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Evaluation of treatment outcomes and factors associated with unsuccessful outcomes in multidrug resistant tuberculosis patients in Baluchistan province of Pakistan

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ABSTRACT

Background: Evaluating treatment outcomes of a cohort of patients is an effective way for analyzing the effectiveness of a program. Information regarding drug resistance pattern, detailed management, treatment outcomes and factors associated with unsuccessful outcomes in multidrug resistant (MDR-TB) patients is missing from Baluchistan province of Pakistan.

Methods: This study was carried out at Programmatic Management of Drug Resistant TB unit at Fatimah Jinnah General and Chest Hospital Quetta. All eligible 186 MDR-TB patients enrolled at the study site from January 1, 2012 to April 30, 2016 were retrospectively followed until the treatment outcomes were reported. Data was abstracted through a standardized data collection form and analysed by SPSS 20. Multivariate binary logistic regression (MVBLR) analysis was used to evaluate factors associated with i) death and treatment failure and ii) lost to follow up. A p-value of <0.05 was considered statistically significant.

Results: The study participants were resistant to a median of four drugs (range 2–8) with majority being resistant to any second-line anti-TB drug (SLD) (55.5%). Among SLD, resistance was highest for ofloxacin (52.2%). The study site had an overall treatment success rate of 71.6%. A total of 129 (69.4%) patients were cured, four (2.2%) completed treatment, 37 died (19.9%), 14 (7.5%) were lost to follow up and two (1.1%) were declared treatment failures. In MVBLR analysis, patients' age of >40 years (OR = 4.249, p-value = 0.001) had statistically significant positive and baseline body weight of >40 kg (OR = 0.256, p-value = 0.002) had statistically significant negative association with death and treatment failure. No factor had statistical significant association with lost to follow up.

Conclusion: Overall treatment success rate was promising but did not achieve the target success rate (≥75%) set by World Health Organization. It can be further improved by paying special attention and providing enhanced management to the patients with risk factors for unsuccessful outcomes.

Introduction

Tuberculosis (TB) is a global public health problem [1]. By causing an estimated 1.6 million deaths in 2017, it is ranked as the leading fatal infectious disease beating the Human Immunodeficiency Virus (HIV) [2]. Although, due to efficient diagnosis [3,4] and treatment through public health interventions, the TB incidence rate is annually falling by 2% and an estimated 54 million deaths have been averted during the last 17 years [2]. But the increasing incidence and spread of drug resistant TB (DR-TB) are putting these achievements at stake. As patients with multidrug resistant TB (MDR-TB) are concurrently resistant to the two most

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effective and well tolerated first line anti-TB drugs i.e. rifampicin (RIF) and isoniazid (INH), they are treated for prolonged periods with less effective, more toxic and expensive second-line anti-TB drugs (SLD). This consequently results in high rates of unsuccessful treatment outcomes in MDR-TB patients. A recently published individual patients' data meta-analysis including data from 25 countries has reported a pooled treatment success rate of 61% in MDR-TB patients [5] as compared to 82% in drug susceptible ones [2].

Pakistan a South Asian country is comprised of four provinces and is the sixth most populous country in the world [6]. Unfortunately, in terms of MDR-TB burden, Pakistan currently ranks fourth globally. In 2017, the estimated incidence of MDR-TB cases in Pakistan was 27,000 with 4.2% (95% confidence interval [CI] = 3.2–5.3%) in newly infected and 16% (95%CI = 15–17%) in previously treated TB patients [2]. Programmatic management of DR-TB (PMDT) in Pakistan was initiated in 2010 and currently there are 24 PMDT units all over the country [7]. Among the four provinces of the country, Baluchistan is the least populated, less developed and by area the largest province of the country [6]. Until 2018, out of 24 working PMDT units in the country [7], only one was located in Baluchistan at Fatimah Jinnah General and Chest Hospital (FJGCH) Quetta. Being the single PMDT unit in the province, it has a wide catchment area of the whole province and even the nearby Afghanistan.

