

Original Article

Risk Factors Associated with Lost to Follow up Among Multidrug Resistance Tuberculosis Patients Registered for Treatment in Programmatic Management of Drug Resistant Tuberculosis Sites of Punjab, Pakistan

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ABSTRACT

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Introduction: Pakistan, a country with a 27 high burden countries of multidrug resistance tuberculosis. To predict the associated risk factors and proportion of loss to follow up among MDR-TB patients treated at PMDT sites of Punjab from 2017 to 2019.

Methodology: This case control study based on the standardized reporting and recording case record forms called as Electronic Nominal Review System (ENRS) of National TB Control Program, Pakistan. A logistic regression model was used to assess risk factors of lost to follow up MDR-TB patients.

Results: A total of 539 patients with MDR-TB were included in the final analysis. Among them, 207 patients (7.5%) had lost to follow up outcome at the end of the study. MDR-TB lost to follow up patients were more likely to report older age (AOR: 1.40, CI: 1.14-1.71, p=0.000), history of lost to follow up from first line drugs treatment (AOR: 0.39, CI: 0.28-0.56, p=0.000), co-morbid (AOR:1.54, CI: 1.24-1.91, p=0.000), adverse reaction of second line drugs (AOR: 0.45, CI: 0.37-0.56, p=0.000), long distance between patient's home and PMDT site (AOR: 0.68, CI: 0.52-0.89, p=0.001).

Conclusion: The history of lost to follow up from first line drugs treatment, co-morbid, older age and long distance were independent risk factors of MDR-TB. Proper training for PMDT sites staff, friendly follow up services and psychological counseling may help to reduce lost to follow up.

Introduction:

There were an estimated 4.2% (95% CI: 3.2-5.3%) new cases and 16% (95% CI: 15-17%) previously treated cases of MDR-TB from 2017 data in Pakistan (WHO, 2018). Drug Resistance Tuberculosis (DR-TB) has become a major health issue with great challenges for public and private health

sectors in Pakistan. Punjab is listed as the most populous province of the Pakistan so 56% cases of Tuberculosis were detected in the Punjab (PTP-Punjab, 2013). Lost to follow up rate in Pakistan is high from the rates reported among MDR-TB patients globally as some authors have also estimated lost to follow up rates of 19.2% from India (Shringarpure, 2015), 29.1% from Taiwan

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(Chiang, 2006), 39% from Korea (Kim, 2001), 40% from Georgia (Kuchukhidze, 2014), 55.6% from Karachi (Rao, 2009) and 30% from Punjab Pakistan (Khurram 2012). National TB Programmes (NTP) is facing the challenges of adherence to treatment and treatment completion among MDR-TB patients globally. Predicting the risk factors of lost to follow among MDR-TB patients would help NTP to plan effective interventions for treating this problem. According to national policy of NTP Pakistan, MDR-TB is defined as resistance to at least both isoniazid and rifampicin. Similarly, cured is the treatment of at least 18 months past culture conversion without evidence of failure and 5 consecutive cultures taken at least 30 days apart are negative after the intensive phase while a MDR-TB patient whose treatment was interrupted for two consecutive months or more was declared as lost to follow up (National guideline, 2018).

Methods:

This case-control study was conducted to evaluate risk factors associated with lost to follow up among patients diagnosed and treated for MDR-TB. Cases were stratified as patients who began MDR-TB treatment from 1st January 2017 through 31st December 2019 and lost to follow up from treatment for more than 2 consecutive months while controls were stratified as patients who began MDR-TB treatment during the same period and were declared cured.

Since 2010, all Programmatic Management of Drug Resistant TB (PMDT Sites) in Punjab, Pakistan have applied standardized programmatic management of MDR-TB and treatment. The provincial tuberculosis control program Punjab (PTP-Punjab)

implemented standardized reporting and recording case record forms called as Electronic Nominal Review System (ENRS), completed by MDR-TB physicians, pharmacist, treatment coordinator and data person. All management decisions and treatment of MDR-TB were made according to the guidelines of National Tuberculosis Control Program Pakistan (NTP-Pakistan) and by the treating MDR-TB team. A standardized second-line treatment regimen was used which included at least 8 months intensive phase of injectable drugs (amikacin or kanamycin or capreomycin), ethambutol, pyrazinamide, ofloxacin, and cycloserine. This treatment regimen was followed by an additional 12 months of continuation phase by omitting the injectable drugs. Treatment duration was based on the culture conversion; therefore, if culture conversion did not occur more quickly the MDR-TB physician could longer the treatment duration. Treatment regimens were individualized based on drug susceptibility testing (DST) results of the patients. Travel incentive and food vouchers were given to MDR-TB patients by the PTP-Punjab, Pakistan.

