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# Unsuccessful treatment outcome and associated risk factors. A prospective study of DR-TB patients from a high burden country, Pakistan

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## Abstract

### Introduction

Tuberculosis (TB), a curable and preventable infectious disease, becomes difficult to treat if resistance against most effective and tolerable first line anti-TB drugs is developed. The objective of the present study was to evaluate the treatment outcomes and predictors of poor outcomes among drug-resistant tuberculosis (DR-TB) patients treated at a programmatic management unit of drug resistant tuberculosis (PMDT) unit, Punjab, Pakistan.

### Methods

This prospective observational study was conducted at a a PMDT unit in Multan, Punjab, Pakistan. A total of 271 eligible culture positive DR-TB patients enrolled for treatment at the study site between January 2016 and May 2017 were followed till their treatment outcomes were recorded. World Health Organization's (WHO) defined criteria was used for categorizing treatment outcomes. The outcomes of cured and treatment completed were collectively placed as successful outcomes, while death, lost to follow-up (LTFU) and treatment failure were grouped as unsuccessful outcomes. Multivariable binary logistic regression analysis was employed for getting predictors of unsuccessful treatment outcomes. A p-value <0.05 was considered statistically significant.

### Results

Of the 271 DR-TB patients analysed, nearly half (51.3%) were males. The patient's (Mean ± SD) age was 36.75 ± 15.69 years. A total of 69% patients achieved successful outcomes with 185 (68.2%) patients being cured and 2 (0.7%) completed therapy. Of the remaining 84 patients with unsuccessful outcomes, 48 (17.7%) died, 2 (0.7%) were declared treatment failure, 34 (12.5%) were loss to follow up. After adjusting for confounders, patients' age > 50

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years (OR 2.149 (1.005–4.592) with p-value 0.048 and baseline lung cavitation (OR 7.798 (3.82–15.919) with p-value <0.001 were significantly associated with unsuccessful treatment outcomes.

## Conclusions

The treatment success rate (69%) in the current study participants was below the target set by WHO (≥75%). Paying special attention and timely intervention in patients with high risk of unsuccessful treatment outcomes may help in improving treatment outcomes at the study site.

## Introduction

Tuberculosis (TB) is an air borne infectious disease which spreads from person to person and mainly affects lungs though it can also affect other body parts such as spine, kidney, and brains. It is preventable and curable; however, successful TB control becomes difficult if mycobacterium tuberculosis, a pathogen causing TB, become resistant to the most effective and tolerable therapy, thus, the resultant condition termed as drug resistant TB (DR-TB). Availability of fewer controlled trials for evidence of efficacy [1] and limited numbers of drugs for effective management of DR-TB [2], lengthy and tiresome regimens coupled with high cost and toxicity [3, 4], least prioritization to health and lack of political will [5], and deficient health resources required for effective control [6] are some of the major factors that have caused failure to achieve definite treatment outcome goals among DR-TB patients. Even though enormous progress in successful treatment of drug-susceptible TB has been made, Pakistan ranks 4th globally in terms of DR-TB according to a recently published list for high burden countries (HBC) regarding DR-TB patients by World Health Organization (WHO) [7]. An estimated 4.2% (95% confidence interval [CI] = 3.2–5.3%) of new TB cases and 7.3% (95%CI = 6.8–7.8) of previously treated TB cases had DR-TB in Pakistan as per WHO global TB report 2020 [8]. According to global tuberculosis community advisory board, the number of TB patients is increasing rapidly at an estimated rate of 25,000 new cases per year in Pakistan [9]. In 2020, WHO reported that 573,000 TB cases fell ill in Pakistan, out of which 46,000 cases died, while 25000 people were affected by DR-TB [10].

According to WHO global TB report 2021, Pakistan accounts for about 5.8% of new cases globally. In 2009, Pakistan's National Tuberculosis Control Program (NTP) succeeded in obtaining approval form Green Light Committee (GLC) for initiating the use of second line drugs (SLDs) pilot projects for the treatment of 400 DR-TB patients in 3 hospitals. The GLC further approved the required means for the medication management of 1500 DR-TB patients in 2010–2011. Programmatic management of DR-TB (PMDT) in Pakistan was initiated in June 2010 with enrollment of 195 DR-TB for treatment whereas, 2372 DR-TB patients started treatment in 2020 [11]. After PMDT protocol implementation, country has seen considerable progress in terms of DR-TB. Despite being the highest DR-TB burden country in Eastern Mediterranean Region (EMRO), fewer studies have been carried out to assess the treatment outcomes and risk factors associated with unsuccessful treatment outcomes among prospective patients. Majority of already reported studies are retrospective [12–17] and cross sectional [18] in nature thus lacking the coherent study design. We could find only one prospective study among DR-TB patients at some other study site [19] at the time of present study initiation, though 33 PMDT unit are functional to date. To evaluate a healthcare program's efficacy, disease managing protocols and the associated outcomes of a patient cohort should be assessed

[20]. In the absence of prospective studies, retrospective do provide initial point for understanding but lesser control on data and absence of key demographic and clinical parameter, bias in exclusion and inclusion criteria with respect to disease and age and absence of TB drugs information to the patients in these studies raise concerns on the validity of these studies. The reported treatment outcome in these studies cannot be generalized. Smaller sample size, absence of sputum culture data, unavailability of AFB culture facility in some studies, limited demographic knowledge about patients potentiate the need for prospective studies. Due to availability of only retrospective studies with already mentioned deficiencies, present prospective research study was designed to have more control on real and required data. Out-patient DR-TB patients at a high burdened PMDT unit in the densely populated province (Punjab) of Pakistan were evaluated for local drug resistance pattern, therapy outcomes, and the identification of risk factors associated with treatment failure to assess the program effectiveness. The findings of this study would help program coordinators to undertake required measures for the improvement of the TB program. To facilitate the healthcare providers in the management of DR-TB patients, identification of the high-risk patients at an earlier stage, information regarding risk factors for unsuccessful treatment outcome, and drug resistance pattern among local population is extremely helpful.