Evaluation of management and treatment outcomes of a cohort of patients is an effective way for analyzing the effectiveness of a program [8]. Very few studies have evaluated the management and treatment outcomes of MDR-TB patients treated at different PMDT-units in Pakistan [9–12].

These studies have reported a variable treatment success rates ranging 40.5–74.6% [9–12]. However, information about MDR-TB patients, their drug resistance pattern, detailed management, treatment outcomes and factors associated with unsuccessful treatment outcomes is lacking from the single PMDT unit located in Baluchistan. Therefore, there was an urgent need to evaluate this information about MDR-TB patients receiving treamtent at PMDT unit FJGCH Quetta. The findings of this study will assess the effectiveness of the unit and will enable the program managers to identify the problems and take appropriate steps to improve its overall performance.

Materials and methods

Study design, settings and population

This was an observational cohort study conducted at PMDT unit at FJGCH Quetta, Baluchistan. All MDR-TB patients irrespective of their gender, age, site of TB, history of TB treatment and comorbidity status who were consecutively enrolled at the study site from January 1, 2012 to April 30, 2016 were included in the study. The patients were retrospectively followed until the treatment outcomes were reported. The data was extracted from the Electronic Nominal Record System (ENRS) by using a purpose developed standardized data collection form. The form included information about patients' socio-demographic, microbiological and clinical data. Patients who suffered from DR-TB other than MDR-TB i.e. mono-DRTB, poly DR-TB and extensive DR-TB (XDR-TB) and who were transferred out to other centres during treatment were not included in the study.

Bacteriology and drug susceptibility testing (DST)

The patients referred to the study site were diagnosed and treated according to the guidelines published by National Tuberculosis Control Program (NTP) [13]. Two sputum samples of all the suspected DR-TB patients referred to the study site were initially evaluated for *Mycobacterium tuberculosis* (MTB) and RIF resistance respectively by direct sputum smear microscopy using Ziehl-Neelsen stain and Xpert MTB/RIF (Cephid, Sunnyvale, CA, USA). Sputum samples of patients with positive results of Ziehl-Neelsen stain and Xpert MTB/RIF were sent to Indus Hospital Karachi laboratory for culture and DST. At the laboratory of Indus Hospital Karachi, DST against RIF, INH, streptomycin (SM) ethambutol (EMB), ofloxacin (OFX), amikacin (AMK), kanamycin (KM), ethionamide (ETH) and capreomycin (CPM) was carried using the agar proportion method on enriched Middlebrook 7H10 medium (BBL, BD, Sparks, MD, USA) at the following concentrations: RIF (1 μg/ml), INH (0.2 μg/ml), SM (2 μg/ml), EMB (5 μg/ml), AMK (4 μg/ml), KM (5 μg/ml), CM (4 μg/ml), OFX (2 μg/ml) and ETH (5 μg/ml). For pyrazinamide (PZA) DST was performed by using Mycobacterial Growth Indicator Tube (Becton Dickinson, Franklin Lakes, NJ) in compliance with the manufacturer's instructions. For all the patients DST was carried out at baseline visit and repeated whenever considered necessary; whereas, sputum smear and culture were performed on monthly basis.

