Prevalence and Analysis of Drug Resistance Pattern of MDR-TB in Retreatment Cases at Allied Hospital, Faisalabad, Pakistan

Sana Arif[1], Qamar Mehboob[2], Waqar Arif[3]

1 *House Officer, Allied Hospital, Faisalabad Pakistan*
Data Collection

2 *Associate Professor, Physiology, Faisalabad Medical University, Faisalabad Pakistan*
Results Compilation, Statistical Analysis

Post Graduate Resident, Plastic Surgery Department, Allied Burn & Reconstructive Surgery Center Faisalabad
3 *Medical University, Faisalabad Pakistan*
Data Collection, Manuscript Writing

ABSTRACT

Background: The prevalence of Multi-Drug Resistance-Tuberculosis (MDR-TB) among retreatment cases is very high. It has become a serious public health issue in Pakistan and can affect greatly TB control strategies. So, we conducted the present research work to update a systematic review of the literature available on MDR-TB cases. **Objective:** To analyze the resistance pattern of multidrug-resistant tuberculosis. To study the prevalence of MDR-TB among new cases, retreatment cases. **Study Design:** Cross-sectional study. **Settings:** Pathology department, Allied Hospital, Faisalabad Medical University, Faisalabad, Pakistan. **Duration:** Six months from January 01, 2020 to June 30, 2020. **Methodology:** In this study, we included new and retreatment tuberculosis cases. Gene mutation RpoB, DNA band sequence detected by using machine, Cepheid gene Xpert IV – 4 Modules, Sr # 806133. Data was collected and analyzed statistically by using SPSS v 20. **Results:** 858 cases were included of age 12 years – 100yrs with the mean age (in years) 42.139 ± 16.823. Two groups of males and females were studied separately. Group I included male patients {456 (56.64%)} and further subdivided into IA [age above 30 years, {354(72.84%)}] and IB [age below 30 years {132 (27.15%)}]. Group II included female patients {372 (43.36%)} and further subdivided into IIA [age above 30 years {239 (64.25%)}] and IIB [age below 30 years {133(35.75%)}]. Out of 858 cases, 347 (40.44%) were New cases, 13 (1.51%) New cases with HIV and 408 (47.55%) were Previously Treated patients (PT). 30 (3.45%) cases were unknown (UK). 28 (3.26%) cases were brought by different lady health workers (LHW) and relapse cases were 32 (3.73%). Overall statistical analysis was found to be highly significant (p=0.000, df= 1, CI= 95%). According to our results, in 517 (60.26%) patients, Mycobacterium Tuberculosis was not detected (MTB-ND). In 214 (24.94%) cases, Mycobacterium Tuberculosis was detected (MTB-D), out of which 13 (6.07%) cases were of First-Line Multi Drug Resistance (MDR). Age of MDR cases was in between 17- 70 years with the mean age (in years) 37.307 ± 17.637. Our results showed MDR more in males (53. 85%) as compared to female patients (46. 15%). Our results showed a significant correlation between status of all cases and their reports (p= -.050). For MTB-ND cases p= 0.000, df =1, CI=95% and for invalid cases p= 0.000, df =5, CI=95%. **Conclusion:** There is a great need to implement national tuberculosis guidelines fully. In order to prevent further emergence of drug resistance, we should focus on effective implementation of directly observed therapy short courses.

Keywords: Multi drug resistance, Retreatment cases, Tuberculosis.

INTRODUCTION

Tuberculosis (TB) has remained a global health problem for last many years.[1] In present condition, there are 22 countries that have almost 80% of the world's TB cases. Unfortunately, documented data of these high burden countries do not reflect the actual figures because of improper data collection processes, or incomplete coverage.[2] In 2020, Gauri Suhas Kulkarni reported that in most of the countries MDR-TB is a major health problem which can be an obstacle to effective TB control.[3] Multiple studies have been conducted for the assessment of the risk factors leading to the increase ratio of MDR-TB.[4] Multidrug-resistant tuberculosis (MDR-TB), resistant to both isoniazid and rifampicin, is a serious health problem, not only for the public health sector but also to the general physicians, as well as the pulmonologists of Pakistan, who are treating TB.[5]

