 patients were found to have RR-TB by Xpert, with a mean age of 31.46±14.67 years, minimum age of 2 years and maximum of 70 years. All patients tested negative for HIV. Out of 202 patients, 77 (38.1%) were males and 125 (61.9%) patients were females. The percentage of married patients was 62.4% (n=126), while 36.6% (n=74) were unmarried, 0.5% (n=1) was divorced, and 0.5% (n=1) was a widow. Seventy-four (36.6%) patients were from rural background, 97 (48%) were from urban, 3 (1.5%) from slums and 28 (13.9%) patients were from town background. Among our cohort, 91(45%) patients did not receive any formal education, 25 (12.4%) completed primary-level, 26 (12.9%) middle-level, 37 (18.3%) secondary-level, and 13(6.4%) intermediate-level education. Only 10 (5%) of patients were graduates or above in education. Maximum number of females, 69 (34.2%) were housewives. 109 (54%) patients were from nuclear families and 93 (46%) were living with extended family.

Most patients (99%) were nonalcoholic and reported no illicit drug taking history, 34 (16.8%) patients gave history of cigarette smoking.

Among co-morbidities 31 patients (15.3%) were diabetic, 3 patients (1.5%) were hypertensive, and none had a history of ischemic heart disease. One hundred and forty-five patients (71.8%) had history of taking ATT with 142 (70.3%) patients having taken oral medication while 4 (2%) took oral and injectable medication and 56 (27.7%) reported no history of ATT. 90 patients (44.6%) had completed ATT and then relapsed. 36 (17.8%) had repeated tuberculosis treatment, ie more than once, while 165 (81.7%) had no repeated medication. 89 (44.1%) patients had a positive contact history with maximum frequency of infection in siblings16(7.9%). Out of total 202 patients 9 patients (4.5%) travelled abroad and only 2 (1%) male patients had history of sexual contact with female sex workers. Out of the 202 patients with RR-TB, 57 patients (28.2%) were new cases, and 145 patients had been previously treated for TB. Fig 1 gives a breakdown of the various characteristics of new and previously treated patients.

Figure 1 shows that more males (77.9%) were previously treated for TB as compared to females (68%), this was found to be the opposite in the case of new RR-TB where more females were affected (22.1% males versus 32% females). These differences were found to be statistically significant (p = 0.019) Of the 145 previously treated patients, 55 reported having taken incomplete treatment course (37.9%) while 90 (62.0%) reported having completed the treatment course. In addition, 36 (24.8%) patients reported having taken 2 or more courses of TB treatment in the past.

Figure 1: Bar Chart depicting the differences between new and previously diagnosed cases of TB based on variables of interest.



The treatment failure rate was 99.3% in previously treated patients compared to 0.7% in new cases. This difference was statistically significant (P < 0.001) (fig-1). One hundred and eighty-five (91.6%) patients suffered from pulmonary RR-TB and 17 (8.4%) patients had RR-EPTB. In RR-EPTB group, 3 patients (17.6%) had bone RR-TB, and 14 patients (82.3%) had lymph nodes RR-TB. It was observed that 92.9% of new cases had pulmonary RR-TB as compared to 91.1% previously treated patients. New cases of RR-EPTB were 7.1% compared to 8.9% patients of previously treated cases. However, this difference was not statistically significant (0.785). Table 1 shows the breakdown of the variables associated with having RR-PTB and RR- EPTB.

Table 1: Variables Associated with Pulmonary and Extra Pulmonary RR-TB

Table 1 shows the breakdown of the variables						
Variable		Pulmonary RR-TB N = 185		Extra pulmonary RR-TB N = 17		p-value
		n	%	n	%	
Sex	Male	75	97.4	2	2.6	0.019*
	Female	110	88	15	12	
Marital Status	Married	121	94.5	7	5.5	0.047*
	Unmarried	64	86.5	10	13.5	
Education	No	85	93.4	6	6.6	0.398
	Yes	100	90.1	11	9.9	
Family Type	Nuclear	99	91.7	9	8.3	0.833
	Extended	86	92.5	7	7.5	
Alcohol	No	183	91.5	17	8.5	1.000
	Yes	2	100	0	0	
Residence	Rural	70	94.6	4	5.4	0.30

