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Original article

# Predictors of poor treatment outcomes in multidrug-resistant tuberculosis patients: a retrospective cohort study

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ABSTRACT

*Objectives:* : We aimed to determine the characteristics, treatment outcomes and risk factors for poor treatment outcomes among multidrug-resistant (MDR) tuberculosis (TB) patients in Khyber Pakhtunkhwa province, Pakistan.
*Methods:* A retrospective cohort study including all patients with MDR-TB who sought care at the MDR-TB unit in Peshawar was conducted between January 2012 and April 2014. Patients were followed until an outcome of TB treatment was recorded as successful (cured or completed) or unsuccessful. Binary logistic regression was used to identify predictors of poor outcome, i.e. unsuccessful treatment outcomes.
*Results:* Overall, 535 patients were included. The proportion of female subjects was relatively higher ($n$ = 300, 56.1%) than male subjects. The mean (standard deviation) age of patients was 30.37 (14.09) years. Of 535 patients for whom treatment outcomes were available, 402 (75.1%) were cured, 4 (0.7%) completed therapy, 34 (6.4%) had disease that failed to respond to therapy, 93 (17.4%) died and two (0.4%) defaulted; in total, 129 (24.1%) had an unsuccessful outcome. We found three significant predictors of unsuccessful treatment during multivariate logistic regression: being married (odds ratio (OR) = 2.17, 95% confidence interval (CI) 1.01, 4.66), resistance to second-line drugs (OR = 2.61, 95% CI 1.61, 4.21) and presence of extensively drug-resistant TB (OR = 7.82, 95% CI 2.90, 21.07).
*Conclusions:* Approximately 75% of the treatment success rate set by the Global Plan to Stop TB was achieved. Resistance to second-line drugs and presence of extensively drug-resistant TB are the main risk factors for poor treatment outcomes. **A. Javaid, Clin Microbiol Infect 2017;▪:1**


## Introduction

Multidrug-resistant (MDR) tuberculosis TB has become a major obstacle to successful TB control worldwide, especially in developing countries [1]. Drug resistance in TB is a human-created phenomenon caused by inaccurate prescribing practices by physicians and patient noncompliance, and it may also be a consequence of primary infection, thus demanding more intensive interventions. MDR-TB treatment is more expensive, longer, less effective and causes more adverse effects compared to drug-susceptible TB treatment [2]. According to the World Health Organization, 9% of estimated MDR-TB patients fail to complete the desired therapeutic outcome, and their disease becomes extensively drug resistant (XDR) (http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf). In Pakistan, the rate of XDR-TB cases has increased with time, from 1.5% in 2006 to 4.5% in 2009 [3]. However, recent estimates based on smaller studies indicate a rate of 2% to 3% [4,5].

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Pakistan is fifth in TB and fourth in MDR-TB among high-burden countries worldwide (http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf). In 2013 globally, a total of 480<thinsp>000 MDR-TB cases were reported, of which 13<thinsp>000 were present in Pakistan [6]. Despite several efforts, case detection rates are quite low (63%), and most patients remain undiagnosed and untreated [7]. Pakistan still harbours the largest population of MDR-TB patients in the Eastern Mediterranean region among MDR-TB countries (http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf). A drug resistance survey conducted in Pakistan showed that the estimated percentage of MDR-TB in newly notified TB cases is 4.3% and in retreatment cases is 19.4% [8]. In selected populations of Khyber Pakhtunkhwa (KPK), 3% of MDR-TB is present in new cases and 26% in previously treated patients [9]. Another study from KPK showed that 17.4% of MDR-TB patients have relatives with MDR-TB and thus are close contacts [10], while it is 4% in new and 19.4% in previously treated patients in Punjab, Pakistan [11].

MDR and XDR-TB cases are on the rise in Pakistan, which highlights the importance of an effective TB control program. Limited information is available about the management and treatment outcomes of MDR-TB in Pakistan. To understand factors responsible for unsuccessful treatment outcomes among MDR-TB patients, we aimed to examine predictors of unsuccessful treatment outcomes among MDR-TB patients in KPK.

## Methods

A retrospective cohort study was carried out at the Programmatic Management of Drug-Resistant TB (PMDT) unit in Lady Reading Hospital, Peshawar. All MDR-TB-suspected individuals were referred to the PMDT unit. It is the largest PMDT unit in KPK and covers a population of over 2 million.