According to the latest Global TB Report, during 2018, approximately 484,000 people developed rifampicin-resistant (RR) /MDR-TB globally, 3.4% new and 18% of previously treated cases of TB, were rifampicin resistant (RR) /MDR-TB.[6] Only in China, 24% of previously treated cases and 7.1% of new cases had MDR-TB, more than the global averages.[7] So, strength MDR-TB management is very difficult to control the prevalence of MDR-TB.[8]

Due to poverty and some other risk factors, the geographic distribution of the disease may vary worldwide, as well as within the country.[9,10] Delayed drug susceptibility testing before MDR-TB diagnosis could result in further transmission of drug resistant TB strains and use of inappropriate regimen of second line drugs would increase the risk of their resistance.[11] In 2019, Gelaw YA reported that low altitude areas and high temperature increases the TB incidence.[12,13]

Pakistan ranks 5th amongst the high burden countries in the world. The prevalence, incidence and mortality per 100,000 populations per year from TB in Pakistan are 340, 265 and 27 respectively.[14] According to a report of the Global Tuberculosis Community Advisory Board, in Pakistan, the number of TB patients is increasing rapidly at an estimated rate of 27,000 new cases per year.[15] World Health Organization (WHO) reported that during 2018, 562000 TB cases fell ill in Pakistan out of which 44000 cases died. While 28000 people fell ill with drug-resistant TB[16]. So, the current study was planned to determine the prevalence and drug resistance patterns of MDR-TB in retreatment case at FMU, Allied Hospital, Faisalabad.

Objective: Our study aims to study the prevalence of MDR-TB among new cases and retreatment cases and to analyze the resistance pattern of MDR-TB. To find out the factors associated with RR-TB among DR-TB patients and also to determine the correlation of RR-TB with MDR-TB.

METHODOLOGY

Study Design: Cross-sectional study.

Settings: Pathology department, Allied Hospital, Faisalabad Medical University, Faisalabad, Pakistan.

Duration: Six months from January 01, 2020 to June 30, 2020.

Sample Technique: Non-probability consecutive sampling.

Sample Size: 858 cases

Inclusion Criteria: Those who were taking anti TB treatment. Previously treated, relapse and new cases. Male, female

Exclusion Criteria: Extra pulmonary TB. Patients with no anti-TB drug treatment.

Data Collection Procedure: This cross-sectional multi-site study was carried out in six months from January 01, 2020 to June 30, 2020 at Allied Hospital Faisalabad, and included 858 cases. Gene mutation RpoB, DNA band sequence detected by using machine, Cepheid Gene Xpert IV – 4 Modules, Sr # 806133, placed at Bio Safety Lab II (BSL-II). Data was collected and analyzed statistically.

RESULTS

858 cases were included of age 12 years – 100yrs with the mean age (in years) 42.139 ± 16.823. Two groups of males and females were studied separately. Group I included male patients {456 (56.64%)} and further subdivided into

IA [age above 30 years, {354(72.84%)}] and IB [age below 30 years {132 (27.15%)}]. Group II included female patients {372 (43.36%)} and further subdivided into IIA [age above 30 years {239 (64.25%)}] and IIB [age below 30 years {133(35.75%)}]. (Table: 1, 2, Fig: 1). Statistical analysis showed p=0.000, df= 1, CI= 95%.

Table 1: Age (in years). n=858.

Statistics		
Age		
N	Valid	858
	Missing	1
Mean		42.1399
Std. Deviation		16.82324
Minimum		12.00
Maximum		100.00
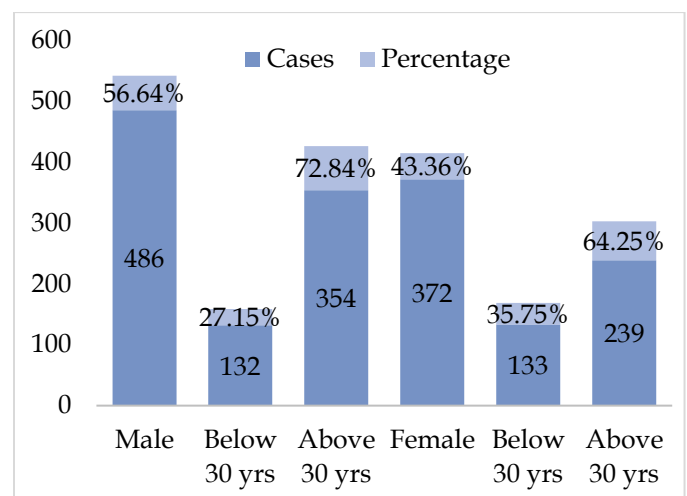
Figure 1: Age and gender distribution of study subjects (n=858)