	Urban	115	89.8	13	10.2	0
Smoking	Yes	34	100	0	0	0.083
	No	151	89.9	17	10.1	
Contact History with RR-TB	Yes	82	92.1	7	7.9	0.802
	No	103	91.2	10	8.8	
Drug Use	Yes	2	100	0	0	1.000
	No	183	91.5	17	8.5	
Treatment course	Completed	84	93.3	6	6.7	0.229
	Incomplete	49	87.5	7	12.5	
Diabetes	Yes	31	100	0	0	0.081
	No	154	90.1	17	9.9	
Repeated TB Treatment	Yes	30	83.3	6	16.7	0.049*
	No	155	93.4	11	6.6	
Treatment Failure	Yes	142	99.3	1	0.7	0.782
	No	3	5.1	56	94.9	

*The *p* values indicate statistically significant differences between the 2 groups based on sex, marital status and repeat TB treatment.

Table 2 shows the various variables in relation to the site of RR-TB. There was a significant difference in the site of TB between males and females ($p = 0.019$), also the difference in marital status of patients with RR-PTB as compared to RR-EPTB was statistically significant (p=0.047). **(**It was observed that there was no statistically significant difference in incidences of RR-PTB and RR-EPTB between individuals who had taken incomplete ATT in the past and those who had not ($p = 0.229$). There was also no significant difference between individuals with RR-EPTB and RR-PTB who had suffered from treatment failure and those who did not have treatment failure ($p < 0.782$). There was a statically significant difference ($p = 0.049$) between patients with PTB and EPTB and those who had taken multiple treatment courses for TB in the past or not, with a higher number of patients with repeated treatment courses (16.7% vs 6.6%) suffering from RR-EPTB.

Table 2: Comparison of means of various factors with new and previously treated RR-TB cases

Variable	**New RR-TB**	**Previously treated RR-TB**	***p* value**	**Remarks**
	Mean ± SD	**Mean± SD**		
Age (years)	29.12 ± 16.53	32.38 ± 13.83	0.155	Not Significant

Table 2: Comparison of means of various factors with new and previously treated RR-TB cases

Income (Rupees)	20719.2± 12428.0	21437.9 ± 15564.8	0.756	Not Significant
Family Member (person)	7.94 ± 4.29	8.04 ± 5.23	0.904	Not Significant

Mean family income of RR-TB patients was 21235.14 ± 14720.79 rupees with maximum income of 100000 rupees and minimum income of 5000 rupees.

DISCUSSION

National TB Program Pakistan has defined 5 principal strategies to control DR-TB, these include early detection, implementing infection control measures, strengthening and regulation of health system, effective treatment, addressing risk factors and social determinants[4]. According to an editorial by Javaid A on DR-TB situation in Pakistan, risk factors associated with DR-TB were contact with TB/DR-TB patients, treatment failure due to any reason, illiteracy, poor socio-economic conditions, additionally, age and sex played a role as well[13].

HIV co-infection with TB is an important public health problem globally, however, various studies have determined that the incidence of HIV/TB co-infection is low in Pakistan[14]. Van den Hof et al[15] performed a meta-analysis on the relationship between DR- TB and HIV in 2015, according to which DR-TB prevalence is 20 percent higher in HIV positive patients as compared to HIV negative patients. Singh S et al[16] conducted a study regarding prevalence of HIV in Pakistan. According to them Pakistan had a very low prevalence rates in the general population that is about 0.04%. Our study supports the hypothesis that DR-TB and HIV coinfection is rare in Pakistan as all of the 202 patients in the study were tested for HIV, but all were negative.

According to Odone et al, a significant association was found between MDR tuberculosis and socioeconomic status. According to them DR-TB was more common in higher socioeconomic status patients as compared to lower[17]. Conversely, this association was not found in our study. Mean family income for our patient was only 21000 rupees.

