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Predictors of unfavorable Treatment Outcome in Patients with Drug-resistant Tuberculosis in a Tertiary Care Hospital; A study from Khyber Pakhtunkhwa

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ABSTRACT

Background: the emergence of Drug-resistant tuberculosis (DR-TB) poses a great challenge to all health authorities throughout the world. DR-TB is difficult to treat due to resistance of its causative agents to anti-TB drugs. Its success rate is lower as compared to drug-susceptible TB.

Objective: The objective of the present study was to determine the predictors of unfavorable treatment outcomes in patients with drug-resistant tuberculosis

Methodology: This study was conducted at Lady Reading Hospital (LRH) and Hayatabad Medical Complex (HMC), Peshawar. This study included all those patients who enrolled for treatment from June 2017 to January 2019. Baseline data of all enrolled patients at LRH was collected where monthly sputum sample results were collected from HMC. Resistance to rifampicin was identified as RR-TB based on Gene-Expert analysis whereas additional resistance was found by sputum DST results. SPSS 20 was used to analyze the data. The mean ± SD was used to represent numerical data frequencies and percentages to describe categorical data, whereas the chi-square test was applied for association among different variables. P-values less than 0.005 were used as significant.

Results: A total of 230 DR-TB cases were included in the present study who were enrolled at the PMDT LRH during the study duration. Among them, 106 (46.0%) were men and 124 (53.91%) were women. The majority of patients 150 (65.2%) had been diagnosed with multidrug-resistant tuberculosis, which was followed by Rifampicin Resistant 60 (26.0%). There was a 158 (68.69%) cure rate and 43 patients (18.6%) died. Age and gender stratification of the result, or cure, did not show any statistically significant associations ($p > 0.05$).

Conclusion: This study has unveiled that the rate of cure for drug-resistant tuberculosis treatment regimens stands at 68.69%, while the death rate is 18.6%. Understanding the factors contributing to poor outcomes and ensuring timely diagnosis with the correct treatment protocol can enhance treatment outcomes and halt the further spread of the disease.

Key words: TB, DR-TB; Treatment Outcomes; Predictors

Introduction

Tuberculosis is an infectious and airborne disease and after the human immunodeficiency virus (HIV) the second most common cause of mortality. The death rate from tuberculosis has lowered by 45% since 1990 as a result of international efforts to manage it. Yet, its worldwide incidence still stands at a terrifying level. Approximately, 9 million persons acquired this medical condition in 2013, and 1.5 million of them lost their lives to it.[1] Its recurrence in the form of drug-resistant tuberculosis poses a challenge for TB control efforts since it includes multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) infectious agents. The rise of multidrug-resistant tuberculosis (MDR-TB) presents a significant challenge to the successful management of tuberculosis (TB), especially in poor nations.1 Drug resistance in tuberculosis is man-made which is occurred due to patients' noncompliance and clinicians' incorrect prescription approaches. Compared to therapy for drug-susceptible TB, multidrug-resistant tuberculosis (MDR-TB) is more expensive, longer, less effective, and has more side effects.[2]

Compared to drug-susceptible TB, multidrug-resistant tuberculosis is much harder to treat, requiring the prescription of second-line medications that are less effective and frequently have serious adverse effects. It requires an extended period of therapy that lasts at least twenty-four months. The success rate of treatment is lower than that of drug-susceptible tuberculosis. Therefore, identifying those with MDR TB and providing them with full therapy is imperative. Inadequate management of multidrug-resistant tuberculosis may adversely affect patient outcomes and elevate the danger of widespread prescription drugs resistance.[3-5] Drug-resistant pathogens can spread quickly among susceptible populations if treatment is not given.[6-8] Due to the very high rates of failure and recurrence associated with typical short-course chemotherapy for multidrug-resistant TB, new ways to treatment are required in developing countries.[9-11]The World Health Organization estimates that 9% of MDR-TB patients do not achieve the intended treatment outcome and develop extensively drug-resistant (XDR) disease. The prevalence of extensively drug-resistant TB infections in Pakistan has increased gradually. It was 1.5 percent in 2006 and increased to 4.5 percent in 2009.[3] Pakistan is ranked fifth in tuberculosis and fourth in MDR-tuberculosis amongst high-burden nations worldwide.6 Despite lots of attempts, only 63% of cases are identified, and the majority of patients go undiagnosed and untreated. According to the assessment of drug resistance in Pakistan, the projected MDR-tuberculosis proportion in newly reported TB patients is 4.3 percent, while the projected rate in retreatment cases is 19.4%.8In Khyber Pakhtunkhwa (KP), 26% of patients who have had prior treatment have MDR-TB, compared to 3% of new infections in particular populations.[9] According to a study from KP, 17.4 percent of MDR-tuberculosis patients had close relatives who also have MDR-tuberculosis.[10] In Punjab, Pakistan, it is 19.4% among individuals who have already had treatment and 4% for new patients.[11]