Treatment protocol

All patients with positive diagnosis for MTB and RIF resistance on rapid DST underwent various clinical laboratory tests at the study site. These tests included screening for HIV and hepatitis, complete blood count, kidney, liver and thyroid function tests, random blood sugar, urinalysis and electrolytes. After completion of baseline laboratory work, the suspected MDR-TB patients were enrolled for treatment with empirical treatment regimen (ETR) based on the recommendations of NTP guidelines [13]. Treatment in all presumed MDR-TB patients except those with documented history of previous use of SLD was initiated with AM/KM/CM + OFX + ETH + Cycloserine (CS)+PZA + vitamin B6. In those patients who had documented history of previous use of SLD, treatment was initiated with the above stated regimen plus para-amino salicylic acid (PSA). Once the DST results became available, patients were then shifted from ETR to individualized treatment regimen (ITR). The ITR was tailored according to the DST results of the patients and consisted of at least four effective or likely effective SLD + PZA + vitamin B6. A drug for which DST result had confirmed susceptibility was considered "effective", whereas, the drug for which DST result was not available but patient had not used it for more than one month was considered "likely effective". All the drugs were administered in maximum recommended doses based on patients' body weight. Patients were treated for a minimum of at least 18 months after sputum culture conversion (SCC). Injectable SLD was administered for at-least eight months and a minimum of six months after SCC. All patients were treated as outpatients and assessed monthly. Patients' treatment adherence was monitored by trained treatment supporters. In order to ensure adherence to treatment, a Home Directly Observed Treatment Linkages (HDL) facilitator paid regular visits to the patients' homes and created links between patients, PMDT unit and District TB officers. All treatment was provided free of cost to the patients with monthly food rations and conveyance allowance to the patients and treatment supporters.

Operational definitions

In present study the following operational definitions were used. **Suboptimal treatment regimen** was defined as the "treatment regimen containing <4 effective or likely effective SLD". **Sputum culture conversion** was defined as "two consecutive negative cultures taken at least 30 days apart following a positive

culture" [14,15]. Treatment outcomes were decided on the basis of WHO guidelines for the management of DR-TB [16]. A patient was declared "**Cured**" if he/she completed his/her treatment as recommended by the guidelines and had five consecutive negative cultures taken at least 30 days apart in the final 12 months of treatment. For declaring a patient cured, one positive culture was allowed in the final 12 months of treatment provided that it was followed by three consecutive negative cultures taken at least 30 days apart. A patient was declared "**Treatment completed**" if he/she completed his/her treatment as recommended by guidelines, had no signs of treatment failure but had no enough culture results in the final 12 months of treatment to declare the patient cured. Treatment outcome "**Died**" was given to any patient who died for any reason during MDR-TB treatment. A patient who had two or more positive cultures in final 12 months of treatment or in whom treatment terminated earlier due to poor clinical or radiological response or adverse event was categorized as "**Treatment Failure**". A patient was declared "**Lost to follow up**" if the treatment was interrupted for two consecutive months without any medically approved reason. Treatment outcomes cured and treatment completed were collectively classified as "**successful treatment outcomes**", whereas, died, treatment failure and lost to follow up were collectively categorized as "**unsuccessful treatment outcomes**".

Data analysis

Data was analysed by using SPSS version 20. Categorical data was presented as frequencies and percentage, whereas, continuous data was presented as mean ± standard deviations. In order to find factors associated with unsuccessful treatment outcomes of (i) death and treatment failure and (ii) lost to follow up, all those variables which had a p-value <0.2 in univariate analysis were entered into multivariate binary logistic regression (MVBLR) analysis. All factors considered in univariate analysis were based on literature review, suggestions from the clinical team and clinical relevance of these factors with MDR-TB treatment outcomes in previously published studies [5,8–10,17–19]. Correlation was checked for all those independent variables which were entered in MVBLR. If independent variables had high correlation with each other (Tolerance value <0.1 and/or Variance inflation factor = 10), one of them was removed from the final model [20]. Discrimination power of final model for evaluating death and treatment failure was assessed by using Receiver Operating Characteristic Curve (ROC) analysis. A p-value of <0.05 was considered statistically significant.

Ethical approval

This study was approved by the Ethics and Research Committee, Faculty of Pharmacy and Health Sciences University of Baluchistan, Quetta. Permission to carry out the study was also taken from the authorities of FJGCH Quetta.

Results

Socio-demographic characteristics of and drug resistance patterns

During the study period a total of 255 DR-TB patients were enrolled at the study site. Among them, 186 met the inclusion criteria and were included in the study (Fig. 1). The mean age of the study participants was 37.07 ± 16.34 years. Majority of them were females (61.3%), rural residents (68.3%), non-smokers (83.9%), previously treated for TB (96.2%) and had no documented comorbidity (90.9%) and history of SLD use (95.2%) (Table 1).