One of the objectives of this study was to identify the association of various factors with new and previously treated RR-TB. In our study, a significant association was found between DR-TB

and female sex, with both new and previously treated RR-TB being more common in females as compared to males. Women made up 43% of the MDR cases studied by Mulisa et al in Ethiopia[18]. In a study conducted in Zambia by Mesenga et al[19], no such difference was identified in patients with RR-TB, although this study was limited by the small number of RR-TB patients in their sample. Conversely, in some international studies it is the opposite, according to Li et al[20], new cases of DR-TB are commonly diagnosed in males as compared to females. Li D et al [20] also found significant association between age of the patient and primary DR- TB (p = <0.01). In our study also, new RR-TB cases were more common in younger age group as compared to previously treated RR-TB. However, this association was statistically not significant in our study.

The percentage of new cases of RR-TB was 27.7% in our study which was comparable to the study conducted in Lahore, Pakistan by Ullah et al which found that DR-TB was 5 times more likely in previously treated patients compared to those being diagnosed for the first time[21]. In Rio de Janeiro, this was reported to be 14.7 % in the study by Marcela Bhering and Afranio Kritski[22] and 18.95% in China as reported by Wan-men Song et al [23]. It has been postulated that the differences in healthcare systems is behind the marked variability in new DR-TB cases in different countries[21]. A significant association was found between treatment failure and DR-TB. We found that among previously treated DR-TB patients' majority had treatment failure as compared to new cases with DR-TB. However, in new DR-TB cases treatment failure was very low.

In a study conducted by Elbrolosy et al in Egypt[24], TB type, contact with TB patient and history of previous TB treatment were found to be independent risk factors for the development of RR-TB. In our study, a significant association was found between repeated treatment and RR-TB. It has been well documented that repeated TB treatment is associated with DR-TB[21], the high number of DR-TB patients with previous history of TB treatment has been postulated to be the consequence of use of inadequate treatment regimens, poor compliance or interruptions in drug supply[25].

The other objective of our study was to determine the factors associated with RR-PTB versus RR-EPTB. The frequency of RR-PTB in our study was 91.5% as compared to RR-EPTB which was 8.5%, which was higher than that in Mumbai as identified by Desai et al (4.4%)[26]. According to Loutet MG[27], the percentage of DR-PTB was 82.9% as compared to DR-EPTB which was 17.1%. RR-EPTB was far less in our study as compared to this study.

Among DR-EPTB patients, the most common site was lymph nodes (82.3%) ,followed by bone TB in 3 patients (17.6%). Similar trend was seen in India in DR-EPTB patients, with nodal TB accounting for 51.3%, followed by bone and spine TB in 27.6%[26]. This contrasted with study from China where pleural TB was the most common site for EPTB followed by lymph nodes[28].

Female preponderance in cases of DR-EPTB was found in the study by Desai and Joshi in India[26], although they reported statistically insignificant difference, this was also reported by Ma et al in China for RR-TB, with an Odds Ratio of 1.6[28]. In our study, there were a statistically significant numbers of females suffering from RR-EPTB compared to males.

According to Loutet MG[27] there was a significant association between DR-PTB, DR-EPTB and previous TB treatment (p= 0.003). According to them DR-PTB is more common in previously treated cases as compared to DR-EPTB. In our study also, RR-PTB was more common as compared to RR-EPTB in new patients with RR-TB. However, the difference was not statistically significant.

It has been observed that diabetics are more likely to be diagnosed with RR-PTB compared to RR-EPTB by Ma.J in China[28]. This was also seen in our study with 100% of the patients with diabetes having DR-PTB and none of patients with diabetes being diagnosed with DR-EPTB. However, this difference was not statistically significant (p=0.081).

The limitation of our study is that no XDR-TB cases could be identified due to the limited drug sensitivity testing availability at the study site at the time of data collection.

CONCLUSION

A significant association was found between variables such as sex, marital status and history of repeated ATT in RR-PTB and EPTB patients. There were no cases of HIV in our study population of DR-TB patients. Females were statistically more likely to be diagnosed with both RR-PTB and EPTB. The previous history of ATT was the most significant risk factor for development of RR-TB. A significant association was found between treatment failure and repeat ATT in previously treated RR-TB patients as compared to new RR-TB cases.

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