The number of multiple drug-resistant and XDR Tuberculosis patients in Pakistan is increasing, indicating the need for a successful TB control program. Regarding MDR-TB treatment results and management in Pakistan, limited information is known. Therefore, the current study was carried out to explore Predictors of unfavorable treatment outcomes in patients with drug-resistant tuberculosis in Peshawar, Khyber Pakhtunkhwa.

Objective

The present study aimed to determine the predictors of unfavorable treatment outcomes in patients with drug-resistant tuberculosis.

Methodology

This study was conducted at Lady Reading Hospital (LRH) and Hayatabad Medical Complex (HMC), Peshawar. This study included all those patients who enrolled for treatment from June 2017 to January 2019 Baseline data of all enrolled patients at LRH was collected where monthly sputum samples results were collected from HMC. For treatment purposes, patients were enrolled at PMDT-LRH for monthly checkups and the provision of drugs. Their sputum samples for monthly culture and Drug Susceptibility were sent to the Provincial Reference Laboratory at Hayatabad Medical Complex, Peshawar every month.

As per the guidelines outlined by the National TB Program, distinct definitions are provided for various types of DR-TB patients. Mono-drug-resistant TB refers to resistance to only one first-line anti-TB drug, while poly-drug-resistant tuberculosis indicates resistance to multiple anti-TB drugs. MDR-TB, a subset of DR-TB, manifests when an isolate of M. tuberculosis demonstrates resistance to at least two critical first-line anti-TB medications, namely rifampicin and isoniazid. Extrapulmonary TB (EP-TB) is characterized by tuberculosis affecting organs other than the lungs, such as the pleura. Pulmonary tuberculosis, on the other hand, pertains to tuberculosis infection within the lung parenchyma.

The NTP's treatment outcome standards for DR-TB have been complied with. According to the definitions, patients were considered cured of DR-TB if they had received treatment for at least 20 months, of which 18 months had passed since the culture was converted and there was no sign of failure to treatment, and if no mycobacterium tuberculosis was shown in at least three successive cultures of sputum obtained near the end of the course of

Table 1. Type of DR-TB among study cases

Types of DR-TB	Frequency (%)
Multidrug Resistant tuberculosis	150 (65.2%)
Rifampicin Resistant tuberculosis	60 (26.0%)
Extensive Drug Resistant tuberculosis	10 (4.3%)
Polydrug Resistant tuberculosis	4 (1.7%)
Mono Drug Resistant tuberculosis	6(2.6%)

management. When patients did not exhibit sputum alteration at the end of the intensive phase, or when they displayed bacteriological reversion during the ongoing phase, or when they created other medications resistance, like quinolone, or when they experienced severe enough adverse drug reactions to warrant stopping treatment, the treatment was deemed to be unsuccessful. Patients were categorized as dead if they passed away for any cause while receiving treatment. In a similar vein, individuals who experienced a treatment interruption lasting longer than two months were determined unsuitable for further monitoring.

Information regarding the socio-demographic characteristics (such as participants age, gender, BMI, comorbid conditions, residence, and contacts), microbiological details (including grading of baseline sputum smear and results of antibiogram assay), and clinical data (such as disease specifics and treatment outcome history with medications) were systematically collected for each patient. Trained personnel utilized standardized forms to gather this information.

The data was analyzed using SPSS 20 software. Numerical data were represented using the mean ± standard deviation (SD), while categorical data were described using frequencies and percentages. To observe any potential effect modification, the treatment outcome (cure) was stratified by gender and age. Statistical significance was determined using the post-stratification chi-square test, with a p-value of 0.05 considered significant.