All patients in the province of Punjab with MDR-TB and registered in all the PMDT Sites for treatment at the Rawalpindi Leprosy Hospital (RLH), Jinnah Hospital Lahore (JHL), Gulab Devi Hospital Lahore (GDH), Mayo Hospital Lahore (MHL), Samli Sanitorium Hospital, Murree (SSM), District head quarter Hospital Sargodha (SARG), District head quarter Hospital Faisalabad (FSD), Nishtar Hospital Multan (NHM), District head quarter Hospital Sialkot (SKT), Bahwal Victoria Hospital Bahawalpur

(BVH), Sheikh Zaid Hospital Rahim Yar Khan (SZH, RYK) and affiliated centers throughout the province during the study period were included in the study. Smear, Culture and drug susceptibility testing were performed at the National TB Reference Laboratory (NRL) and Institution of Public Health (IPH). All included patients were DST confirmed MDR-TB. Sputum cultures and smears were performed monthly until treatment completion. Died, treatment failure, transferred out, still under treatment and extensively drug-resistant TB patients were excluded during the analysis. Proportions were compared between lost to follow up and cured/treatment completed MDR-TB patients using the chi-square test or

Fisher exact tests for demographic characteristics (age, gender, residence and unemployed) and possible risk factors for lost to follow up (pre-treatment body weight (Kg), baseline smear Positive, use of alcohol or tobacco, type of patient, Disease location, TB treatment history, previous history of lost to follow up from TB treatment, time of treatment of the patients during study (2017-2019), resistance pattern at diagnosis, Culture conversion dates, MDR-TB treatment interruption, side effects appeared during the intensive phase, changed the residence during MDR-TB treatment, and long distance between patient's home and treatment center). Factors which were associated with lost to follow up in univariate analysis at