The resistance to drugs and the outcomes of a treatment regimen are greatly affected by local epidemiology, and if taken into consideration, it helps to devise an optimized empirical therapy. The present study was aimed to assess the pattern of resistance to the treatment regimen and factors associated with unsuccessful treatment outcome among DR-TB patients at the PMDT unit which serve a treatment hub to a densely populated geographic location with no previous studies with the suitability of the current treatment protocols.

## Methodology

### Study population and site

A prospective observational study was carried out at PMDT unit, at pulmonology ward, Nishtar Medical University (NMU), Multan, Punjab, Pakistan. Free of cost necessary diagnostic services are provided to DR-TB patients by pathology and radiology departments of NMU, Hospital. Samples for drug susceptibility testing (DST) are sent to national reference laboratory (NRL), Islamabad, Pakistan. Resistance to rifampicin (R) is considered as pre-requisite for the 18-month DR-TB treatment post sputum culture conversion with second line anti-TB drugs (SLDs). A total of 271 culture confirmed DR-TB patients got enrolled for treatment at the study site between January 2016 and May 2017. Written or oral consent, whichever applicable was obtained from the enrolled patients. All the patients were briefed about the study objectives. The study was approved by the Institutional Ethical Review Board (IRB), NMU, Hospital, Multan, Pakistan.

### Diagnosis and treatment of DR-TB patients

WHO definitions were followed regarding patient identification and diagnosis [21]. Diagnosis and treatment of DR-TB patients at PMDT units in Pakistan have previously been discussed elsewhere [19, 22]. In summary, suspected DR-TB cases, referred to the study site, were initially collected with two sputum samples for sputum microscopy (Zielh-Neelson stain) and Gene Xpert for rifampicin resistance. After obtaining Rifampicin resistance and positive sputum microscopic results, patients were initiated for DR-TB treatment with empirical regimen, except those with previous history of fluoroquinolones, as recommended by national guidelines for DR-TB [22]. Sputum samples for DST result were sent to National reference laboratory (NRL) Pakistan. Patients were documented for any comorbidity before the initiation of

the therapy with the help of their medical record. Enrolled patients were given conventional long regimen treatment (LTR). On the availability of sputum culture and DST results against all first line (FLDs) and second line (SLDs) anti-TB drugs, study participants were shifted to individualized regimen based on patient specific resistance pattern. The aim was to have at least 4 likely effective anti-TB SLDs with maximum recommended daily dose.

Patients, enrolled in study, received medication for a minimum of 18-months after culture conversion. Culture conversion was defined as the consecutive two negative sputum culture results collected at least 30 days apart. Injectable anti-TB drugs were administered for at least 8-months, for a minimum of 6-month post culture conversion during the intensive phase. DR-TB patients were treated as out-patients, and they were assessed on regular monthly interval. Medication adherence was monitored by specially trained support staff. Patients were provided cards, and each dose administered was marked on individual patient card. These cards were counter evaluated on monthly visit by clinician. Treatment compliance was confirmed by a home facilitator. Health facilitator paid home visits and acted as link between patients and PMDT unit treatment staff. Patients were provided free medication for monthly usage. In addition to medication, patients and therapy supporter were entitled to receive transport charges and monthly food ration.

## Data collection

A standardized and comprehensive data collection form was used for patients' socio-demographic, microbiological and clinical data. WHO guidelines defined criteria for management of DR-TB were followed for reporting of treatment outcomes. Cure and treatment completion were grouped under successful/favorable outcomes, whereas death, treatment failure and loss to follow up (LFTU) were categorized as unsuccessful/unfavorable outcomes. Treatment efficacy was calculated by the successful treatment outcome (sum of cured+treatment completed cases) divided by the sum of all cases (cured + treatment completed + died + treatment failure + loss to follow up). Loss to follow up patients have been grouped in "unsuccessful treatment outcome" which is in-line with the WHO and national tuberculosis program (NTP), Pakistan guidelines. Similar grouping has been reported in the published literature as well [23, 24]. As loss to follow up DR-TB patients abort the treatment and hence ultimately impact the overall success rate (cured and completed) of the study and study site performance.

Patients suffering with co-morbidities were recorded for their known diagnosis. Patients were evaluated on monthly basis by disease specialist as per NTP, Pakistan guidelines. Information about demographics and clinical history (age, gender, marital and residential status, smoking, previous TB history, length of disease, previous SLDs use, co-morbidities) and baseline parameters (laboratory, DST result, sputum grading, cavitation) along with monthly clinical data input were recorded. Laboratory tests, conducted on monthly basis, included complete blood count (CBC), serum electrolytes, liver function tests (LFTs), renal function tests (RFTs), random blood glucose and uric acid. Thyroid test, hepatitis, and HIV screening were done at the initiation of therapy. Visual and audiometry tests were done on recommendation of clinician for some patients and were repeated when deemed necessary on physician judgment. All patients were treated free of cost on ambulatory basis with monthly support allowance and transportation charges. Patients clinical record was used for the identification of any co-morbidity. Patients having more than three times levels of the upper value of transaminases or screened confirmed hepatitis (A, B, and C) were defined as hepatitis patient at baseline.