Results

A total of 230 patients were included in this study who were enrolled at the PMDT-LRH for treatment. The mean age of the study population was 33.55 ± 16.88 years. Out of 230 individuals, 106 (46.0%) were men and 124 (53.91%) were women (Figure 1). Among study cases, 33 (14.4%) were from an age group lower than 18 years of age, 147 (63.9%) were from 18-40 years of age, 39 (16.9%) were from 41 to 60 years of age whereas 11 (4.8%) were from age more than 60years of age (Figure 2)

The majority of patients 150 (65.2%) had a diagnosis of multidrug-resistant tuberculosis, which was followed by rifampicin-resistant 60 (26.0%), Extensive Drug Resistant 10 (4.3%), Mono Drug Resistant 6(2.6%), and poly-resistant tuberculosis 4 (1.7%) (Table 1). If we talk about treatment outcomes. There was a 158 (68.69%) cure rate. 43 patients (18.6%) died while receiving therapy; 6 patients (2.6%) reported treatment failure; and 15 patients (6.52%) were lost to follow-up. 8 (3.47%) were not included as they had not finished their therapy (Table

Table 2. Treatment outcome of study cases

Treatment outcomes	Frequency (%)
Cured	158 (68.69%)
Died	43 (18.6%)
Failed	6 (2.6%)
Lost to follow up	15 (6.52%)
Not evaluated	8 (3.47%)

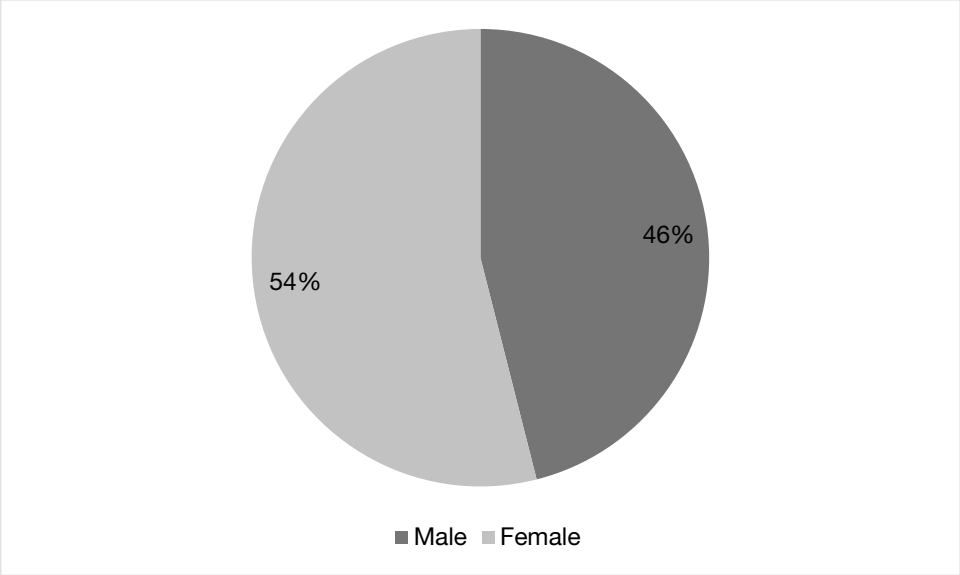

Figure 1. Gender distribution of study cases

2). Remarkably, among patients with MDR-TB, 38 individuals (16.52%) had received a diagnosis of TB for the first time. The remaining cases N=192 (83.47%) included retreatments. These findings contrast with previously published research. Mono-resistant tuberculosis had the highest cure rate (100%) and was followed by MDR-TB (71.30%) and RRTB (58.68%). Except for one individual, all of the patients (98.12%) had pulmonary tuberculosis and were on long-term, standardized, or customized DR-TB therapy regimens.

Univariate analysis identified several factors that were independently associated with unsuccessful treatment outcomes, including male gender, residing in rural areas, age over 60 years, a sickness duration exceeding one year, and prior utilization of second-line drugs. (Table 3).

Discussion

Presently, drug-resistant tuberculosis (DR-TB) presents a substantial public health challenge. Precise diagnosis and effective treatment of DR-TB are essential not only for curing affected individuals but also for preventing the further spread of resistant strains. The success rate of treatment for DR-TB, particularly multi-drug-resistant TB (MDR-TB), is notably low compared to drug-susceptible TB. Hence, it is critical to evaluate the effectiveness of management strategies, treatment outcomes, and factors contributing to poor treatment results. This assessment aims to gain insights and identify opportunities for enhancing the treatment outcomes of MDR-TB by identifying predictors associated with unfavorable

