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Predictors of Poor Outcomes among Patients Treated for Multidrug-Resistant Tuberculosis at Tertiary Care Hospital in Pakistan

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Abstract: The treatment of multi drug-resistant tuberculosis (MDR TB) presents a major challenge. Its treatment is increasingly available, however, there is little information available on characteristics, treatment outcomes and risk factors for poor outcomes in such patients in Pakistan.This study was a retrospective study conducted at the programmatic management of drug resistant TB unit (PMDT), Lady Reading Hospital Peshawar and included all MDR-TB patients registered from January 2012 to March 2013. Results showed that a total of 366 MDR-TB patients was included in this study that were registered during this cohort and completed their treatment. The treatment success rate was 78.7%. In univariate analysis, poor outcomes were associated with age≥ 44 years (OR,0.241; 95% CI, 0.136-0.430, P<0.001), rural residence (OR,0.484; 95% CI, 0.262-0.894, P=0.019), lung cavitation (OR, 0.018; 95% CI, 0.007-0.047, P<0.001), previous use of SLD's (OR,2.115; 95% CI, 1.049-4.263, P=0.033), resistance to SLD (OR, 2.471; 95% CI, 1.456-4.193, P=0.001) and resistance to ofloxacin (OR, 2.500; 95% CI, 1.479-4.226, P<0.001). Whereas multivariate logistic regression analysis, showed that poor outcomes were associated with patients with age ≥ 44 years (OR 0.183, 0.064-0.521, P=0.001), baseline lower body weight (OR 4.399, 0.005-0.042, P=0.001) and cavitatory lungs (OR 0.015, 0.005-0.042, P<0.001). In conclusion: MDR-TB patient needs special attention for better treatment outcomes. The presence of older age, lower body weight, rural area residence, resistance to ofloxacin, treated with SLD's in past, SLD resistance and cavitary disease are independent prognostic factors for poor outcome in patients with MDR-TB.

Key words: Multi-Drug Resistance TB · Treatment Outcomes · Peshawar · Pakistan

INTRODUCTION

Tuberculosis (TB) is a contagious and airborne disease and ranks as the second leading cause of death from a single infectious agent after the human immunodeficiency virus (HIV). Due to global efforts for its command, the mortality rate of TB has decreased 45% since 1990 but despite of all these global efforts to control, the global burden of TB remains enormous and in 2013, 9 million people fell ill with this disease and 1.5 million died from it [1].

As on one side, it is controlled due to programmatic Directly observed treatment short courses (DOTS) strategies, but at the same time its resurgence in the form of drug resistant tuberculosis (DR-TB), of which multidrug resistant tuberculous agents (MDR-TB) and extensively drug resistant tuberculous agents (XDR-TB) is alarming for TB control efforts. MDR-TB is an entirely man-made problem that arises when patients are improperly treated or fail to take their prescribed medications appropriately, it remains a massive burden for TB care and control globally. Globally in 2013, an

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estimated 480,000 people developed multidrug-resistant TB (MDR-TB) and there were an estimated 210,000 deaths from it [1]. On average, an estimated 9% of people with MDR-TB have XDR-TB [1]. According to WHO 3.7% of new cases and 20% of previously treated cases are estimated to have MDR-TB [1].

MDR-TB is significantly more difficult to treat than drug-susceptible TB, requiring the use of less effective second line drugs, which are often associated with major side effects. It has a prolonged treatment with a minimum duration of 24 months [2]. Treatment success rate is lower as compared with drug susceptible TB. So it is very necessary to find out MDR-TB patient and given complete treatment. Inadequate treatment of MDR-TB can lead to worse patient outcomes, while increasing the risk of extensive drug resistance [3-5]. Without treatment, drug-resistant strains can spread rapidly within vulnerable populations [6-8]. Because standard short-course chemotherapy for multidrug-resistant tuberculosis have been associated with unacceptably high rates of failure and relapse new approaches to treatment in poor countries are needed [9-11].