### Statistical analysis

Data was analyzed by statistical package of social sciences version 26 (SPSS Inc., Chicago, IL). Continuous variables were presented as means ± SD (standard deviation), medians and ranges, whereas categorical data was presented as frequencies and percentages. Univariate logistic regression analysis was used to evaluate association between independent variables and unsuccessful treatment outcomes. All variables, considered in univariate logistic regression analysis were based on literature review and suggestions from clinical team at the study site. P-value $< 0.05$ was used to describe statistical significance of any included variable. Multivariable logistic regression analysis was used to assess the risk factors for unsuccessful treatment outcomes. Relevant independent variables with p-value $< 0.2$ in univariate logistic regression analysis were included in the multivariable logistic regression analysis [25]. P-value $< 0.05$ was used to describe statistical significance of any included variable in final analysis.

## Results

### Description of the DR-TB patients

Among 308 enrolled DR-TB patients, 37 patients did not meet the inclusion criteria and were excluded. Pregnant women (5), children age $< 18$ years (31) and intellectually disable patient (1) were among the excluded from the study. Of the 271 DR-TB patients, 134 (49.5%) patients were only rifampicin resistant and 128 (47.23%) were resistant to both isoniazid and rifampicin (MDR-TB). Both rifampicin resistant (RR) and MDR patients were nearly the 97% of the cohort. Poly drug resistant (PDR) patient (1) included in the study had resistance against rifampicin and pyrazinamide. There were 8 extensively drug resistant (XDR) TB patients accounting to 2.95% of the cohort.

### Patient characteristics

The socio-demographic and baseline clinical characteristics of the 271 DR-TB patients included in the study are shown in Table 1.

### Drug resistance pattern

Drug resistance pattern among all 271 DR-TB patients was documented. Among FLDs, after rifampicin, the rate of resistance was highest for isoniazid (49.4%) followed by pyrazinamide (23.6%), ethambutol (16.6%) and streptomycin (8.1%). Noticeable number of patients were found to be resistant to SLDs (26%). After the availability of DST results for SLDs drug resistance, resistance was highest for *ofloxacin* (Ofx) (24.7%), followed by *kanamycin* (Km) (3%), *amikacin* (Am) (1.8%), *capreomycin* (Cm) (1.5%), and *ethionamide* (Eto) (0.7%). More detailed resistance pattern is given in Table 2.

### Treatment outcomes

Of the 271 patients included in the final analysis, 69% achieved successful treatment outcomes (cured and treatment completed) while unsuccessful treatment outcome included 48 (17.7%) died, 34 (12.5%) loss to follow up, and 2 (0.73%) treatment failure patients (Table 3). Cause of death among DR-TB patients was either TB or clinical conditions due to TB disease progression i.e., cardiac arrest, Myocardial infarction, or chronic illness.

**Table 1. Patients' socio-demographic, baseline clinical characteristics (N = 271).**

| Variable | No. (%) |
|---|---|
| **Gender** | |
| Female | 132 (48.7) |
| Male | 139 (51.3) |
| **Age (Years) (Mean ± SD = 36.75 ± 15.69)** | |
| Age < 50 years | 210 (77.5) |
| Age ≥ 50 years | 61 (22.5) |
| **Marital Status** | |
| Unmarried | 76 (28.0) |
| Married | 195 (72.0) |
| **Residence** | |
| Rural | 131 (48.3) |
| Urban | 140 (51.7) |
| **Employment status** | |
| No | 165 (60.9) |
| Yes | 106 (39.1) |
| **Smoking status** | |
| Non-smoker | 240 (88.6) |
| Active +Ex-smoker | 31 (11.4) |
| **Treatment Registration Category** | |
| New | 38 (14.0) |
| Relapse | 6 (2.2) |
| Treatment after failure | 198 (73.1) |
| Treatment after Loss to follow up | 26 (9.6) |
| Others | 3 (1.1) |
| **Previous TB treatment** | |
| No | 38 (14.0) |
| Yes | 233 (86.0) |
| **Previous use of SLDs** | |
| No | 244 (93.4) |
| Yes | 17 (6.3) |
| **Comorbidity** | |
| No | 226 (83.4) |
| Yes | 45 (16.6) |
| **Patient weight at baseline (Kg) (Mean ± SD = 45.44±11.61)** | |
| < 40 Kg | 188 (69.4) |
| ≥40 Kg | 83 (30.6) |
| **Haemoglobin Level at baseline** | |
| Normal | 82 (30.3) |
| < Normal | 189 (69.7) |
| **Baseline Smear grading** | |
| Neg | 23 (8.5) |
| *Scanty**+1 | 133 (49.1) |
| ***+2‡+3 | 115 (42.4) |
| **Baseline Pulmonary Cavitation** | |
| No Cavitation | 119 (43.9) |
| Cavitation | 152 (56.1) |
| **Resistance to all five FLDs** | |

(*Continued*)

**Table 1.** (Continued)

| Variable | No. (%) |
|---|---|
| No | 257 (94.8) |
| Yes | 14 (5.2) |
| **Resistance to SLDs** | |
| No | 200 (73.8) |
| Yes | 71 (26.2) |