Study participants were resistant to a median of four drugs (range 2–8) with majority being resistant to five drugs (27.4%). A total of 55.5% patients were resistant to any SLD. Among SLD, resistance was highest for OFX (52.2%) followed by ETO (7%) (Table 2).

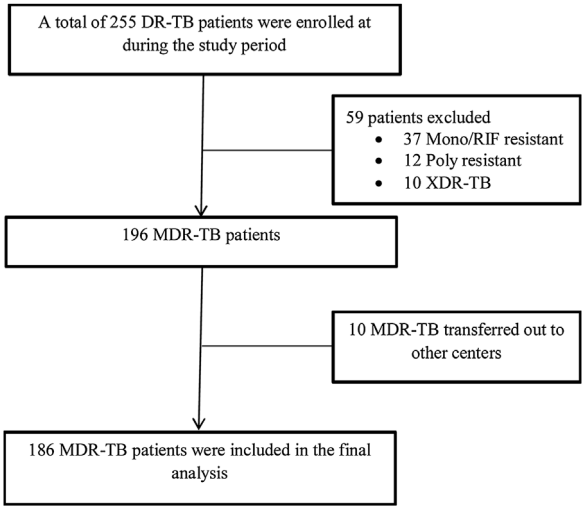

Fig. 1. Inclusion and exclusion of study participants.

Treatment regimen

Out of 186 enrolled patients, six had a previous history of MDR-TB treatment and treatment in them was treatment was initiated on the basis of their previous DST results. In the remaining 180 patients, treatment was initiated with ETR. Once the DST results became available (mean 75 days, interquartile range 60–87) patients were then shifted to ITR. The availability of DST reports resulted in the modification of regimen in 98/180 (54.4%) patients by adding PAS to the treatment regimen.

Sputum culture conversion

Out of 185 pulmonary MDR-TB patients, 150 (81.1%) patients achieved sputum culture conversion. Among them 92 (61.3%) patients were culture converted at two months of treatment. The mean time to sputum culture conversion was 61 ± 13.5 days. Of 35 patients who did not achieve SCC, 24 died and 11 were lost to follow up before SCC.

Treatment outcomes and factors associated with unsuccessful outcomes

Of 186 patients included in the final analysis, 129 (69.4%) were cured, four (2.2%) completed the treatment successfully, 37 died (19.9%), 14 (7.5%) were lost to follow up and two (1.1%) were declared treatment failures. The study site had an overall treatment success rate of (71.6%) (Table 3).

In MVBLR analysis, the variable of patients' age of >40 years (OR = 4.249, 95% p-value = 0.001) and baseline body weight (OR = 0.256, p-value = 0.002) had statistically significant associations with the outcome of death and treatment failure. Patients with age >40 years were 4.249 times more likely to develop death and treatment failure than patients with age ≤40years. Whereas, patients with baseline body weight of >40 kg were significantly less likely to develop death and treatment failure than their counterparts with baseline body weight of ≤40 kg. This model fit was based on non-significant Hosmer Lemeshow (p-value = 0.482) and overall classification percentage of 80.6% from classification table (Table 4). Receiver operating characteristic curve analysis by non-parametric method revealed a fair discrimination power of the final model (AUC = 0.762, 95%CI: 0.676–0.847, p-value < 0.001) (Fig. 2).

Table 1
Patients' baseline socio-demographic, clinical and microbiological characteristics.

