Factors associated with new and re-treated Multidrug-Resistant Tuberculosis in Khyber Pakhtunkhwa

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Author Contributions

SK MAK SMN conceived idea, SK AK AL AJ drafted the study, MAK SMN collected data, MAK SMN did statistical analysis & interpretation of data, SK AK AL AJ critical reviewed manuscript, Both approved final version to be published.

Declaration of conflicting interests

The Authors declares that there is no conflict of interest.

Abstract

Background: The resurgence of Tuberculosis (TB) in the form of Multi-drug Resistant Tuberculosis (MDR-TB) is a major threat to all efforts of TB control programme throughout the world. Previous treatment with antituberculosis (ATT) and its related risk factors associated with MDR-TB is of great importance. Therefore, this study was conducted with the aim to find out the factors associated with development in new and previously treated MDR-TB.

Methodology: A retrospective record review study was conducted at Programmatic Management of Drug Resistant TB (PMDT) Unit, Lady Reading Hospital (LRH) Peshawar, Pakistan on all enrolled MDR-TB patients from January 2012 till December 2015. Data collection included social-demographic characteristics, past medical history and behavioral risk factors. Data was analyzed using multiple logistic regressions after transferring into SPSS version 20.

Results: : In this study a total of 1168 MDR-TB patients included from the year 2012 to 2015. Among the study cases majority of the patients (56.2%) were female and 49.8% were from group age 21 to 40 years of age. Twenty three percent of the study cases were age less than 40 Kg at their baseline of treatment. Most of the patients 66.8% were from rural area and 78.3% were unmarried. Among study cases number of patients declared as re-treated were of higher number (1013) as compared to new cases (155). In both groups numbers of female patients (7.3% & 49.0%) were high as compared to male. Significant associations were found between re-treated and new MDR-TB cases factors such as marital status ($P < 0.002$), family history of TB ($P< 0.001$), duration of illness ($p < 0.002$) and smoking or other drugs etc addicts ($P < 0.004$).

By multiple logistic regression, the significant potential factors include Family history with TB, past treatment, drugs etc addiction, aged people showed positive significant association within retreatment studied MDR-TB cases by AOR [(95%CI) 5.26(2.76 - 86), ($P < 0.004$)] drug abuse/smoking etc [11.35 (1.17 - 34.61), ($P < 0.002$), aged people [(9.3 (2.76 – 11.78), ($P < 0.001$)].

Conclusion: This study concluded that gender, previously treated patients, patients with longer time of duration, smoking or drug abuse and marital status were factors significantly associated with previously treated MDR-TB cases and previously treated with new patients also treated with antitubercolous treatment. These findings would be beneficial to our TB control programme and help in the control of TB/MDR-TB and cut off the chain of disease and lower the prevalence and incidence of TB/MDR-TB.

Key Words: TB; MDR-TB; Peshawar

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Introduction

The occurrence of TB in its resistance forms especially Multidrug-Resistant Tuberculosis (MDR-TB) is challenging all efforts of Global TB control and still remains a disease of global concern.[1] Rate of MDR-TB is increasing throughout the world both in developed and developing countries and effected all population with all ages groups. According to World Health Organization (WHO) report, TB infected one-third of the world's population and affected 9.4 million people annually with approximately 2 million deaths occur each year due to this disease.[1]

In the present time it's more severe types MDR-TB is a type, which is caused by a Mycobacterium Tuberculosis strain that showed resistant to at-least two most powerful first line anti-tuberculosis drugs named Isoniazid (INH) and Rifampicin (RMP).[2-4] Its treatment is very difficult as compared to drug susceptible TB as it approximately took two years for the complete resolve of the illness with more drugs of severe side effects with high cost. It is known as man-made disease and one of the main factors responsible for this disease is lack of knowledge of TB infection and treatment. Other factors like overcrowding, poor living conditions, alcohol consumption, drug abuse, immigration, gender, age, HIV/AIDS and poor socioeconomic status are point out by different studies to associate with higher risk of developing MDR-TB.[2-6] Due to a rapid increase in the incidence of MDR-TB, it is very important to find out the responsible factors and tried to resolve that factors as early as possible to stop its spreading further and get a good outcome.