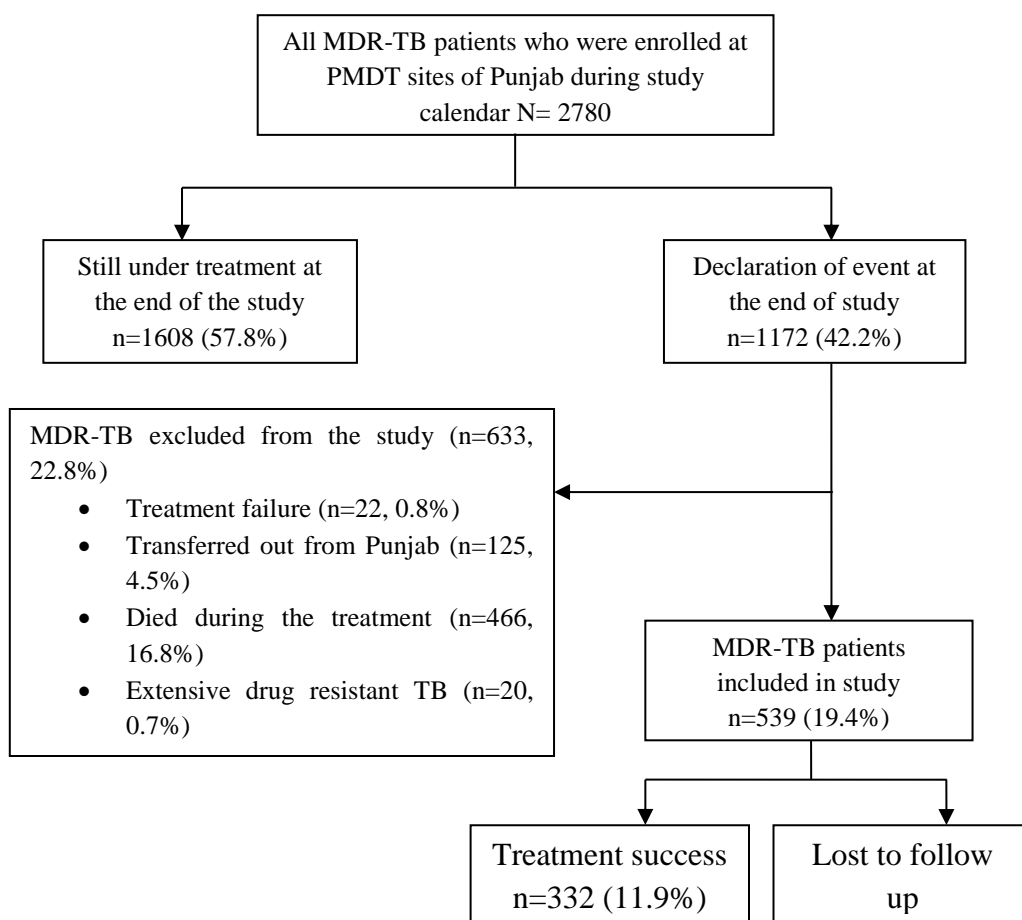


Figure 1. Inclusion and exclusion criteria of study participants.

p<5% were assessed in multivariate analysis using a logistic regression model. The present study met the measures set by the Institutional Review Board of PTP-Punjab for retrospective analyses of routinely accumulated programmatic data.

Results:

During study calendar (1st January 2017 and 31st December 2019), 2780 patients were initiated on MDR-TB treatment in Punjab, of whom 1172 (42.2%) had declaration of an outcome. Of the 1172 MDR-TB patients, 633 (22.8%) were excluded during data analysis for the following reasons: treatment failure, transfer out from Punjab, died during the MDR-TB treatment and extensively drug resistance tuberculosis (defined as MDR-TB plus resistance to an injectable (Amikacin, Capreomycin, Kanamycin) and a fluoroquinolones (Levofloxacin, Moxifloxacin, Ofloxacin)). A total of 539 (19.4%) MDR-TB patients were included in the analysis of risk factors for lost to follow up. Of these, 332 (11.9%) had a successful outcome according to NTP-Pakistan definitions and 207 (7.5%) were lost to follow up from treatment (Fig. 1).

Table 1 summarized the disease and demographic characteristics of the included MDR-TB patients. Among the overall cohort, the mean age was 33 years (SD=14, Range=15-80) and the majority of patients

were male 289 (53.6%).The proportion of previously first line drugs (FLD) treated patients (81.1%) was high and approximately one sixth had a history of second line drugs (SLD).

Over one third of MDR-TB lost to follow up patients reported unemployed status (20.3%) or house wife/students (35.3%), while use of tobacco (11.1%), baseline sputum negative (20.3%) and baseline culture negative (15%) was low. There were numerous differences in disease characteristics among MDR-TB lost to follow up vs. MDR-TB patients with a successful outcome. MDR-TB patients who were declared lost to follow up from the treatment were significantly more likely to be pulmonary (99.5% vs. 97.3%), have a history of lost to follow up during the treatment of first line drugs (30.4% vs. 6.9%), co-morbid (33.3% vs. 16%), to have contaminated baseline culture results (17.9% vs. 4.2%), have adherence from second line drugs (61.4% vs. 20.5%) and have long distance between patient’s home and treatment site (19.3% vs. 9.3%) than MDR-TB patients with a successful outcome. The baseline body weight less than or equal to 36 kg and culture conversion after 3 or more months was also significantly lower in lost to follow up patients vs. those with a successful outcome (18.4% vs. 25.6%) and (16.9% vs. 25.3%) respectively.