Treatment duration of MDR-TB is at least 24 months and during this high side effected second line drugs (SLD's) are used and its cure rate is low as compared to Drug-Susceptible TB. As this disease is increasing day by day so it is very necessary to know the predictors for unsuccessful treatment outcomes and try to resolve the problem about these predictors so that we are able to control this dangerous disease and lower the death rate from it.

Pakistan is one of the top listed countries ranking 4th among top 22 MDR-TB countries. Based on 4.2% primary resistance and 19% resistance in re-treatment cases, WHO has estimated an annual incidence of about 15000 MDR-TB cases in Pakistan [12]. The increasing rate of MDR and XDR-TB in Pakistan underscores the importance of effective treatment programs of drug-resistant TB. Expanding access to MDR- TB therapy is urgently needed, yet poor implementation of such therapy can worsen the problem of XDR-TB. Understanding risk factors for poor treatment outcomes among MDR-TB patients is necessary to improve treatment outcomes [13,14]. We therefore examined the patient registered in Lady Reading Hospital from January 2012 to December 2012 who received a second line therapy for DR-TB to determine overall treatment outcomes and predictors for poor treatment outcomes in this study.

MATERIALS AND METHODS

Study Design and Settings: Due to the increasing rate of DR-TB in Pakistan instead of DOTS TB programme DR-TB patients were treated through programmatic management of drug resistant TB (PMDT). Different PMDT sites are working; Lady Reading Hospital Peshawar (LRH) is one of these. LRH has treated MDR Patients from 2008 from their own resources. In 2012, National TB Control Programme (NTP) declared that PMDT at LRH. LRH is one of the best treatment country site of Pakistan.

This was a retrospective cohort study conducted at PMDT-LRH Peshawar, Pakistan. All confirmed pulmonary MDR-TB patients who were consecutively enrolled for treatment at the study site from January 2012 to March 2013 were included in the study. All patients enrolled in the study were treated on an ambulatory based strategy and were seen monthly by a team of clinicians (Professor, Assistant Professor and two medical officers). All registered patients were started on a standardized treatment regimen and shifted to individualized regimens once DST results were obtained.

Sputum smear (Ziehl–Neelsen (ZN) technique), [15] culture (on both liquid and solid media) [16,17] and chest radiographs (CXR) were performed at enrollment and monthly during the intensive phase of treatment, whereas during a continuation phase smears were performed monthly and culture and CXR at bimonthly. All patients were tested at baseline for human immunodeficiency virus (HIV) using ICT method and blood investigations were performed at baseline and at every month as per guidelines.

Medication adherence was monitored by trained treatment supporters and directly observed therapy facilitators. Patients were psychologically evaluated and personalized counseling was provided to them on monthly follow up visits. For contact screening, infection control measures at home and create a liaison with the regional District TB officer and their nearest DOTS center, home visits were arranged to each patient. Adverse events were managed rapidly and aggressively, with permanent removal of a drug from the treatment regimen as a last resort. Patients received counseling to maximize adherence, nutritional support and transportation reimbursement for the clinic visits.

Regimen Design and Patient Management: All patients who were registered here were started on standardized/empiric treatment regimen (ETR). ETR was

comprised of Pyrazinamide, Levofloxacin, Ethionamide, Cycloserine and Amikacin. This combination is according per guidelines. Treatment on ETR was continued until the result of DST. After the result of DST, all patients were started on an individualized treatment regimen (ITR) based on the DST profile for that patient. Regimens to treat MDR-TB and XDR-TB cases were individually tailored on the basis of DST results [15].

In general, regimens contained at least five drugs to which the infecting strain was susceptible, including a second-line injectable agent for at least 6 months after documented sputum culture conversion. The total treatment duration included a minimum of 12-18 months of treatment after culture conversion which was regularly pursued by M. tuberculosis smears and cultures up to the end of treatment. Culture conversion was defined as at least 2 negative cultures for at least 30 days apart.