Pakistan is among the top listed countries and ranking 4th among the top 22 high MDR-TB burden countries and WHO has estimated annual incidence of approximately 15000 MDR-TB cases in Pakistan.[1,7] The increasing rate of DR-TB in Pakistan underscores the importance of effective treatment programs for DR-TB. There is an urgent need for extensive research to elaborate efficient diagnosis, treatment, and control of MDR-TB as poor implementation of treatment protocols leads to further resistance, which emerge in the form of XDR-TB. Different researchers point out in different studies that the greatest risk for the development of MDR-TB is mostly related with their previous treatment with anti-TB medication.[8,9] However, very little is known regarding this issue and other factors associated with developing MDR-TB in the present center. Therefore, this study was performed with the aim to determine the factors associated with the development of MDR-TB in new and previously treated TB.

Methodology

Study design and settings

Pakistan is among the top TB burden countries and due to increasing rate of DR-TB throughout the country, patients are treated through Programmatic Management of Drug Resistant TB (PMDT). Different PMDT sites are functional in the country; Lady Reading Hospital Peshawar (LRH), Pakistan is one of most sophisticated health care setup in the Khyber Pakhtunkhwa Province. By utilizing its own resources, the LRH provided support for MDR patients between 2008 and 2012. In 2012 the National TB Control Programme declared the hospital as its PMDT site.

This retrospective cohort study was conducted at PMDT-LRH Peshawar, Pakistan. All confirmed pulmonary MDR-TB patients who were consecutively enrolled for treatment at the study site between January 2012 and December 2015 were included in the study. All the enrolled patients were treated on an ambulatory based care model and were properly examined by a team of clinicians on a monthly basis. All registered patients were initially started on a standardized treatment regimen, and then shifted to individualized regimens according to individual drug susceptibility test results.

Sputum smear, culture, and chest radiographs (CXR) were obtained at the time of enrollment, and then monthly during the intensive phase of treatment, whereas the continuation phase was accompanied by monthly smear and bimonthly culture and chest radiograph. All patients were tested at baseline for HIV, and blood investigations were performed at baseline, and at every month as per national DR-TB guidelines. Patients' compliance and medication adherence was closely monitored by trained treatment supporters and directly observed therapy facilitators. All patients were psychologically assessed, and personalized counseling was provided on monthly follow up visits. Home visits were arranged for individual patient for contact screening, infection control measures at home and to create a liaison with the regional district TB officer. Adverse events if any, associated with second line drugs were monitored and managed promptly, utilizing multiple approaches of counselling, administering ancillary drugs and in rare cases, permanent removal of any culprit drug from the treatment regimen as a last resort. Patients received counseling to maximize adherence, nutritional support, and transportation reimbursement for their ambulatory visits.

The study cases were divided into two groups i.e. new and previously treated MDR-TB. New MDR-TB cases were defined as cases where upon MDR-TB diagnosis had not undergone previous TB treatment of any kind, while previously treated MDR-TB cases were defined as

cases where upon MDR-TB diagnosis had already received anti-TB treatment.

Data collection and analysis

Both paper-based as well as electronic documentation were used for efficient and proper utilization of data. Parameters included in documentation were patients' demographics and their clinical and microbiological data. Demographics data included gender, age, weight, co-morbidities, area of residence, and close contacts. Clinical data included history and outcome of previous TB treatment, previous medication history of any second line drugs and radiological findings at baseline chest x-ray. Microbiological data was composed of baseline sputum smear grading, DST result, and monthly microbiological culture status.

The Statistical Package for Social Sciences (SPSS) version 20.0 was used for data entry and data analysis. Descriptive analysis was presented as mean and standard deviations (SD) for normally distributed numerical variables. For categorical variables, the data was presented as frequency (n) and percentage (%). The Pearson chi-square test or Fisher's exact test was applied to determine the differences of proportion for both groups. Simple logistic regression and multiple logistic regression analysis were used to determine the potential factors associated with new and previously treated MDR-TB cases.

Ethical Approval

The ethical certificate was obtained from the Ethical Board of Postgraduate Medical Institute Peshawar Pakistan.