Table 1. Disease and demographic characteristics of multidrug resistance tuberculosis patients registered for treatment in Programmatic Management of Drug Resistant Tuberculosis sites from January 2017 through December 2019, Punjab, Pakistan

Characteristics	Total (n=539) n(%)	Treatment success (n=332) n(%)	Lost to follow up (n=207) n(%)	P-value
Gender				0.759
Male	289 (53.6)	176 (60.9)	113 (39.1)	
Female	250 (46.4)	156 (62.4)	94 (37.6)	
Age (year)				0.005
Mean (SD, Range)	33 (14, 15-80)	30 (13, 15-74)	37 (14, 16-80)	
Employment Status				0.907

Association of Risk Factors Among Lost to Follow up Multidrug Resistance Tuberculosis Patients in Punjab

Employed	234 (43.4)	142 (42.8)	92 (44.4)	
Unemployed	109 (20.2)	67 (20.2)	42 (20.3)	
House wife/Student	196 (36.4)	123 (37.0)	73 (35.3)	
FLD History				0.163
No	102 (18.9)	69 (20.8)	33 (15.9)	
Yes	437 (81.1)	263 (79.2)	174 (84.1)	
History of LFU from FLD treatment				<0.001
No	453 (84.0)	309 (93.1)	144 (69.6)	
Yes	86 (16.0)	23 (6.9)	63 (30.4)	
Co-morbid				<0.001
No	417 (77.4)	279 (84.0)	138 (66.7)	
Yes	122 (22.6)	53 (16.0)	69 (33.3)	
Use of tobacco				0.246
No	489 (90.7)	305 (91.9)	184 (88.9)	
Yes	50 (9.3)	27 (8.1)	23 (11.1)	
Location of disease				0.008
Pulmonary	529 (98.1)	323 (97.3)	206 (99.5)	
Extra-pulmonary	10 (1.9)	09 (2.7)	01 (0.5)	
Baseline body weight				0.049
≤ 36 kg	123 (22.8)	85 (25.6)	38 (18.4)	
> 36 kg	416 (77.2)	247 (74.4)	169 (81.6)	
Baseline smear				0.383
Positive	410 (76.1)	248 (74.7)	162 (78.3)	
Negative	121 (22.4)	79 (23.8)	42 (20.3)	
Contaminated	08 (1.5)	05 (1.5)	03 (1.4)	
Baseline culture				<0.001
Positive	408 (75.7)	269 (81.0)	139 (67.1)	
Negative	80 (14.8)	49 (14.8)	31 (15.0)	
Contaminated	51 (9.5)	14 (4.2)	37 (17.9)	
Culture conversion after 3/ more months				0.002
Yes	119 (22.1)	84 (25.3)	35 (16.9)	
No	420 (77.9)	248 (74.7)	172 (83.1)	
Adverse reaction of SLD				<0.001
Yes	195 (36.2)	68 (20.5)	127 (61.4)	
No	344 (63.8)	264 (79.5)	80 (38.6)	
Long distance				0.001
No	468 (86.8)	301 (90.7)	167 (80.7)	
Yes	71 (13.2)	31 (9.3)	40 (19.3)	

FLD= first line drugs, LFU= lost to follow up, SLD= second line drugs

Using the univariable analysis (Table 2), the rate of lost to follow up was found to be significantly higher among older age (OR: 1.40, CI: 1.14-1.71, p=0.000), history of lost to follow up from first line drugs treatment (OR: 0.39, CI: 0.28-0.56, p=0.000), co-morbid (OR:1.54, CI: 1.24-1.91, p=0.000), adverse reaction of second line drugs (OR:0.45, CI:0.37-0.56, p=0.000), long distance between patient’s home and PMDT site (OR: 0.68, CI: 0.52-0.89, p=0.001) and culture conversion after 3 or more months (OR: 1.15, CI:1.06-1.25, p=0.023). Lost to

follow up rate was not affected by baseline body weight and baseline culture results.

In multivariable analysis (Table 2), various predictors remained significantly associated with lost to follow up during treatment. MDR-TB lost to follow up patients were more likely to report older age (AOR: 1.58, CI: 0.95-2.63, p=0.079), history of lost to follow up from first line drugs treatment (AOR: 0.14, CI: 0.08-0.24, p=0.000), treatment started in 2017 or 2018 (AOR : 1.53, CI:1.09-2.41, p =0.028), co-morbid (AOR:1.80, CI: 1.09-2.96, p=0.021), adverse reaction of second line drugs (AOR:0.21, CI:

0.09-0.46, p=0.000), long distance between patient’s home and PMDT site (AOR: **0.51**, CI: 0.28-0.95, p=0.033) while Culture conversion after 3 or more months of

treatment (AOR = 1.24, CI: 1.20–1.48, p=0.145) were not found to be significantly associated with lost to follow up.