FLDs, first-line anti-TB drugs; SLDs, second line anti-TB drug; TB, tuberculosis

*1–9 Acid Fast Bacilli/100 High Power Field

**10–99 Acid Fast Bacilli/100 High Power Field

*** 1–9 Acid Fast Bacilli/ High Power Field

‡ >9 Acid Fast Bacilli/ High Power Field; Kg, Kilogram; SD, Standard Deviation

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**Table 2. Drug resistance pattern of studied patients (N = 271).**

| Resistant Drugs | No. (%) |
|---|---|
| Isoniazid (H) | 134 (49.4) |
| Ethambutol (E) | 45 (16.6) |
| Pyrazinamide (Z) | 64 (23.6) |
| Streptomycin (S) | 22 (8.1) |
| All First Line Drugs (FLDs) | 14 (5.2) |
| Any Second Line Drugs (SLDs) | 71 (26.2) |
| Amikacin (Am) | 5 (1.8) |
| Kanamycin (Km) | 8 (3.0) |
| Capreomycin (Cm) | 4 (1.5) |
| Ofloxacin (Ofx) | 67 (24.7) |
| Ethionamide (Eto) | 2 (0.7) |
| RH | 262(97.0) |
| RH + Ofx | 63 (23.2) |
| HRZ | 63 (23.2) |
| HRZ + Ofx | 39 (14.3) |
| HRE | 44 (16.2) |
| HRE + Ofx | 25 (9.3) |
| HRZE | 29 (10.7) |
| HRZE + Ofx | 19 (7) |
| HRES | 15 (5.5) |
| HRS + Ofx | 13 (4.8) |
| HRZS | 18 (6.6) |
| HRZS + Ofx | 11(4.0) |
| HRES + Ofx | 9 (3.3) |
| HREZ + Km + Am + Ofx | 1 (0.3) |
| HRZ + Km + Am + Ofx | 5 (1.8) |
| All FLDs + Ofx | 9 (3.3) |
| HR + Ofx + Km | 8 (2.9) |
| All FLDs + Ofx + Eto | 1 (0.3) |
| HR + Cm | 4 (1.4) |
| HRS + Ofx + Km | 4 (1.4) |
| HRS + Ofx + Km + Moxifloxacin | 1 (0.3) |

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**Table 3. Treatment outcomes of the study participants (N = 271).**

| Treatment outcomes | No. (%) |
|---|---|
| **Successful Treatment outcomes** | **187 (69.0)** |
| Cured | 185 (68.3) |
| Completed | 2 (0.7) |
| **Unsuccessful Treatment Outcome** | **84 (31.0)** |
| Died | 48 (17.7) |
| Failed | 2 (0.7) |
| Loss to follow Up | 34 (12.5) |

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## Predictors of unsuccessful treatment outcomes

In univariable logistic regression analysis, the age of participants > 50 OR 2.333 (1.294–4.206), p-value 0.005, married subjects OR 2.008 (1.075–3.752), p-value 0.029, individuals with SLIs resistance OR 4.17 (1.151–19.343), p-value = 0.031), individuals with baseline cavitation (OR 7.147 (3.701–13.804), p-value < 0.001), resistance to all five FLDs OR 0.356 (0.078–1.626) p-value 0.182, Co-morbidity OR 0.587 (0.276–1.25) p-value 0.167 , history of SLDs use OR 2.07 (0.77–5.569) with p-value 0.15, resistance to fluoroquinolones OR 2.067 (1.165–3.670) with p-value 0.013 and 4 or more than 4 resistant drugs OR 1.568 (0.867–2.836) with p-value 0.136 were associated with poor treatment outcome as described in Table 4.

In multivariable logistic regression analysis, after adjusting the marital status, history of SLDs use, co-morbidity, resistance to all FLDs, resistance to fluoroquinolones, resistance to second line injectables (SLIs) and resistance to 4 or more than 4 drugs, significant association was observed between DR-TB patients with age ≥ 50 years OR 2.149 (1.005–4.592) with (p-value 0.048) and baseline lung cavitation OR 7.798 (3.82–15.919) with (p-value <0.001) and unsuccessful treatment outcome as presented in Table 5.

## Discussion

By the end of the study period, treatment outcomes for 271 patients (100%) were available, and 187 (69%) patients achieved treatment success. The study site did not reach the WHO criteria of ≥ 75% target [26]. Treatment success rate of our study was lower comparable to success rates reported elsewhere, [15, 27–29] but better than studies from Bahawalpur Pakistan (59.2%) and 60% [16, 30], China (57%) [31], a meta-analysis [32], meta-analysis [29, 33–35] and GLC-supported DOTS-plus projects [36].

High loss to follow up rate (12.5%) in our study caused decreased success rate. Higher loss to follow up rate in our study could be due to factors such as lack of TB disease knowledge, distance of patients' residency from healthcare settings, fading of symptoms during the early months of anti-TB treatment, age or gender of subjects, and adverse drug effects associated with treatment. Cure rate of our study was better than most of the studies carried elsewhere in world. This could possibly be due to use of individualized regimens and competent people hired by PMDT to provide directly observed treatment (DOT) throughout the treatment duration (18 months) [29, 37, 38]. Additional factors such as age > 65 years, non-alcoholics, and HIV negative status were also observed in our study subjects which are predictive of the success of TB treatment [39]. A mortality rate of 17.7% was observed in our study which was similar to studies reported elsewhere [29, 33, 36, 37] but lower than a study in Peru (53.2%) [40]. A possible reason for the lower mortality rates in the afore mentioned studies [29, 33, 36, 37] might be the masking of deaths by high loss to follow up rates.

**Table 4. Univariable logistic regression analysis of risk factors associated with unsuccessful treatment outcomes among DR-TB patients (N = 271).**