Results

In this study a total of 1168 MDR-TB patients included for study purpose. These all patients were enrolled for MDR-TB through Programmatic Management of Drug Resistant TB treatment system from the year 2012 to 2015. At the time of analysis all patients achieved their final treatment outcomes. Among the study cases majority of the patients (56.2%) were female and 49.8% were from group age 21 to 40 years of age. Twenty three percent of the study cases were age less than 40 Kg at their baseline of treatment. Most of the patients 66.8% were from rural area and 78.3% were unmarried. Majority of the patients were from poor family and 39.1% the patients were daily labour and 33.3% females were housewife. Eighty three percent of the patients had any TB contacts present in household and 66.2% among the total patients became ill for less than 1 year before enrollment for MDR-TB treatment. Most of the patients (86.7%) treated for simple TB treatment in the past before registration for treatment. Diabetes Mellitus and important predictor for lower immune system also found here in these patients. DM was present among 19.1% of the study cases. As TB is the disease of poor, here in this study 69.8% of the patients were monthly income up to Rs. 10,000. Thirty nine percent of the patients living with family members of 8 to 9 family members per family and among them 39.3% were illiterate (Table 1).

Among study cases number of patients declared as re-treated were of higher number (1013) as compared to new cases (155). In both groups numbers of female patients (7.3% & 49.0%) were high as compared to male. Similarly unmarried patients were high among re-treatment cases and 57.7% cases of rural patients were from re-treatment cases. Majority of study cases (62.3%) were any household TB contacts and were from re-treatment patients group whereas illness time of 55.6% were more than one year and these patients also belongs to re-treatment study groups (Table 2).

Table 1: Baseline socio-demographic characteristics of multi drug resistant tuberculosis patients from Pakistan (n = 1168)

Patients characteristics	No. of patients	Percentage
Gender		
Male	511	43.8
Female	657	56.2
Age (years)		
0 – 10	09	0.8
11 – 20	294	25.2
21 – 30	392	33.6
31 – 40	185	15.8
41 – 50	119	10.2
51 – 60	97	8.3
>61	72	6.2

Weight (Kg)		
<40	268	23.0
40-55	666	57.0
56-65	105	9.0
>66	129	11.0
Residence		
Urban	389	33.3
Rural	779	66.7
Marital status		
Married	370	31.7
Unmarried	798	68.3
Occupation		
Labour	457	39.1
Student	201	17.2
House wife	389	33.3
Others	121	10.4
Family history of TB		
Yes	861	73.7
No	307	26.3
Duration of Illness		
Less than or equal to 1 year	486	41.2
Greater than 1 year	682	58.8
Registration Group		
New	155	13.3
Re-Treatment	1013	86.7
Diabetes Mellitus		
Yes	223	19.1
No	945	80.9
Smoking		
Yes	71	6.1
No	1097	93.9
Monthly income (Rs)		
8000	510	43.7
10,000	201	26.1
15,000	389	30.2
No. of family members in a house		
4-7	506	43.3
8-9	462	39.6
>11	200	17.1
Literacy		
Illiterate	459	39.3
Primary	299	25.6
Middle	202	17.3
Metric	106	9.1
Intermediate	71	6.1
Graduate	31	2.6

Table 2: Socio demographic characteristics of new Vs previously treated MDR-TB cases

Patients characteristics	New (155)	Re-treatment (1013)
Gender		
Male	70 (6.0)	441 (37.8)
Female	85 (7.3)	572 (49.0)
Age Group		
0 – 10	4 (0.3)	5 (0.4)
11 – 20	41 (3.5)	253 (21.6)
21 – 30	47 (4.0)	345 (29.5)
31 – 40	19 (1.6)	166 (14.1)
41 – 50	17 (1.4)	102 (8.7)
51 – 60	16 (1.3)	81 (6.9)
>61	11 (0.9)	61 (5.2)
Weight (Kg)		
<40	48 (4.1)	220 (18.8)
40-55	67 (5.7)	599 (51.2)
56-65	18 (1.5)	87 (7.4)
>66	22 (1.8)	107 (9.1)
Residence		
Urban	53 (4.5)	336 (28.7)
Rural	102 (8.7)	677 (57.9)
Marital status		
Married	49 (4.1)	321 (27.4)
Unmarried	166 (14.2	632 (54.1)
Occupation		
Labour	58 (4.9)	399 (34.1)
Student	33 (2.8)	168 (14.3)
House wife	51 (4.3)	338 (28.9)
Others	13 (1.1)	108 (9.2)
Family history of TB		
Yes	133 (11.3)	728 (62.3)
No	22 (1.8)	285 (24.4)
Duration of Illness		
Less than or equal to 1 year	123 (10.5)	363 (31.0)
Greater than 1 year	32 (2.7)	650 (55.6)
Diabetes Mellitus		
Yes	38 (3.2)	185 (15.8)
No	117 (10.0)	828 (70.8)
Smoking		
Yes	17 (1.4)	54 (4.6)
No	128 (10.9)	969 (82.9)
Monthly income (Rs)		

As shown in Table 3, significant associations were found between re-treated and new MDR-TB cases factors such as marital status (P < 0.002), family history of TB (P< 0.001), duration of illness (p < 0.002) and smoking or other drugs etc addicts (P < 0.004).