Bacteriologic Studies and Drug Susceptibility Testing: Sputum smear microscopy was performed using Ziehl-Nelsen (ZN) technique and was done in microscopy laboratory in Chest Unit, Lady Reading Hospital, Peshawar [15] and for culture and DST samples collected were sent to the National Reference Laboratory (NRL) Islamabad, of the National Tuberculosis Program (NTP) (a BSL3 laboratory with proficiency testing approved by Supra National Lab in Belgium) and Agha Khan University Hospital Laboratory Karachi respectively. Mycobacterial cultures were performed on both liquid and solid media. Sediments were cultured at 37°C using Löwenstein-Jensen (LJ) medium and the Mycobacteria Growth Indicator Tube (Becton Dickinson Diagnostic Instruments Systems, Sparks, MD, USA). Drug susceptibility testing was performed on *M. tuberculosis* isolates from sputum (DST) was performed using the standard agar proportion method on enriched Middlebrook 7H10 medium (BBL, Beckton Dickinson) [16, 17]. DST was performed on all culture positive isolates against first line [isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S)] and second line anti TB drugs [(amikacin (Am), kanamycin (Km), capreomycin (Cm), ofloxacin (Ofx), ethionamide (Eto), cycloserine (Cs) and para-amino salicylic acid (PAS)].

Data Collection and Analysis: A paper-based (DR-TB 01) and computerized record system (ENRS: Electronic Nominal Recording/Reporting System) was constituted. These both systems (hard and soft) included patients demographic, clinical and microbiological data. Demographic data included sex, age, weight, co-morbidities, area of residence and close contacts. Clinical data included history and outcome of previous TB treatment, previous use of second line drugs and radiological findings at baseline chest X-ray whereas microbiological data included sputum smear grading at baseline and DST results of the baseline visit and microbiological culture status at monthly follow up visits. Analysis was performed using SPSS (SPSS version 16, SPSS Inc., Chicago, IL) after exporting the data from ENRS and DR-TB01. Differences in proportions were assessed using Pearson's Chi-Squared test, with $P<0.05$ considered significant. Comparisons of demographic, socioeconomic and HIV status and TB-related characteristics, as well as treatment outcome parameters between patient subgroups were performed using the Chi-squared test for categorical variables and the Mann– Whitney U-test for continuous variables. To estimate the predictors of poor treatment outcome, multivariate logistic regression analysis with Wald statistical criteria using the backward elimination method was performed. All the factors considered in the univariate analysis were entered into the multivariate analysis. A p-value 0.05 was regarded as statistically significant.

Ethical Approval: The study was approved by Research and Ethics Committee of the Postgraduate Medical Institute, Peshawar, Pakistan.

Definitions: Treatment outcomes were defined according to recommendations from the WHO MDR-TB working group.

Cure was defined as at least five negative sputum cultures in the last 12 months of treatment. A single positive culture was allowed if it was followed by a minimum of three negative cultures.

Treatment failure was defined as two or more positive cultures in the last 12 months of treatment, or if a medical decision was made to terminate treatment due to poor response or adverse events.

Default was defined as an interruption of two or more consecutive months of treatment. Patients were recorded as dead if they died during treatment, regardless of the cause.

Serious adverse events were defined as those that resulted in any change to the anti-TB drug regimen, either changing the dose of a drug, or temporarily or permanently removing a drug from the regimen.