### *Study population*

All drug-resistant TB patients who were enrolled in the PMDT unit between January 2012 and April 2014 constituted the cohort. TB patients with any drug resistance were eligible, but only patients with MDR/XDR-TB were included, while patients with drug resistance not fulfilling the criteria for MDR/XDR-TB, patients who transferred or moved during follow-up and patients who were receiving treatment at the time of analysis were excluded (Fig. 1). The definitions are presented in Table 1 [12]. Patients were followed until treatment outcome was recorded or until April 2016.

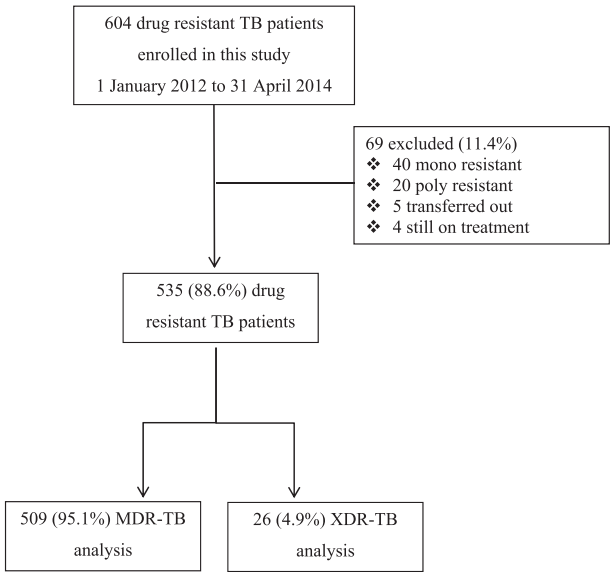


**Fig. 1.** Flowchart showing patient enrollment and eligibility. MDR, multidrug resistant; TB, tuberculosis; XDR, extensively drug resistant.

### *Variables and definitions*

The main outcome variable, treatment outcome, was measured as successful or unsuccessful; successful treatment included cure and treatment completion, while unsuccessful treatment included default, treatment failure and death. The definitions are shown in Table 1. We also collected information from the patients about known (diagnosed) comorbidities.

All registered patients were examined by specialist clinicians on a monthly basis; patients were then managed under the auspices of a green-light committee. The green-light committee included an infectious diseases specialist, who approved protocols related to MDR-TB diagnosis. As per the rules of our national TB guidelines, blood samples were investigated every month. Diagnosis of comorbidities was taken from patient medical records; hepatitis was defined as documentation of hepatitis (A, B or C) due to any cause and/or transaminases more than three times the upper limit of normal at the baseline visit.

### *Data collection procedure*

The sociodemographic (age, weight, gender, comorbidities, residence, contacts), microbiologic (baseline sputum smear grading, drug susceptibility testing (DST) results, monthly microbiologic culture status) and clinical data (disease, treatment outcome history with drugs) of each patient were collected on standard forms by a trained collector.

### *Microbiologic studies*

Our clinical samples consisted of 604 specimens from patients with drug-resistant disease. At least one sample for TB diagnosis was taken from all patients. The sample was divided equally into two parts, and each part was uniquely coded. One part was used for smear microscopy and Xpert MTB/RIF assay (Cepheid), while the other part was used in Löwenstein-Jensen culture medium and DST. The first *Mycobacterium tuberculosis* isolate per patient was considered for analysis. Smear preparation of specimens and Xpert MTB/RIF assay was done as described elsewhere [9].

The confirmed *M. tuberculosis* isolates were further subjected to DST. DST was performed against the first-line drugs isoniazid, rifampicin, ethambutol and streptomycin and against the second-line drugs kanamycin, amikacin, ofloxacin, capreomycin and ethionamide using the 1% proportion method on Middlebrook 7H10 medium as per standard guidelines (Becton Dickinson) (http://tbcindia.gov.in/index1.php?lang=1&level=1&sublinkid=4160&lid=2807). DST was performed for the first-line drug pyrazinamide using BACTEC 7H12 medium in accordance with the manufacturer's instructions. For the reference control strain, we used H37RV, which is characteristically susceptible to all anti-TB drugs. The case was considered MDR-TB if the isolate of *M. tuberculosis* showed resistance to at least two of the most important first-line anti-TB drugs, rifampicin and isoniazid, as confirmed by DST (Table 1).

### *Treatment protocol*

All registered patients at the study site diagnosed by Xpert MTB/RIF received empirical treatment with a standardized regimen consisting of kanamycin/amikacin/capreomycin + ethionamide +

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