By multiple logistic regression, the significant potential factors include Family history with TB, past treatment, drugs etc addiction, aged people showed positive significant association within retreatment studied MDR-TB cases by AOR [(95%CI) 5.26(2.76 - 86), (P < 0.004)] drug abuse/smoking etc [11.35 (1.17 - 34.61), (P < 0.002), aged people [(9.3 (2.76 – 11.78), (P < 0.001)].

8000 10,000 15,000	63 (5.3) 51 (4.3) 41 (3.5)	447 (38.2) 150 (12.8) 348 (29.7)
No. of family members in a house		
4-7 8-9 >11	76 (6.5 63 (5.3) 16 (1.3)	430 (36.8) 399 (34.1) 184 (15.7)
Literacy		
Illiterate	63 (5.3)	396 (33.9)
Primary	37 (3.1)	262 (22.4)
Middle	27 (2.3)	175 (14.9)
Metric	12 (1.0)	94 (8.0)
Intermediate	11 (0.9)	60 (5.1)
Graduate	5 (0.4)	26 (2.2)

Discussion

Multidrug Resistant TB is deadly disease that challenging all efforts against TB and continue remain factors for human morbidity and mortality as well as striking the most vulnerable age group of the society. Its treatment is very difficult treatment due to high number of drugs with severe side effects for a very long duration up to two years with lower successful outcome rate as compared to drug susceptible TB.[2,10] So it is of much important to stop its spreading and limit its rate. For this it is very important to identify the risk factors associated with MDR-TB. Identification of specific risk factors help in treatment selection by selecting appropriate treatment regimen for each patient, thus preventing delay in the initiation of treatment and hence achieved successful outcomes. For improvement in the treatment and reduce its high cost it is very important to sustained this practice of finding the risk factors of the disease and try to control those risk factors and implement daily DOTS by training house hold of patient and specially treatment supporter of patient. Different studies have been conducted throughout the world for finding the risk factors of MDR-TB and all these studies concluded that older age, lower socioeconomic status, lower weight, bacilliary load, severity of disease and previously use anti-TB drugs. So this study was conducted at Khyber Pakhtunkhwa to find out factors associated with MDR-TB among new and re-treatment cases.[11-14]

Another important characteristic is age of patient. In this study the most effected people by this disease were of age lower than 40 years of age. Few more studies also concluded that the young people were most affected by this disease. Few other studies also explained the same situation.[15,16] This study also stated that majority of the patients in both groups were very poor and this observation were also explained by some other studies.[17,18]

Another important characteristics is that majority of the patients in both group belongs from rural area where prevalence of disease is greater due to poverty and unavailability of health services and poor infectious control measurement and specially in those family where already patient present.

This study also explains the factors related with MDR-TB in new as well as retreated patients. For successful management of TB/MDR-TB and for achievement of successful outcomes it is very important to find out these factors and try to resolved these factors as early as possible. An important factor is drug abuse or smoking which can alter the efficacy of treatment or may cause failure in achieving successful outcome. Few studies also favored this finding as described by Read et al., in a longitudinal cohort study, conducted at the National Masan Tuberculosis Hospital in the Republic of Korea in the year 2013 [19] by salama et al in 2007,[20] and by Magee in 2014 in a study from Georgia. [21]

Another important factor is comorbid Diabetes Mellitus (DM), which can also affect treatment and occurrence of MDR-TB. Few other studies also favour this findings.[19-21] Now a day according to global report DM is one of the important factors in the resurgence of TB/MDR-TB as DM degrade the immune system and due to lower immune system patient become sensitive to MTB and also recovery against disease is slow so achievement of successful outcomes is much difficult. Hence patient with DM remain ill for long time and treated again and again for any disease and hence resistance also developed.