Table 1: Baseline characteristics of study cases

Patients characteristics	No. of patients (%) n = 366	Median (range)
Demographic		
Gender		
Male	165 (45.1)	
Female	201 (54.9)	
Age (Years)		29.9 (10-79)
≥14	14 (3.8)	
15-44	288 (78.7)	
45-64	57 (15.6)	
≥65	7 (1.9)	
Weight (Kg)		44.84 (18-78)
<40	104 (28.4)	
40-60	246 (67.2)	
>60	16 (4.4)	
Residence		
Urban	115 (31.4)	
Rural	251 (68.6)	
Marital Status		
Married	181 (49.5)	
Unmarried	184 (50.3)	
Widow	1(0.3)	
Patients contact status		
No Contact	263 (71.85)	
Drug-susceptible TB	57 (15.6)	
Drug-resistant TB	46 (12.6)	
Previous TB treatment		
Yes	332 (90.7)	
No	34 (9.2)	
Duration of TB disease (years)		3 (2-7.6 yrs)
Previous TB treatment episodes		3 (1-5 Episodes)
Less than or equal to 1 year	215 (58.7)	
Greater than 1 year	151 (41.3)	
Previous use of second-line drug		
Yes	41 (11.2)	
No	325 (88.8)	
Registration Group		
New	34 (9.2)	
Relapse	48 (13.11)	
Category I Failure	111 (30.32)	
Category II Failure	132 (36.06)	
Others	41 (11.20)	
Lung Cavitation at baseline chest x-ray		
No cavitation	233 (63.6)	
Unilateral cavitation	38 (10.4)	
Bilateral cavitation	95 (26.0)	
Smear grading at baseline		
Negative	37 (10.1)	
Scanty (1-9 AFB/100HPF)	4 (1.10)	
+1 (10-99 AFB/100HPF)	120 (32.8)	
+2 (1-9 AFB/HPF)	80 (21.85)	
+3 (>9 AFB/HPF)	125 (34.15)	

RESULTS

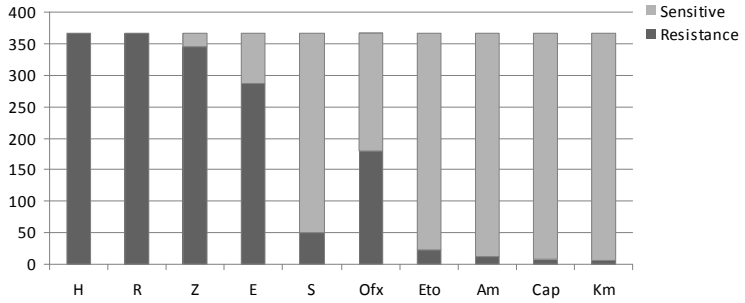
From January 2012 and March 2013 a total of 393 DR-TB patients were registered at PMDT site LRH and start on treatment. Among these registered cases, 366 (93.1%) were found to be infected with MDR-TB; the remaining 27 were all infected with strains with some other level of drug resistance (Other than MDR and XDR-TB). This stdudy included only MDR-TB patients.

Baseline Patient Characteristics: Baseline characteristics of patients treated in the 2012 cohort at this center are described in Table 1. These patients were from different district of Khyber Pakhtunkhwa, FATA and Afghanistan, but maximum no of the patients (32%) were from district Peshawar where LRH is located and two hundred and fifty one (68.60%) cases were from rural areas. Median age was 29.2 years, ranging from 10 to 79 years; 54.9% were female. Most of the patient 246 (67.2%) were placed in 40-60 kg baseline weight ranging from 18-78 kg with an average of 44.84 kg. Approximetely Fifty percent study cases were married at the time of treatment. Fifty seven patients (15.6%) were in close contacts of drug-susceptible TB and 46 (12.6%) patients were of drug resistance TB and ninety percent of the patients were previously treated with first line anti tuberculosis drugs (FLD-ATT). Patients had been ill with TB for a median of 3 years and had received a median of three previous TB treatment episodes. Approximately 50.5% patients had undergone a DOTS category-II treatment regimen at least once and 36.06% of these patients had failed a category-II regimen at least once. Fourty one patients (11.2%) had also taken at least one second-line drug in their previous treatment.

Drug Resistance Pattern: The baseline resistance patterns are shown in Figure 1. High levels of first-line resistance were observed. All of the strains (100%) were resistant to isoniazid and rifampicin, followed by pyrazinamide 345 (94.5%), ethmburol 286 (78.1%) and streptomycin 51 (13.9%).

Overall, 185 strains (50.5%) were resistant to at least one SLD. The most common second-line resistance was to ofloxacin (180, 49.2%), followed by ethionamide (22, 6.0%), Amikacin (12, 3.2%), followed by Capreomycin (8, 2.1%) and kanamycin (7, 1.9%). No resistance to cycloserine and PAS was observed.