Variable	Mean ± SD	*n* (%)
Gender		
Female		114 (61.3)
Male		72 (38.7)
Age (years)	37.07 + 16.34	
<20		27 (14.5)
21–40		99 (53.2)
41–60		40 (21.5)
>60		20 (10.8)
Weight (kg)	45.32 ± 10.84	
<30		14 (7.5)
31–45		82 (44.1)
46–60		76 (40.9)
>60		14 (7.5)
Residence		
Rural		127 (68.3)
Urban		59 (31.7)
Smoking		
Non-smokers		156 (83.9)
Active + ex-smokers		30 (16.1)
Drug addiction		
No		184 (98.9)
Yes		2 (1.1)
Previous treatment regimen		
New patients		7 (3.8)
Category I		112 (60.2)
Category II		59 (31.7)
Others		8 (4.3)
History of SLD use		
No		177 (95.2)
Yes		9 (4.8)
Sputum smear grading at baseline visit		
Negative		19 (10.3)
Scanty (1–9 AFB/100 HPF)		9 (4.8)
+1 (10–99 AFB/100 HPF)		40 (21.5)
+2 (1–9 AFB/HPF)		35 (18.8)
+3 (>9 AFB/HPF)		82 (44.1)
Comorbidity		
No		169 (90.9)
Yes		17 (9.1)
Types of comorbidities		
Diabetes mellitus		11
Hepatitis		4
HIV-AIDS		1
COPD		1

AFC, Acid Fast Bacilli; COPD, chronic obstructive pulmonary disease; HIV-AIDS, Human Immunodeficiency Virus-Acquired Immune Deficiency Syndrome; HPF, High Power Field; SD, standard deviation.

Table 2
Patients' baseline drug resistance pattern.

Variable	*n* (%)
Number of resistant drugs at baseline visit	
Two	18 (9.7)
Three	36 (19.4)
Four	44 (23.7)
Five	51 (27.4)
Six or more	37 (19.5)
Resistance to pyrazinamide	129 (69.4)
Resistance to ethambutol	105 (56.6)
Resistance to streptomycin	84 (45.2)
Resistance to all five first line anti-TB drugs	56 (30.1)
Resistance to any second line anti-TB drug	103 (55.5)
Resistance to ofloxacin	97 (52.2)
Resistance to ethionamide	13 (7.0)
Resistance to injectable second line anti-TB drugs	3 (1.6)

Table 3
Patients' treatment outcomes.

Treatment outcome	No. (%)
Successful	133 (71.6)
Cured	129 (69.4)
Treatment completed	4 (2.2)
Unsuccessful	53 (28.4)
Died	37 (19.8)
Lost to follow up	14 (7.5)
Failed	2 (1.1)

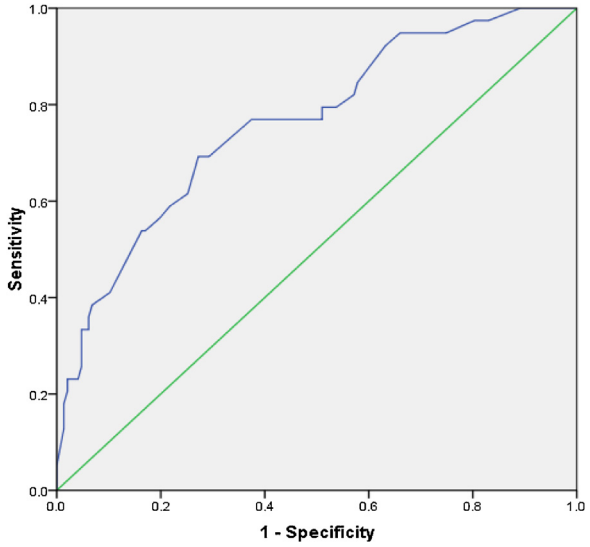

Fig. 2. ROC curve of discriminatory power of final model predicting death and treatment failure.

A total of 14 (7.5%) patients were lost to follow up. In univariate analysis, patients' gender (OR = 4.435, 95%CI: 1.335–14.735) and baseline body weight (OR = 9.816, 95%CI: 1.256–76.728) had statistically significant association with lost to follow up, but none of the factors achieved statistical significant in multivariate analysis. This model fit was based on non-significant Hosmer Lemeshow (p-value = 0.702) and overall classification percentage of 92.5% from classification table (Table 5).