Previous treatment is most important factor in MDR-TB. Previous treatment with unsuccessful outcome is of much concerned as treatment failure and defaulted patient is the most contributing factor for occurrence of MDR-TB and this study also pointed out this factor and this is also concluded by some other studies as a French study found a higher risk of MDR-TB in both new

Table 3: Univariate analysis of factors potentially contributing to new and previously treated MDR-TB

Patients characteristics	New (155)	Re-treatment (1013)	P-value
Gender			
Male	70 (6.0)	441 (37.8)	
Female	85 (7.3)	572 (49.0)	0.7284
Age Group			
0 – 10	4 (0.3)	5 (0.4)	
11 – 20	41 (3.5)	253 (21.6)	
21 – 30	47 (4.0)	345 (29.5)	
31 – 40	19 (1.6)	166 (14.1)	1.0000
41 – 50	17 (1.4)	102 (8.7)	
51 – 60	16 (1.3)	81 (6.9)	
>61	11 (0.9)	61 (5.2)	
Weight (Kg)			
<40	48 (4.1)	220 (18.8)	
40-55	67 (5.7)	599 (51.2)	
56-65	18 (1.5)	87 (7.4)	0.0136
>66	22 (1.8)	107 (9.1)	
Residence			
Urban	53 (4.5)	336 (28.7)	
Rural	102 (8.7)	677 (57.9)	0.854
Marital status			
Married	49 (4.1)	321 (27.4)	
Unmarried	166 (14.2	632 (54.1)	0.002
Occupation			
Labour	58 (4.9)	399 (34.1)	
Student	33 (2.8)	168 (14.3)	
House wife	51 (4.3)	338 (28.9)	
Others	13 (1.1)	108 (9.2)	
Family history of TB			
Yes	133 (11.3)	728 (62.3)	< 0.001
No	22 (1.8)	285 (24.4)	
Duration of Illness			
Less than or equal to 1 year	123 (10.5)	363 (31.0)	
Greater than 1 year	32 (2.7)	650 (55.6)	< 0.002
Diabetes Mellitus			
Yes	38 (3.2)	185 (15.8)	
No	117 (10.0)	828 (70.8)	0.3677
Drug **abuse / Smoking**			
Yes	17 (1.4)	54 (4.6)	
No	128 (10.9)	969 (82.9)	0.004
Monthly income (Rs)			

8000	63 (5.3)	447 (38.2)	
10,000	51 (4.3)	150 (12.8)	0.0142
15,000	41 (3.5)	348 (29.7)	
No. of family members in a house			
4-7	76 (6.5	430 (36.8)	
8-9	63 (5.3)	399 (34.1)	0.210
>11	16 (1.3)	184 (15.7)	
Literacy			
Illiterate	63 (5.3)	396 (33.9)	
Primary	37 (3.1)	262 (22.4)	
Middle	27 (2.3)	175 (14.9)	0.304
Metric	12 (1.0)	94 (8.0)	
Intermediate	11 (0.9)	60 (5.1)	
Graduate	5 (0.4)	26 (2.2)	

and previously treated patients from sub-Saharan Africa, while patients from North Africa were at higher risk of MDR-TB only after previous treatment.[22] Similarly in Hong Kong, a study reported that MDR-TB patients who had a previous history of TB medication were found to be positive association with the occurrence of MDR-TB.[23]

Household contacts with positive disease are other factors responsible for MDR-TB in both of the study groups. As these individuals are continuously remains a source of infection and other households remain at high risk to catch the infected particles. Another study from the same centre conducted between January 2012 and December 2012. In this study a total of 154 index MDR-TB cases were include. For study purpose their home visits were conducted. Of 610 contacts who studied, 41 (17.4%) were diagnosed with MDR-TB and 10 (4.2%) had TB.[3] So it is very important that regular contact screening advised for each patients.

Conclusion

This study concluded that gender, previously treated patients, patients with longer time of duration, smoking or drug abuse and marital status were factors significantly associated with previously treated MDR-TB cases and previously treated with new patients also treated with antitubercolous treatment. These findings would be beneficial to our TB control programme and help in the control of TB/MDR-TB and cut off the chain of disease and lower the prevalence and incidence of TB/MDR-TB. Furthermore such studies to investigate the cause of MDR-TB in new as well as re-treatment cases should be conducted so that preventive measures can be taken.

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