Significant overlap was seen between 179 strains resistant to ofloxacin which were also resistant to Pyrazinamide.



H: Isoniazid R: Rifampicin Z: Pyrazinamide
E: Ethambutol Ofx: Ofloxacin Eto:Ethionamide
Am: Amikacin Cap: Capreomycin Km: Kanamycin

Fig. 1: Drug resistance pattern among 366 MDR-TB patients

Table 2: Resistance patterns of study cases

Drugs	No. of Cases (%)
Resistance to 2 FLD's	8 (2.2)
Resistance to 3 FLD's	42 (11.5)
Resistance to 4 FLD's	309 (84.42)
Resistance to 5 FLD's	7 (2.0)
HR	8 (2.2)
HEZS	1 (0.3)
HREZ	271 (74.1)
HRES	7 (1.9)
HREZS	7 (1.9)
Any SLD Resistance	185 (50.54)
Resistance to single SLD	167 (45.62)
Resistance to 2 SLD	18 (4.9)
Only resistance to Cm	1 (0.3)
Only resistance to Eto	4 (1.9)
Only resistance to Ofx	162 (44.3)
FQ+Eto	18 (4.9)
HRZ+Ofx	10 (2.7)
HRES+Ofx	1 (0.3)
HREZ+Ofx	144 (39.3)
HRZS+Ofx	7 (1.9)
HEZS+Ofx	1 (0.3)
HREZ+Eto	1 (0.3)
HREZ+Cm	1 (0.3)
HRZES+Ofx	2 (0.6)
HREZ+Ofx+Eto	18 (4.9)

At the start of treatment, 309 of all MDR-TB cases (84.42%) had resistance to all first line oral anti-TB drugs with a median resistance to 3.0 anti-TB drugs (range 2-5) (Table 2).

Treatment Regimens: All registered cases were started on an Empiric regimen at the start of treatment on the basis of Gene Xpert Rif resist results and this regimen was continuous till DST result. DST results were available at a median of 69.86 days (range 30–183 days) after treatment initiation. For 126 (34.42%) patients started empirically, the receipt of DST results did not cause any change to the regimen. The most common drugs added to treatment regimens after treatment initiation were PAS (224 patients), followed by ethambutol (23 patients) (not included in the ETR and where susceptibility was later demonstrated on DST) and augmentin and clarithromycin (added as an additional agent when more efficacious second-line drugs were no longer usable). The two most common reasons for stopping drugs in the regimen were the development of resistance and severe adverse events (cycloserine 7, amikacin 12, pyrazinamide 4) (resulting in the permanent removal of the drug from the regimen) (Table 3).

Treatment Outcomes: Treatment outcomes of 366 patients were given here. Overall, 288 (78.7%) of 366 patients were recorded as being successfully treated at the end of treatment and 78 (21.31%) patients recorded as being unsuccessfully treated; 54 (14.8%) died during treatment, 23 (6.3%) were classified as treatment failures and 1 (0.3%) did not furnish treatment (Table 4).

Of the 54 patients who died, six patients died within the first month of starting treatment. The remainder survived for a median of 10 months of treatment (range 2–27 months). Nine patients died after two months treatment, five after 3 month, three died after 4 months of treatment, 3 after 5 months, 4 were after 6 months, 4 after seven, 2 after nine months of treatment, one patient died each after 11,12 and 13 months of treatment, 2 after 13, one patient died each after 14,15,16, 17 and 19 months of treatment, one each after 22,23,24 months, two after 25 and three patients died after 27 month of their treatment. Among these 54 patients culture conversion occurred in 22 patients whereas remaining 32 patients remained culture positive at their time of death.