In our study, we included, out of 858 cases, 347 (40.44%) New cases, 13 (1.51%) New cases with HIV, 408 (47.55%) Previously Treated patients (PT). 30 (3.45%) cases were unknown (UK). 28 (3.26%) cases were brought by different lady health workers (LHW) and relapse cases were 32 (3.73%). (Table 2)

Table 2: Details of status of the cases (n=858)

Status	Cases	Percentage
New	347	40.44
New. HIV	13	1.51
PT	408	47.55
UK	30	3.45
LHW	28	3.26
F.up New/PT (Relapse)	32	3.73

PT= Previously Treated, UK= Unknown, LHW= Cases brought by Lady Health Worker, F.up= Follow up/Relapse

In our study, we used following definitions:[17]

➢ New case: All TB cases that never took treatment for TB or has taken the treatment for less than 1 month.
➢ Retreatment case: Includes cases of failure, relapse, treatment after default, and others.
➢ MDR-TB case: A suspected case who is bacteriologically confirmed of Tuberculosis and has Mycobacterium TB resistant to first-line anti-TB drugs, either with or without resistance to other anti-TB drugs, based on drug sensitivity testing (DST) results.

According to our results, in 517 (60.26%) patients, Mycobacterium Tuberculosis was not detected (MTB-ND). In 214 (24.94%) cases, Mycobacterium Tuberculosis was detected (MTB-D), out of which 13 (6.07%) cases were of First-Line Multi Drug Resistance (MDR). These cases included 3 (23.08) new cases and 10 (76.92%) were Previously Treated patients. Out of 13 MDR cases, 7 (53.85%) were male and 6 (46.15%) were female. Age of MDR cases was in between 17- 70 years with the mean age (in years) 37.307 ± 17.637.

Our results showed MDR more in males (53.85%) as compared to female patients (46.15%). We did not check 2nd-line MDR because of limitations of Gene Xpert. Line Prob Assay (LPA) was not functioning. In 201 (93.93%) cases, Mycobacterium Tuberculosis was detected but they did not show MDR so we labeled them as Non-Resistant/ not detected, cases (ND). Errors appeared in 117 (13.64%) cases due to different factors like temperature or in correct sequence of nucleotide bases. Reports of 10 (1.16%) cases were invalid. (Table 3,4)

Table 3: Categories of multidrug-resistant tuberculosis cases (n=858)

Status			Cases	Percentage
MTB-ND			517	60.26
MTB-D			214	24.94
	MDR		13	6.07
		New	3	23.08
		PT	10	76.92
		Male	7	53.85
		Female	6	46.15
	ND		201	93.93
Errors			117	13.64
Invalid			10	1.16

MTB-ND = Mycobacterium Tuberculosis Not Detected, MTB-D = Mycobacterium Tuberculosis Detected, MDR = Mycobacterium Tuberculosis Detected with Multi Drug Resistance, ND = Mycobacterium Tuberculosis Detected with No Resistance

Table 4: Age of MDR cases (n=13)

Statistics		
MDR		
N	**Valid**	13
	Missing	846
Mean		37.3077
Std. Deviation		17.63701
Minimum		17.00
Maximum		70.00

All the data was collected and statistically analyzed through SPSS v 20. Chi-Square and T- Test were applied, where needed. Our results showed a significant correlation between status of all cases and their reports (p= -.050). For MTB-ND cases p= 0.000, df =1, CI=95% and for invalid cases p= 0.000, df =5, CI=95%.