Discussion

To the best of our knowledge this is the first study which evaluated the drug resistance pattern, detailed management, treatment outcomes and factors associated with unsuccessful outcomes in MDR-TB patients in Baluchistan province of Pakistan. In contradiction with the global epidemiology of male predominance in TB patients, majority of the current study participants were females. Similar high proportion of female MDR-TB patients (53.1%) has been reported by another a study conducted in Peshawar, Pakistan [10]. As females in poor societies take care of patients at home, this perhaps make them more susceptible to contagious diseases like TB [21,22]. Moreover, due to the deeply rooted gender discrimination in tribal societies like in Baluchistan and Khyber Pukhtoonkhwa of Paksitan, mostly males decide about the females health needs and they are not allowed to visit health facilities alone. Due to socioeconomic marginalization of females and the stigma associated with TB, female TB patients in the country are reported to have a comparatively greater delay in seeking healthcare and seek low quality care [23–25]. This delay and substandard care may result in faulty management of TB and consequently the emergence of MDR-TB.

Table 4
Factors associated with death and treatment failure.

Variable	Died + failed *n* (%)	Univariate analysis OR (95%CI)	p-value	Multivariate analysis OR (95%CI)	p-value
Gender					
Female	28 (24.6)	Referent		Referent	
Male	11 (15.3)	0.554 (0.256–1.197)	0.133	0.648 (0.271–1.550)	0.329
Age (years)					
<40	24 (32.0)	Referent		Referent	
>40	15 (13.5)	2.816 (1.363–5.816)	0.005	4.249 (1.862–9.700)	0.001
Weight (kg)					
<40	19 (15.1)	Referent		Referent	
>40	20 (33.3)	0.332 (0.160–0.688)	0.003	0.256 (0.109–0.602)	0.002
Residence					
Rural	29 (22.8)	Referent			
Urban	10 (16.9)	0.690 (0.311–1.529)	0.360	–	
Smoking					
Non-smokers	32 (20.5)	Referent			
Active + ex-smokers	7 (23.3)	1.179 (0.465–2.992)	0.728	–	
Comorbidity					
No	36 (21.3)	Referent			
Yes	3 (17.6)	0.792 (0.216-2.905)	0.725	–	
Previous treatment regimen					
New patients	2 (28.6)	Referent			
Category I	20 (17.9)	0.543 (0.098–3.004)	0.485	–	
Category II	13 (22.0)	0.707 (0.123–4.072)	0.697	–	
Unknown	4 (50.0)	2.500 (0.292–21.399)	0.403	–	
History of SLD use					
No	36 (20.3)	Referent			
Yes	3 (33.3)	1.958 (0.467–8.211)	0.358	–	
Baseline sputum					
Negative	3 (15.8)	Referent			
Scanty,+1	7 (14.3)	0.889 (0.204–3.866)	0.875	–	
+2,+3	29 (24.8)	1.758 (0.478–6.466)	0.396	–	
Resistance to PZA					
No	8 (14.0)	Referent		Referent	
Yes	31 (24.0)	1.937 (0.829–4.531)	0.127	1.803 (0.720–4.514)	0.208
Resistance to EMB					
No	17 (21.0)	Referent			
Yes	22 (21.0)	0.998 (0.490–2.034)	0.995	–	
Resistance to SM					
No	24 (23.5)	Referent			
Yes	15 (17.9)	0.707 (0.343–1.454)	0.346	–	
Resistance to OFX					
No	14 (15.7)	Referent		Referent	
Yes	25 (25.8)	1.860 (0.897–3.859)	0.096	2.830 (0.641–12.493)	0.170
Resistance to ETO					
No	34 (19.7)	Referent		Referent	
Yes	5 (38.5)	2.555 (0.786–8.304)	0.119	3.563 (0.924–13.744)	0.065
Resistant to all five FLD					
No	29 (22.3)	Referent			
Yes	10 (17.9)	0.757 (0.341–1.683)	0.495	–	
Number of resistant drugs					
2	2 (11.1)	Referent			
3–5	29 (22.1)	2.275 (0.494–10.470)	0.291	–	
>6	8 (21.6)	2.207 (0.417–11.669)	0.352	–	
Initial treatment regimenOptimalSuboptimal	14 (15.9) 25 (25.5)	Referent1.810 (0.873–3.755)	0.111	Referent0.637 (0.142–2.863)	

CI, confidence interval; EMB, ethambutol; ETO, ethionamide; FLD, first line anti-TB drugs; kg, kilogram; OFX, ofloxacin; OR, odds ratio; PZA, pyrazinamide; SLD, second line anti-TB drugs; SM, streptomycin.