Table 3: Overview of drugs given to the study cases

	Given in initial Regimen	Added later to Regimen	Remove from Regimen	Totally given to patients
First Line				
Ethambutol (E)	0	23	0	23 (6.28)
Pyrazinamide (Z)	366	0	6	360 (98.36)
Second Lind Drugs				
Amikacin (Am)	366	0	12	354 (96.72)
Capreomycin (Cm)	0	12	0	12 (3.27)
Clarithromycin	0	20	0	20 (5.46)
Fluroquinolone (Lfx)	366	0	0	366 (100)
Cycloserine (Cs)	366	0	7	159 (98.08)
Ethionamide (Eto)	366	0	0	366 (100)
PAS	0	224	0	224 (61.20)
Augmentin	0	20	0	20 (5.46)

Table 4: Treatment outcomes of study cases (n=366)

Treatment Outcomes				
Cure	Died	Treatment Failure	Lost to	Total
288 (78.7%)	54(14.8%)	23 (6.3%)	1(0.3%)	366 (100%)

Table 5: Univariate analysis of factors potentially contributing to the unsuccessful treatment outcomes (n=366)

	Treatment Outcomes				
Patients characteristics	Unsuccessful Outcomes	Successful outcomes	95% Cl	Odd Ratio	P.value
Demographic					
Gender	No.%	No.%			
Male	32 (19.4)	133 (80.6)			
Female	46 (22.9)	155 (77.1)	0.488-1.346	0.811	0.417
Age (Years)					
≤44	49 (16.3)	252 (83.7)			
>44	29 (44.6)	36 (55.4)	0.136-0.430	0.241	<0.001
Weight (Kg)					
≤39	34 (32.7)	70 (67.3)			
>40	44 (16.8)	218 (83.2)	1.427-4.057	2.406	0.001
Residence					
Urban	15 (13.6)	95 (86.4)			
Rural	63 (24.6)	193 (75.4)	0.262-0.894	0.484	0.019
Duration of Illness before current treatment					
≤ 1 year	41 (19.1)	174 (80.9)			
> 1 year	37 (24.5)	114 (75.5)	0.439-1.201	0.726	0.211
Previous use of second-line drug					
Yes	14 (34.1)	24 (80.9)			
No	64 (19.7)	114 (75.5)	1.049-4.263	2.115	0.033
Lung Cavitations at baseline chest x-ray					
No cavitation	5 (2.1)	228 (97.9)			
Cavitation	73 (54.9)	60 (45.1)	0.007-0.047	0.018	<0.001
Resistance to SLD					
Yes	53 (28.5)	133 (71.5)			
No	25 (13.9)	155 (86.1)	1.456-4.193	2.471	0.001
Resistance to PZA					
Yes	74 (21.4)	271 (78.6)			
No	4 (19.0)	17 (81.0)	0.379-3.554	1.161	0.794
Resistance to E					
Yes	62 (21.7)	224 (78.3)			
No	16 (20.0)	64 (80.0)	0.598-2.049	1.107	0.746

Table 5:Continued

Patients characteristics	Treatment Outcomes: Unsuccessful Outcomes	Successful outcomes	95% Cl	Odd Ratio	P.value
Resistance to S					
Yes	11 (21.6)	40 (78.4)			
No	64 (21.3)	248 (78.7)	0.496-2.091	1.018	0.961
Resistance to Ofx					
Yes	52 (28.9)	128 (71.1)			
No	26 (14.0)	160 (86.0)	1.479-4.226	2.500	<0.001
Resistance to Eto					
Yes	6 (27.3)	16 (72.7)			
No	72 (20.9)	272 (79.1)	0.535-3.750	1.417	0.481

Table 6: Multivariate analysis showing predictors for unsuccessful treatment outcomes of MDR-TB patients (n=366)

	B	SE	Wald	df	Sig.	Exp(B)	95% CI: Lower	95% CI: Upper
Age ≥ 44	1.699	0.534	10.136	1	0.001	0.183	0.064	0.521
Weight ≤ 39	1.481	0.451	10.789	1	0.001	4.399	1.817	10.646
Lung Cavitation	4.226	0.538	61.612	1	<0.001	0.015	0.005	0.042

Note: Only those predictors given in Table which are significant in analysis

B: Beta, SE: Standard Error, df: Degree of freedom, Exp (B) (Exponantion of B coefficient): OR, CI: confidence interval

Twenty three (6.3%) patients were classified as treatment failure and were removed from treatment due to failure of therapy after a median of 24.5 months on treatment (range 19–30 months).