Table 6: Gender status cross tabulation

Gender * Status * Report Cross tabulation									
Count									
Report			Status						Total
			New	New HIV	PT	UK	LHW	Relapse	
MTB-ND	Gender	Male	78		408				486
		Female	31		0				31
	Total		109		408				517
MDR	Gender	Female		3			10		13
	Total			3			10		13
ND	Gender	Female	201						201
	Total		201						201
Error	Gender	Female	37			30	18	32	117
	Total		37			30	18	32	117
Invalid	Gender	Female		10					10
	Total			10					10
Total	Gender	Male	78	0	408	0	0	0	486
		Female	269	13	0	30	28	32	372
	Total		347	13	408	30	28	32	858

DISCUSSION

Multi Drug Resistance-TB is a manmade phenomenon. Factors like poor adherence to treatment, use of inadequate regimens and inappropriate directly observed treatment short-course (DOTS) leads to increase in the drug resistance levels in our country. The improperly treated or undiagnosed patients with resistant strains of TB are being a continuous source of ongoing transmission of resistant strains. In a resource-limited country such as Pakistan, there are limitations to the affordability and availability of drug sensitivity testing (DST) facilities. So, most of the MDR is diagnosed presumptively based on the lack of response to treatment or relapse of symptoms in TB cases. In present study, our results showed very low prevalence of MDR-TB, namely 0.349% in new TB cases and 1.165% in retreatment cases, as compared to other studies.

In present study, our results showed very low prevalence of MDR-TB, namely 0.349% in new TB cases, 1.165% in retreatment cases and in new/ re-treatment (both) cases is 1.515% as compared to other studies. In their study, Rashid A. Khan[4] et al showed prevalence of MDR-TB in new/ re-treatment (both) cases as 40.2%, Abdul Majeed Akhtar et al[18] showed 41% cases, Angrup[19] et al as 5-12.7% cases and Datta[20] et al as 5.75% cases. Gauri Suhas Kulkar[3] et al showed 0.10 % in new TB cases and 4.3% in retreatment cases while Mistry[21] et al showed 24-30% in new TB cases and 11.67%in retreatment cases. In another study conducted by Zhengwei Liu[8] et al 1.1% new TB cases and 3.4% retreatment cases were reported.

In present study we also found less prevalence in new cases (0.35%) while high prevalence in retreatment cases (1.16%).

After a non-systematic search of the literature, G B Migliori[22] et al reviewed the core published documents and guidelines to provide public health workers and clinicians with an updated and easy-to-consult document arising from consensus of Global Tuberculosis Network (GTN) experts., including the recently published MDR-TB WHO rapid advice and guidelines. They reported that early diagnosis and successful treatment of MDR-/XDR-TB depend on universal DST. In another study forwarded by Angelo Iacobino[23] et al, it was mentioned that human errors may contribute to the development of DR because of the improper use of anti-TB drugs.

In 2020, Xu-Bin Zheng[24] et al reported that in China, most of the patients did not receive proper MDR-TB treatment so their delayed diagnosis resulted in poor quality of MDR-TB care. It is the need of the day that regulated patient management, including rapid diagnosis and high-quality MDR-TB treatment should be enhanced.

Regarding the limitation of the study, all new and retreatment cases were not subjected to DST because of the limitation of resources. Only suspected patients i.e. category-I failure and category-II failure were subjected to DST. This could be the most probable reason for the low prevalence of MDR-TB in our study.

CONCLUSION

In Pakistan MDR-TB is a serious public health problem which greatly affects TB control strategies. The prevalence of MDR-TB among retreatment cases is high. The National TB guidelines should be fully utilized by focusing on expansion and effective implementation of directly observed therapy short courses. It will prevent further emergence of drug resistance.

LIMITATIONS

The study was limited to cases of Faisalabad Division. Nationwide sample collection can change the outcome.

SUGGESTIONS / RECOMMENDATIONS

We suggest that more and more TB preventive programs should be introduced. The findings of our research work support the recommendations of finding the high rate of MDR and to implement a strategy for those cases that have dropped out of their treatment protocol to control the multi-drug resistance-TB.

CONFLICT OF INTEREST / DISCLOSURE

No conflict of interest to be declared.

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