In current study, a high degree of drug resistance to SLD particularly to OFX (52.2%) was observed. This was in compliance with the rate of OFX resistance reported by other studies conducted in Pakistan. Studies conducted at PDMT units of Peshawar and Multan have reported the OFX resistance of (52.7%) and (48.9%) respectively [9,10]. The national guidelines recommend that treatment in presumed MDR-TB patients with no documented history of SLD use should be initiated with AM/KM/CM + OFX + ETH + CS + PZA + Vitamin B6, and when the DST shows resistance to any SLD, PAS should be added to the above stated regimen [13]. Due to high prevalence of SLD resistance in current cohort, in current cohort pre-XDR TB (MDR-TB plus resistance to anyone of SLD) was more prevalent (55.5%) than MDR-TB (44.5%). Because of high prevalence of pre-XDR TB in the current cohort, initial treatment regimen was modified and optimized by the addition of PAS in 98/180 (54.4%) patients. This puts a question mark on the appropriateness of guidelines recommended above-mentioned ETR at the study site and other PMDT units in Pakistan [9,10] and needs the urgent attention of NTP. In order to solve this issue, it is suggested that the recent WHO guidelines recommendations regarding MDR-TB treatment should be considered and adopted across the country [26,27].

In current study, 71.6% patients achieved successful outcomes. This was comparatively better than treatment success rates reported by studies conducted other PMDT units in the country i.e. Karachi (42.64%) [11] and Multan (40.5%) [9]. But the results of these two studies should be interpreted with the caution that, at the time of evaluating treatment outcomes, 33.4% patients in Karachi [11] and 13.8% in Multan [9] were still under treatment. However, the study site did not achieve the target set by WHO (≥75%) [28],

Table 5
Factors associated with lost to follow up.

Variable	Lost to follow up *n* (%)	Univariate analysis OR (95%CI)	p-value	Multivariate analysis OR (95%CI)	p-value
Gender					
Female	4 (3.5)	Referent		Referent	
Male	10 (13.9)	4.435 (1.335–14.735)	0.015	3.461 (0.963–12.436)	0.057
Age					
<40	10 (7.9)	Referent			
>40	4 (6.7)	0.829 (0.249–2.758)	0.759	–	
Weight (kg)					
<40	1 (1.3)	Referent		Referent	
>40	13 (11.7)	9.816 (1.256–76.728)	0.029	6.601 (0.809– 53.868)	0.078
Residence					
Rural	11 (8.7)	Referent			
Urban	3 (5.1)	0.565 (0.152–2.106)	0.395	–	
Smoking					
Non-smokers	13 (8.3)	Referent			
Active + ex-smokers	1 (3.3)	0.379 (0.048–3.014)	0.359	–	
Previous TB treatment					
No	2 (28.6)	Referent		Referent	
Yes	12 (6.7)	0.180 (0.031– 1.025)	0.053	0.150 (0.021–1.048)	0.056
Resistance to SLD					
No	4 (4.8)	Referent			
Yes	14 (9.7)	2.124 (0.641–7.034)	0.218	–	

CI, confidence interval; kg, kilogram; OR, odds ratio; SLD, second line anti-TB drugs; TB, tuberculosis; SM, streptomycin.

and the treatment success rate was comparatively lower than an MDR-TB cohort treated at PMDT unit in Peshawar, Pakistan (75.2%) [10]. Comparable treatment success rates among MDR-TB patients have been reported from Nepal (70%) [29] and Dominican Republic (72%) [30]. Mortality rate in the current study (19.8%) was comparable to the rate observed at PMDT unit in Peshawar (19.3%) [10], but comparatively lower than the rate observed in Multan (25%) [9] and higher than the rate observed in Karachi (9.57%) [11].