The only defaulted patient was lost unfortunetly after 17 months of treatment. Culture conversion was occur at 3rd month and culture was negative till the time of default.

Treatment Duration: Among successfully treated patients, the median total treatment duration was 24 months (range 14–34 months), which was a median of 21 months after culture conversion (range 17–27 months). The injectable was given for a median of 9 months (range 6–12 months). All patients classified as failing treatment were continued on the injectable for the duration of treatment.

Factors Associated with Poor Outcomes: Our univariate analysis (Table 5) showed that certain demographic and clinical characteristics, such as patient with or greater than 44 years of age (P<0.001), lower weight (≤ 39) (P=0.001) rural residence (P=0.05), cavitatory lungs at baseline (P<0.001), previous use of SLD's (P=0.03), resistance to second line drugs at treatment initiation (P<0.001) and resistance to ofloxacin (P<0.001) were associated with poor treatment outcomes.

In a multivariate regression model, patients with age ≥ 44 years (OR 0.183, 0.064-0.521, P=0.001) and lungs cavitation at baseline chest X-ray (OR 0.015, 0.005-0.042, P= <0.001) at the start of anti- TB treatment were independent risk factors of poor treatment outcome in MDRTB. Lower body weight (≤ 39 Kg) at start of treatment increased the risk more than four-fold (OR 4.399, 1.817-10.464, P=0.01) (Table 6). This model fit was based on non significant Hosmer and Lemeshow test (P=0.803) and overall percentage of 87.2% from classification table.

DISCUSSION

The present study, designed to present characteristics, treatment outcomes of MDR-TB patients and identify critical predictors of poor treatment outcomes of patients with MDR-TB.

The demographic profile of patients in the present study was similar to other series, with a majority of female patients in the economically productive age group (25-54 years) [14-19].

Out of these 366 patients, 288 (78.7%) patients achieved successful outcome. Hence the study site reached the target of treatment success rate >75% set by "The Global Plan to Stop TB 2011-2015" [20]. This result is comparatively lower than 82% cure rate obtained in Germany [21] and more than some other studies like 49% in a study conducted in south Africa [22], 64% in New York [23], 59.2% from a study conducted in Taiwan [24] and 66% in Estonia, Germany, Italy and the Russian Federation [25]. Nearly similar results also are found in some other studies i.e. 51–77% [14, 26-31].

Treatment failure among this cohort approached 6.3% which is somewhat higher than other study where failure rates range between 0 and 4% among MDR-TB patients [32, 33].

In current study low default rate (1.0%) contributed to better treatment success rate. This rate is lower than other study i.e. a study conducted in Uzbekistan (14%) [33], as in South Africa (29.0%) [34] and South Korea (32.0%) [35]. It could be attributed to free of cost treatment, tracing patients on phone in case of delay in scheduled monthly visits and giving monthly food ration and conveyance allowance to both patients and their treatment supporters and home visits done by Treatment coordinator HDL and created and established linkages between patients, DTO and nearest periphery DOTS centres and PMDT LRH which possible play important role in low default rate.

The 14.8% mortality rate is not too different from a study conducted in South India [36] and lower than a study conducted in South Africa (36%) [34].

Differences in mortality rate were found as compared to some other studies (5-19%) [37-41]. In some studies this rate is lower as compared to the present study, the possible reason for this might be the high default rates (7, 11, 12%) and this high default rates masking their death rate [37, 41, 42].

As well as predictors for poor outcomes of this cohort was concerned; different variables were tested in univariate and multivariate analysis. Some of the factors that did not influence the treatment outcome included gender, previous TB treatment, duration of sickness and resistance to FLD's, while some factors like age, weight, residence, lung cavitation, previous use of SLD's, resistance to SLD's and resistance to ofloxacin were found to be associated with poor outcomes and this was also shown by some other studies [25, 33, 38, 42].