Table 2. Factors associated with lost to follow up among multi drugs resistance tuberculosis patients on treatment at Programmatic Management of Drug Resistant Tuberculosis sites of Punjab, Pakistan.

Factors	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P	AOR (95% CI)	P
Age (≤ 45 Years)	1.40 (1.14-1.71)	0.000	1.58 (0.95-2.63)	0.079
History of lost to follow up from first line drugs treatment	0.39 (0.28-0.56)	0.000	0.14 (0.08-0.24)	0.000
Time Period of treatment (2017 or later)	1.51(1.07-2.32)	0.090	1.53(1.09-2.41)	0.028
Co-morbid	1.54 (1.24-1.91)	0.000	1.80 (1.09-2.96)	0.021
Baseline body weight	1.16 (1.01-1.34)	0.051	-	-
Baseline culture result	1.22 (0.75-2.01)	0.422	-	-
Adverse Reaction of SLD	0.45 (0.37-0.56)	0.000	0.21 (0.09-0.46)	0.000
Long distance between patient’s home and PMDT sites	0.68 (0.52-0.89)	0.001	0.51 (0.28-0.95)	0.033
Culture conversion after 3 or more months	1.15 (1.06-1.25)	0.023	1.24 (1.21-1.49)	0.145

SLD= Second line drugs, PMDT= Programmatic Management of Drug Resistant Tuberculosis

Discussion:

Lost to follow up from MDR-TB treatment is of public health and medical concern as MDR-TB patients are at higher risk of morbidity and mortality and may contribute to spread of MDR-TB in the society (Franke 2008). Lost to follow up rate from MDR-TB treatment in Punjab are known to be high than the WHO suggested target of 5% and lost to follow up MDR-TB patients have an increased risk of transmission of resistant tuberculosis, mortality and resistance amplification within the community. According to national guidelines a lost to follow up patient of MDR-TB can produce 10 to 15 more cases in a year. We estimated that 7.5% of all patients initiating treatment for MDR-TB were lost to follow-up and that 61.4% had adverse reaction of second line drugs at the time of lost to follow up. A similar rate of lost to follow up among retreatment patients of MDR-TB (6.2%) in

Punjab while a high rate of these cases (30%) in Rawalpindi, a city of Punjab, has been documented in other studies (Akhtar 2016, Khurram 2011). The statistical analysis of our study demonstrates high risk of lost to follow up when stratified by co-morbid, baseline body weight, culture conversion after 3 or more months, long distance and this finding is similar to previous studies throughout the world who also predict a direct relationship to these factors and poor MDR-TB treatment success (Brust 2010, Gler 2012, Tupasi 2016). In another study older age was also predicted as a risk factor of lost to follow up among MDR-TB patients (Lalor 2013) and our study also supported this prediction.

Poor treatment success rate was reported in some previous studies, to be associated with predictors such as gender (male), smoking, employment status and initial smear result (Jeon 2011, Jain 2014, Duraisamy 2014). Our study was not provided statistically

significant evidence to document the role of any of these factors in prediction of treatment success of MDR-TB patients. It is important for National TB Control and Provincial TB Control Programmes to overcome local risk factors for lost to follow up MDR-TB patients. Some studies have observed association between lost to follow up and alcohol abuse [Chiang 2010, Cavanaugh, 2012]. We were not able to study this risk factor in our study as Punjab is an “Islamic state” so that use of alcohol is banned in the Punjab and this study was also based on record, which are the some limitations.

Conclusion:

This study evaluated the risk factors of lost to follow up during treatment in MDR-TB patients receiving anti-tuberculosis therapy from PMDT sites of Punjab. About one sixth of the patients were treatment success. Currently, the Provincial TB Control Program of Punjab has many components like installation of Gene Xpert machines in different districts of Punjab, Anti tuberculosis drugs resistance referral systems, outreach workers, Social support and regular patient follow up. More comprehensive approach, effective solutions addressing co-morbid, easier access to PMDT sites, modification of PMDT staff behaviors, an ensured monitoring of drug adherence for every patient and emphasizing on motivating MDR-TB patients to come to the PMDT sites to receive therapy are essential to treatment completion. Proper training for PMDT sites staff, friendly follow up services and psychological counseling may help to reduce lost to follow up.

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