In multivariate analysis, patients' age >40 years and baseline weight of ≤40 kg emerged as the risk factors for death and treatment failure. Older age has previously been reported as a risk factor for unsuccessful outcomes in MDR-TB patients [9,10,31,32]. Because of general physical deterioration, co-morbidities, complicated medication schedule, malnutrition and compromised immunity, older age patients respond poorly to anti-TB treatment [33–36]. The concurrence of these factors make older age a risk factor for unfavourable outcomes in TB patients. In the current cohort patients who had baseline weight of >40 kg had statistically significant negative association with death and treatment failure. It implies that patients with baseline body weight of ≤40 kg were at significantly greater risk of developing death and treatment failure. Similar positive association between low body weight and unfavourable treatment outcomes have been reported by studies conducted elsewhere [9,10,36,37]. Poor absorption from gastrointestinal tract is one of the major reasons of sub-therapeutic serum concentration of anti-TB drugs. Malnourishment is believed to be a contributing factor for lower serum drug levels in TB patients [38]. It not only reduces the gastrointestinal absorption of drugs but also increase the renal clearance of free drugs, subsequently resulting in sub-therapeutic drug levels and poor treatment outcomes. Moreover, inadequate dosing of drugs in underweight patients could be another cause of sub-therapeutic serum drug concentration and high incidence of death and treatment failure in these patients [38].

In present study, a total of 14 (7.5%) patients were lost to follow up. This rate was in the range reported in literature (1.1–21%) [9–11,39,40]. Comparing it to the treatment default rates reported by other studies conducted elsewhere in Pakistan, it was higher than the rate observed in Peshawar (1.1%) and lower than lost to follow up rates observed in studies conducted in Multan (18.3%) [9] and Karachi (11.11%) [11]. In current cohort, 11 out of 14 patients were lost to follow up during the intensive phase of treatment and before SCC. As culture positive patients are highly infective, this makes it an alarming issue and threat to the public health. Relief of symptoms after treatment initiation with effective regimen, lack of information about the total duration of MDR-TB treatment and dangers of incomplete treatment could be possible reasons for lost to follow up. In current study, in univariate analysis, male gender and baseline body weight of >40 kg had statistically significant associations with lost to follow up, but none of the factors reached the level of significance in multivariate analysis.

Conclusion

Although, overall treatment success rate at the study site was promising, but it was still below the WHO target of achieving successful outcomes in MDR-TB patients and has room for further improvement. Patients' lost to follow up particularly before SCC was an alarming issue. It needs remedial measures including treating patients as inpatients until SCC, decentralization of treatment, and educating patients and treatment supporters about the duration of MDR-TB treatment and hazards of incomplete treatment. Rate of successful outcomes at the study site may be further improved by providing special attention and enhanced clinical management to the patients with identifiable risk factors of poor outcomes. Nutritional counselling to increase energy intake and provision of nutritional supplements should be considered in patients weighing ≤40 kg. Moreover, therapeutic drug monitoring in patients with baseline body weight ≤40 kg may offer a better chance to manipulate each patient's anti-TB therapy.

Even though all DR-TB patients from Baluchistan are referred to the study site, but being a retrospective study from a single centre its findings cannot be generalized. Moreover, we were unable to abstract information about the incidence and frequency of adverse events and treatment regimen modification due to adverse events, and its effects of treatment outcomes. Furthermore, as we have included consecutive patients in this study, its findings should be interpreted with the potential limitation of selection bias.

Conflict of interest

None declared.

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Ethical approval

Not required.

Authors' contribution

NA, IK, and SK conceptualized the study design. IK collected the data. IK and G entered the data. NA, AK and IA analysed and interpreted the data. NA wrote and all the authors critically reviewed the manuscript. NA also supervised the study.

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