Present study suggested that age is a positive association with poor outcomes. Likewise, our finding, older age has been previously reported as predictor of poor treatment outcomes in MDR-TB patients in DOTS-plus projects in five resource limited countries [43]. This is because aged people respond poorly to drugs and their recovery is slow as compared to young people. The study showed s that poor outcome has been observed with increased age.

The present study showed that baseline lower body weight increase risk factor of poor treatment outcomes and such finding also was conformed by various studies conducted elsewhere [38, 44-46].

The present authors found that poor outcome of MDR-TB treatment is strongly associated with living in rural areas. One speculative explanation of this phenomenon is that patients of rural areas are from far-flung with limited health facilities, difficult implementation of DOTS, low education level, poor socio-economic condition with malnutrition, leading to uneffective pharmacological response of drugs. Rationally, the most important tool for improving the treatment outcome of MDR-TB in rural areas is patient education. Knowing the aforementioned fact, strong emphasis should be given to effective patient counselling and education in rural areas for better results.

Cavitation of the lungs was also a predictor of poor outcomes in the present study. Patients with lung cavitation documented on their first visit have poorer outcomes as compared to those who have no cavitation. Patients with bilateral cavities were more vulnerable to poor outcomes as compared to unilateral or no cavitatory lungs. Same findings has also been observed in some other studies [43,47]. Possible reason for this factor is that presence of cavities in lungs is associated with poor penetration of drugs resulting in decreased efficacy [13].

Several studies emphasize the important role of resistance to ofloxacin in poor MDR-TB treatment outcome [24, 28, 29, 38, 40, 48]. In the present study, resistance to ofloxacin was 53.6%. Two reasons might contribute to the high drug resistant proportions: First, fluoroquinolones have been widely used in the treatment of respiratory tract bacterial infections because of their better effects and slight adverse effects. Second, has also prescribe fluoroquinolones for drug resistant TB patients as well as and some drug susceptible TB patients who can't tolerate first line anti-tuberculosis drugs. This finding further emphasises the importance of ofloxacin in MDR-TB treatment regimens and highlights the need for preserving susceptibility to ofloxacin, as well as pointing out the clinical value of ofloxacin resistance in the definition of XDR-TB.

One alarming point is that patients resistant to ofloxacin were also resistant to pyrazinamide and both the drugs were used for treatment of MDR and XDR-TB. This issue is of great importance and needs efficient clinical attention.

This study also suggested use of SLD's as the strongest risk factor for poor MDR-TB outcomes. Rational use of SLD's with proper monitoring should highly be encouraged.

Being study from a single centre was the major limitation of the present study and need to be conducted such study from different centres and on a large scale to find out such predictors. But with limitation it is also encouraging that in such difficult areas and very busy hospital and with limited resources this centre achieved such a comparable cure rate and conducted such study which is helpful for other newly organized centres and encourage PMDT staff to do more. The findings of the current study have several clear implications for TB control efforts. In the light of these findings, it could be concluded that to reduce drug-resistant tuberculosis transmission in the community, improvement of treatment outcome, via ensuring adherence and paying special attention to aged patients, rural residents, SLD's resistance patients and those who are resistant to ofloxacin, is especially needed in addition to extensive use of rapid diagnostic methods and highly effective aggressive tuberculosis treatment. It is known that interruption of the drug-resistant tuberculosis transmission cycle is possible if the cure rate is >60%. A cure rate of ≥80% is needed to achieve a 10-fold reduction in multidrug-resistant tuberculosis incidence within 20 years [49] and for achievement of such rate it is necessary that on top priority with better public information, communication and advocacy, judicious use of anti-tubercular drugs, regular clinical, radiological and bacteriological followup in specialized centres with access to standardized tuberculosis laboratory for accurate drug susceptibility testing and due to it, it is possible to impel patients to seek medical care when they encounter their first TB symptoms and thereby to shorten patient delay and to detect less advanced disease.

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