| Variable | Unsuccessful treatment outcome No. (%) | OR (95% CI) | p-value |
|---|---|---|---|
| **Gender** | | | |
| Female | 41 (31.1) | Referent | |
| Male | 43 (30.9) | 0.994 (0.594–1.664) | 0.982 |
| **Age (years)** | | | |
| <50 | 56 (26.7) | Referent | |
| ≥ 50 | 28 (45.9) | 2.333 (1.294–4.206) | **0.005** |
| **Weight** | | | |
| ≥ 40 | 55 (29.3) | Referent | |
| < 40 | 29 (34.9) | 1.299 (0.749–2.251) | 0.352 |
| **Marital status** | | | |
| Unmarried | 16 (21.1) | Referent | |
| Married | 68 (34.9) | 2.008 (1.075–3.752) | **0.029** |
| **Residence** | | | |
| Rural | 42 (32.1) | Referent | |
| Urban | 42 (30.0) | 0.908 (0.543–1.520) | 0.714 |
| **Employment** | | | |
| No | 53 (32.1) | Referent | |
| Yes | 31 (29.2) | 0.873 (0.514–1.485) | 0.617 |
| **Comorbidity** | | | |
| No | 74 (32.7) | Referent | |
| Yes | 10 (22.2) | 0.587 (0.276–1.250) | **0.167** |
| **History of TB Treatment** | | | |
| No | 12 (31.6) | Referent | |
| Yes | 72 (30.9) | 0.969 (0.463–2.027) | 0.933 |
| **History of SLD use** | | | |
| No | 76 (30.0) | Referent | |
| Yes | 8 (47.1) | 2.070 (0.770–5.569) | **0.150** |
| **Smoking** | | | |
| No | 74 (30.7) | Referent | |
| Yes | 10 (33.3) | 1.128 (0.504–2.529) | 0.769 |
| **Baseline sputum grading** | | | |
| Negative | 3(13.0) | Referent | |
| Scanty, +1 | 44 (33.1) | 3.296 (0.929–11.691) | **0.065** |
| +2, +3 | 37 (32.2) | 3.162(0.884–11.317) | **0.077** |
| **Lung cavitation at baseline** | | | |
| No | 13 (10.9) | Referent | |
| Yes | 71 (46.7) | 7.147 (3.701–13.804) | < **0.001** |
| **Resistance to H** | | | |
| No | 40 (29.2) | Referent | |
| Yes | 44 (32.8) | 1.186 (0.708–1.985) | 0.517 |
| **Resistance to Z** | | | |
| No | 62 (30.0) | Referent | |
| Yes | 22 (34.4) | 1.225 (0.675–2.222) | 0.504 |
| **Resistance to E** | | | |
| No | 73 (32.3) | Referent | |
| Yes | 11 (24.4) | 0.678 (0.325–1.414) | 0.300 |
| **Resistance to S** | | | |

(*Continued*)

**Table 4.** (Continued)

| Variable | Unsuccessful treatment outcome No. (%) | OR (95% CI) | p-value |
|---|---|---|---|
| No | 77 (30.9) | Referent | |
| Yes | 7 (31.8) | 1.042 (0.409–2.659) | 0.931 |
| **Resistance to all 5 FLDs** | | | |
| No | 82 (31.9) | Referent | |
| Yes | 2 (14.3) | 0.356 (0.078–1.626) | **0.182** |
| **Resistance to FQ** | | | |
| No | 55 (27.0) | Referent | |
| Yes | 29 (43.3) | 2.067 (1.165–3.670) | **0.013** |
| **Resistance to any SLI** | | | |
| No | 78 (29.8) | Referent | |
| Yes | 6 (66.7) | 4.178 (1.151–19.343) | **0.031** |
| **Number of resistant drugs** | | | |
| <4 | 60 (28.7) | Referent | |
| ≥ 4 | 24 (38.7) | 1.568 (0.867–2.836) | **0.136** |

OR Odds ratio; CI, Confidence Interval; SLDs, Second line anti-TB drugs; Scanty, 1–9 Acid Fast Bacilli/100 High Power Field; +1, 10–99 Acid Fast Bacilli/100 High Power Field; +2, 1–9 Acid Fast Bacilli/ High Power Field; +3 >9 Acid Fast Bacilli/ High Power Field; FLDs, First line anti-TB drugs; FQs, Fluoroquinolones; SLIs, Second line Injectables.

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In multivariable analysis, patients' age ≥ 50 years emerged as a risk factor for death and treatment failure. The younger the research participants, the more likely they are to be healed. Older age is a well-known risk factor for treatment failure in both drug-susceptible and drug-resistant tuberculosis because of these factors. According to the 2014 Global Burden of Disease estimates, the majority of TB-related deaths occurred among the elderly [41]. Age 40 years and above is found to be risk factor for treatment failure in the previous studies as well [19, 42–44]. There is a poor response of older patients towards anti-TB treatment due to general fatigue, co-morbidities, complex medication schedule, poor diet and deficient immunity as stated in studies carried out previously [45–47]. The risk of mortality in DR-TB patients was more than two times greater in older patients, and the risk doubled with every 10 years rise in age [44]. Turkey has documented a similar increased risk of adverse treatment results in elderly DR-TB patients [48]. These factors make older age a risk factor for unfavorable treatment outcomes in patients with DR-TB.

Lung cavitation at baseline was another predictor of poor treatment outcomes in our study which is in line with studies conducted in other parts of world [33, 37, 43, 46, 49]. Patients with lung cavities on their baseline chest X-ray were considerably more likely to have unsatisfactory treatment results in the present group and had more severe and advanced illness and took longer to seek medical help. Cavitary illness is related with a higher degree of infectiousness because to the larger organism burden. Reduced efficacy of antibacterial drugs due to reduced penetration in the presence of lung cavities could be a reason for the poor outcomes in this group of patients [49]. Several studies using qualitative smears and cultures concluded the presence of higher mycobacterial loads in the sputum of patients with cavitary TB [50–52] which could result in a high recurrence rate [53, 54]. Several prior studies have established that cavitary illness is a risk factor for poor treatment results in DR-TB patients, which is consistent with our findings. [37] revealed bilateral lung cavitation as a risk factor for poor treatment results in 15% and 10% of DR-TB patients, respectively, and connected it to mortality and treatment failure. DR-TB patients with bilateral cavitary illness were 2.6 times more likely to

**Table 5. Multivariable logistic regression analysis of risk factors for unsuccessful treatment outcome.**

| Variable | OR 95% CI | p-value |
|---|---|---|
| Age ≥ 50 Years | 2.149(1.005–4.592) | **0.048** |
| Marital status | 2.116 (0.985–4.546) | 0.055 |
| Comorbidity | 0.561(0.242–1.3) | 0.178 |
| Previous use of SLDs | 2.484 (0.722–8.548) | 0.149 |
| Baseline Sputum grading (Negative) | Referent | |
| Scanty, +1 | 2.27(0.553–9.32) | 0.255 |
| +2, +3 | 1.653(0.397–6.881) | 0.49 |
| Baseline Lung Cavitation | 7.798(3.82–15.919) | **<0.001** |
| Resistance to All Five FLDs | 0.192(0.03–1.234) | 0.082 |
| Resistance to FQs | 1.174(0.498–2.766) | 0.715 |
| Resistance to SLIs | 4.094(0.645–25.987) | 0.135 |
| Resistance to ≥ 4 drugs | 1.612(0.626–4.155) | 0.323 |

B, beta; S.E, Standard error; OR Odds ratio; CI, Confidence Interval; SLDs, Second line anti-TB drugs; Scanty, 1–9 Acid Fast Bacilli/100 High Power Field; +1, 10–99 Acid Fast Bacilli/100 High Power Field; +2, 1–9 Acid Fast Bacilli/ High Power Field; +3 >9 Acid Fast Bacilli/ High Power Field; FLDs, First line anti-TB drugs; FQs, Fluoroquinolones; SLIs, Second line injectables

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have unsatisfactory treatment results in a Russian research [33]. Similar findings which suggests that treatment outcome is adversly affected due to presence of lung cavitation at the basline have been reported in another study among DR-TB patients in Pakistani population [19].

Single center study at one of the high burden sites in the geographic area may pose limitation to the study. Although patients of all types of drug resistance were included in the study, yet the generalization of results needs that future research at multicenter PMDT unit sites should be carried out. Patients who died were documented as having died during treatment with the actual reason of death, yet there is need to further evaluate the association of risk factors related to mortality.

## Conclusion

Treatment success rate of our study was not promising as it was low than the WHO global End TB set goal of 75% success rate, thus it needs improvement. The low success rate may be attributed to high loss to follow up rate which needs serious efforts to engage the loss to follow up patients by proper counselling, educating them about their disease, and strategies formulation to enhance patient compliance to therapeutic plan and medication. Rational use of medication may increase the success rate with early detection of resistance pattern and individualized regimen. This study was conducted on subjects from a single center; hence the findings of this study should be confirmed through multi-centered and increased sample size research.

## Supporting information

**S1 Data.**
(XLSX)

## Author Contributions

**Conceptualization:** Asif Massud, Amer Hayat Khan.

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**Formal analysis:** Asif Massud, Nafees Ahmad.

**Investigation:** Asif Massud.

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**Project administration:** Asif Massud.

**Resources:** Muhammad Shafqat.

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**Validation:** Long Chiau Ming.

**Writing – original draft:** Asif Massud.

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## References

1. Mitnick CD, Castro KG, Harrington M, Sacks LV, Burman W. Randomized trials to optimize treatment of multidrug-resistant tuberculosis: the time for action is now. PLOS medicine. 2007; 4(11):e292.
2. Caminero J. Treatment of multidrug-resistant tuberculosis: evidence and controversies. The International Journal of Tuberculosis and Lung Disease. 2006; 10(8):829–37. PMID: 16898365
3. Diel R, Vandeputte J, de Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. European Respiratory Journal. 2014; 43 (2):554–65. https://doi.org/10.1183/09031936.00079413 PMID: 23949960
4. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov A, Tupasi T, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. The International Journal of Tuberculosis and Lung Disease. 2004; 8(11):1382–4. PMID: 15581210
5. Abubakar I, Zignol M, Falzon D, Raviglione M, Ditiu L, Masham S, et al. Drug-resistant tuberculosis: time for visionary political leadership. The Lancet infectious diseases. 2013; 13(6):529–39. https://doi.org/10.1016/S1473-3099(13)70030-6 PMID: 23531391
6. Nathanson E, Nunn P, Uplekar M, Floyd K, Jaramillo E, Lönnroth K, et al. MDR tuberculosis—critical steps for prevention and control. New England Journal of Medicine. 2010; 363(11):1050–8. https://doi.org/10.1056/NEJMra0908076 PMID: 20825317
7. WHO. WHO global lists of high burden countries for tuberculosis (TB), TB/HIV and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021–2025: background document. Geneva: World Health Organization; 2021 2021.
8. WHO. Global tuberculosis report 2020. Geneva: World Health Organization, 2020 2020. Report No.: 9789240013131 (electronic version) 9789240013148 (print version).
9. Arif S, Mehboob Q, Arif W. Prevalence and Analysis of Drug Resistance Pattern of MDR-TB in Retreatment Cases at Allied Hospital, Faisalabad, Pakistan. Annals of Punjab Medical College (APMC). 2020; 14(4):331–5.
10. NTP P. TB profile Pakistan 2020. Available from: https://ntp.gov.pk/tb-profile-pakistan/.
11. WHO. Diagnosis, notification and treatment of RR/MDR-TB patients in Pakistan 2020. Available from: https://app.powerbi.com/view?r=eyJrIjoiZDhjNDM0YmMtOGExOS00ODIxLWEzMjktZDk0NmI4YTAwODgwIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9.
12. Saeed W, Naseem A, Ahmed J. Retrospective audit of patients treated for MDR-TB in re-treatment category. J Ayub Med Coll Abbottabad. 2009; 21(2):94–8. PMID: 20524480
13. Rao NA, Mahfooz Z, Irfan M. Treatment outcome of multi-drug resistant tuberculosis in a tertiary care hospital in Karachi. Journal of Pakistan Medical Association. 2009; 59(10):694.
14. Muhammad I, Haque AS, Waheed Z, Khan JA. Treatment outcome of multi-drug resistant tuberculosis treated as outpatient in a tertiary care center. Eur Respiratory Soc. 2011.
15. Khan I, Ahmad N, Khan S, Muhammad S, Ahmad Khan S, Ahmad I, et al. Evaluation of treatment outcomes and factors associated with unsuccessful outcomes in multidrug resistant tuberculosis patients in Baluchistan province of Pakistan. Journal of Infection and Public Health. 2019; 12(6):809–15. doi: https://doi.org/10.1016/j.jiph.2019.04.009. PMID: 31056438

16. Atif M, Ahmad W, Ahmad N, Malik I, Sarwar S. Treatment outcomes among multidrug-resistant TB patients in Bahawal Victoria Hospital, Bahawalpur, Pakistan: a retrospective record review. Transactions of The Royal Society of Tropical Medicine and Hygiene. 2020; 114(10):733–41. https://doi.org/10.1093/trstmh/traa040 PMID: 32556195

17. Khan MA, Mehreen S, Basit A, Khan RA, Jan F, Ullah I, et al. Characteristics and treatment outcomes of patients with multi-drug resistant tuberculosis at a tertiary care hospital in Peshawar, Pakistan. Saudi medical journal. 2015; 36(12):1463. https://doi.org/10.15537/smj.2015.12.12155 PMID: 26620989

18. Khurram M, Bushra H, Fahim M. MDR-TB in Pakistan. J Infect DW Ctries. 2012; 6(1):29–32.

19. Ahmad N, Javaid A, Basit A, Afridi AK, Khan MA, Ahmad I, et al. Management and treatment outcomes of MDR-TB: results from a setting with high rates of drug resistance. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2015; 19(9):1109–14, i-ii. Epub 2015/08/12. https://doi.org/10.5588/ijtld.15.0167 PMID: 26260834.

20. Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. The Lancet. 2005; 365(9456):318–26. Epub 2005/01/25. https://doi.org/10.1016/S0140-6736(05)17786-1 PMID: 15664227.

21. WHO. Definitions and reporting framework for tuberculosis– 2013 revision: updated December 2014 and January 2020. Geneva: World Health Organization; 2013 2013.

22. NTP. National guidlines for the Programmatic Management of Drug-resistant Tuberculosis (PMDT), Pakistan 2014. Available from: http://ntp.gov.pk/ntp-old/uploads/ntp_1368669324_National_Guidelines_PMDT.zip.

23. Javaid A, Ullah I, Masud H, Basit A, Ahmad W, Butt Z, et al. Predictors of poor treatment outcomes in multidrug-resistant tuberculosis patients: a retrospective cohort study. Clinical Microbiology and Infection. 2018; 24(6):612–7. https://doi.org/10.1016/j.cmi.2017.09.012 PMID: 28970158

24. Naz F, Ahmad N, Wahid A, Ahmad I, Khan A, Abubakar M, et al. High rate of successful treatment outcomes among childhood rifampicin/multidrug-resistant tuberculosis in Pakistan: a multicentre retrospective observational analysis. BMC infectious diseases. 2021; 21(1):1–11.

25. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. American journal of epidemiology. 1993; 138(11):923–36. https://doi.org/10.1093/oxfordjournals.aje.a116813 PMID: 8256780

26. Organization WH, Initiative ST. Treatment of tuberculosis: guidelines: World Health Organization; 2010.

27. Seddon JA, Hesseling AC, Godfrey-Faussett P, Schaaf HS. High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study. Thorax. 2014; 69(5):458–64. https://doi.org/10.1136/thoraxjnl-2013-203900 PMID: 24064441

28. Ganzaya S, Naranbat N, Bissell K, Zachariah R. Countrywide audit of multidrug-resistant tuberculosis and treatment outcomes in Mongolia. Public Health Action. 2013; 3(4):333–6. https://doi.org/10.5588/pha.13.0052 PMID: 26393057

29. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. The Lancet Infectious diseases. 2009; 9(3):153–61. https://doi.org/10.1016/S1473-3099(09)70041-6 PMID: 19246019

30. Atif M, Bashir A, Ahmad N, Fatima RK, Saba S, Scahill S. Predictors of unsuccessful interim treatment outcomes of multidrug resistant tuberculosis patients. BMC infectious diseases. 2017; 17(1):1–12.

31. Alene KA, Yi H, Viney K, McBryde ES, Yang K, Bai L, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug resistant tuberculosis in Hunan Province, China. BMC infectious diseases. 2017; 17(1):1–11.

32. Falzon D, Mirzayev F, Wares F, Baena IG, Zignol M, Linh N, et al. Multidrug-resistant tuberculosis around the world: what progress has been made? European Respiratory Journal. 2015; 45(1):150–60. https://doi.org/10.1183/09031936.00101814 PMID: 25261327

33. Shin SS, Pasechnikov AD, Gelmanova I, Peremitin G, Strelis A, Andreev Y, et al. Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia. The International Journal of Tuberculosis and Lung Disease. 2006; 10(4):402–8. PMID: 16602404

34. Batyrshina Y, Petrenko T. Effectiveness of national standardized and WHO regimens and risk factors of unfavorable outcomes in treatment of patients with MDR-TB in Novosibirsk Oblast, Russian Federation. European Respiratory Journal. 2014; 44(Suppl 58).

35. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PloS one. 2009; 4(9):e6914. https://doi.org/10.1371/journal.pone.0006914 PMID: 19742330

36. Nathanson E, Lambregts-van Weezenbeek C, Rich ML, Gupta R, Bayona J, Blöndal K, et al. Multidrug-resistant tuberculosis management in resource-limited settings. Emerging infectious diseases. 2006; 12(9):1389. https://doi.org/10.3201/eid1209.051618 PMID: 17073088

37. Rodriguez M, Monedero I, Caminero J, Encarnación M, Dominguez Y, Acosta I, et al. Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. The International journal of tuberculosis and lung disease. 2013; 17(4):520–5. https://doi.org/10.5588/ijtld.12.0481 PMID: 23485386

38. Mitnick CD, Franke MF, Rich ML, Alcantara Viru FA, Appleton SC, Atwood SS, et al. Aggressive regimens for multidrug-resistant tuberculosis decrease all-cause mortality. PloS one. 2013; 8(3):e58664. https://doi.org/10.1371/journal.pone.0058664 PMID: 23516529

39. Chaves Torres NM, Quijano Rodríguez JJ, Porras Andrade PS, Arriaga MB, Netto EM. Factors predictive of the success of tuberculosis treatment: A systematic review with meta-analysis. PloS one. 2019; 14(12):e0226507-e. https://doi.org/10.1371/journal.pone.0226507 PMID: 31881023.

40. Franke MF, Appleton SC, Bayona J, Arteaga F, Palacios E, Llaro K, et al. Risk factors and mortality associated with default from multidrug-resistant tuberculosis treatment. Clinical infectious diseases. 2008; 46(12):1844–51. https://doi.org/10.1086/588292 PMID: 18462099

41. WHO. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis: World Health Organization; 2014.

42. Javaid A, Shaheen Z, Shafqat M, Khan AH, Ahmad N. Risk factors for high death and loss-to-follow-up rates among patients with multidrug-resistant tuberculosis at a programmatic management unit. American journal of infection control. 2017; 45(2):190–3. https://doi.org/10.1016/j.ajic.2016.07.026 PMID: 27769706

43. Kurbatova EV, Taylor A, Gammino VM, Bayona J, Becerra M, Danilovitz M, et al. Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. Tuberculosis. 2012; 92(5):397–403. https://doi.org/10.1016/j.tube.2012.06.003 PMID: 22789497

44. Drobniewski F, Eltringham I, Graham C, Magee J, Smith E, Watt B. A national study of clinical and laboratory factors affecting the survival of patients with multiple drug resistant tuberculosis in the UK. Thorax. 2002; 57(9):810–6. https://doi.org/10.1136/thorax.57.9.810 PMID: 12200527

45. Sharma SK, Mohan A. Multidrug-resistant tuberculosis. The Indian journal of medical research. 2004; 120(4):354–76. Epub 2004/11/03. PMID: 15520486.

46. Tang S, Tan S, Yao L, Li F, Li L, Guo X, et al. Risk factors for poor treatment outcomes in patients with MDR-TB and XDR-TB in China: retrospective multi-center investigation. PLoS one. 2013; 8(12): e82943. https://doi.org/10.1371/journal.pone.0082943 PMID: 24349402

47. Naidoo K, Hassan-Moosa R, Mlotshwa P, Yende-Zuma N, Govender D, Padayatchi N, et al. High Rates of Drug-induced Liver Injury in People Living With HIV Coinfected With Tuberculosis (TB) Irrespective of Antiretroviral Therapy Timing During Antituberculosis Treatment: Results From the Starting Antiretroviral Therapy at Three Points in TB Trial. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020; 70(12):2675–82. Epub 2019/10/18. https://doi.org/10.1093/cid/ciz732 PMID: 31622456; PubMed Central PMCID: PMC7931836.

48. Tahaoğlu K, Törün T, Sevim T, Ataç G, Kir A, Karasulu L, et al. The treatment of multidrug-resistant tuberculosis in Turkey. New England journal of medicine. 2001; 345(3):170–4. https://doi.org/10.1056/NEJM200107193450303 PMID: 11463011

49. Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest. 2000; 117(3):744–51. Epub 2000/03/14. https://doi.org/10.1378/chest.117.3.744 PMID: 10713001.

50. Murthy S, Chatterjee F, Crook A, Dawson R, Mendel C, Murphy M, et al. Pretreatment chest x-ray severity and its relation to bacterial burden in smear positive pulmonary tuberculosis. BMC medicine. 2018; 16(1):1–11. https://doi.org/10.1186/s12916-018-1053-3 PMID: 29779492

51. Rathman G, Sillah J, Hill P, Murray J, Adegbola R, Corrah T, et al. Clinical and radiological presentation of 340 adults with smear-positive tuberculosis in The Gambia. The International Journal of Tuberculosis and Lung Disease. 2003; 7(10):942–7. PMID: 14552563

52. Matsuoka S, Uchiyama K, Shima H, Suzuki K, Shimura A, Sasaki Y, et al. Relationship between CT findings of pulmonary tuberculosis and the number of acid-fast bacilli on sputum smears. Clinical imaging. 2004; 28(2):119–23. https://doi.org/10.1016/S0899-7071(03)00148-7 PMID: 15050224

53. Zha BS, Nahid P. Treatment of drug-susceptible tuberculosis. Clinics in chest medicine. 2019; 40 (4):763–74. https://doi.org/10.1016/j.ccm.2019.07.006 PMID: 31731983

54. Jo K-W, Yoo J-W, Hong Y, Lee JS, Lee S-D, Kim WS, et al. Risk factors for 1-year relapse of pulmonary tuberculosis treated with a 6-month daily regimen. Respiratory medicine. 2014; 108(4):654–9. https://doi.org/10.1016/j.rmed.2014.01.010 PMID: 24518046