Table 3. Predictors of unfavorable outcome

Statics	Value	Df	Asymp. Sig. (2 –tailed)	Exact Sig. (2-tailed)	Exact Sig. (1-tailed)
No of cases	230	-	-	-	
Pearson Chi -Square	3.29	1	0.05	-	-
Likelihood Ratio		1	0.71		
Fisher's Exact Test				0.75	.050
Continuity Correction		1	0.95		
Linear – by - Linear Association	-	1	0.71	-	

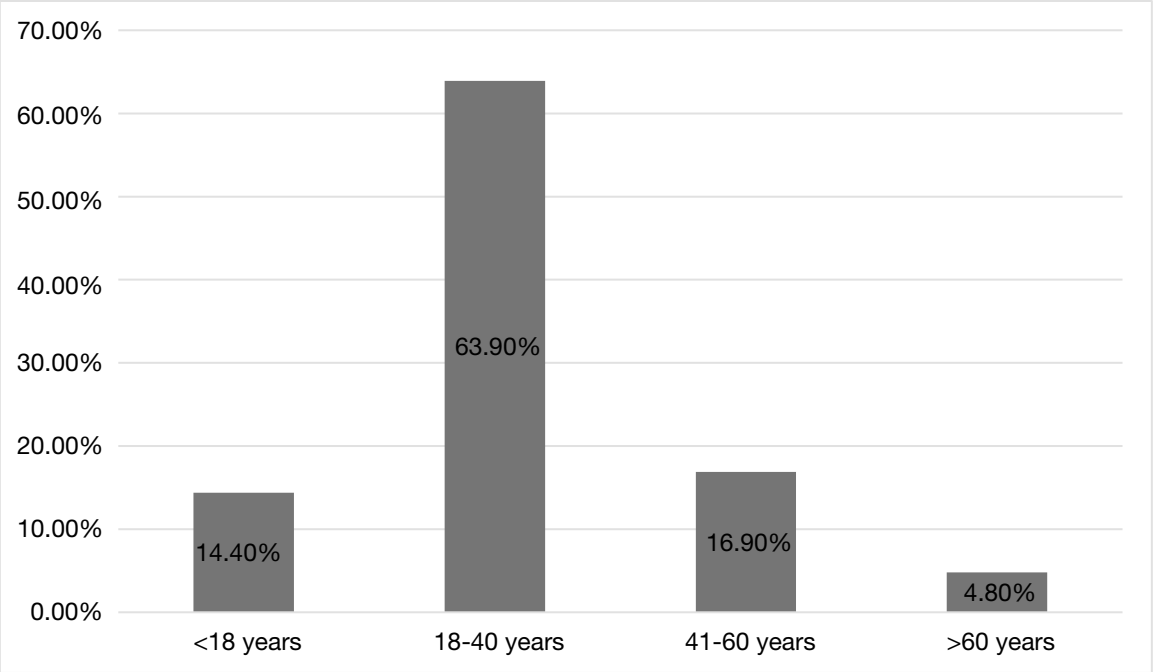

Figure 2. Age wise distribution of study of study cases

treatment outcomes among DR-TB patients

Out of 230 individuals, 106 (46.0%) were men and 124 (53.91%) were women. In contrast to our study, a previous study reported 52% males and 48% females in their study.[9] Another study done by Nair et al. reported comparable results to our study and reported male predominance.[12]

The present study showed that the success rate among these patients was 68.69%. This rate was higher in a study conducted in China in which a 44.6% cure rate was documented.[13] Potential explanations for the improved success rate may include the presence of trained treatment supporters who administer daily directly observed treatment throughout the treatment period (lasting more than 18 months) and the adoption of customized treatment plans at the highest recommended dosages for most patients. Previous research has indicated that daily directly observed treatment and personalized treatment plans are associated with positive treatment outcomes in various published studies.

In a similar study conducted at the same center in 2015, the rate of unsuccessful outcomes was 21.3%. Among these 14.8% died, 6.3% failed to their treatment and 0.3% were lost to follow up.[9] Another study also reported comparable results to our finding and reported that 17% of the patient died, 6% of patients failed their treatment, and loss of follow-up was observed in 16% of patients.[13]

A Taiwanese study found that 82.4 percent of a group of DR-tuberculosis participants managed throughout five years experienced therapeutic success. In that research, treatment failure was identified in 2.6% of cases, 2.9% of patients failed to follow-up and the mortality rate was 12.1%.[14] The differences between their studies and ours might be accounted for by variances in sample sizes. According to a recent meta-analysis, 61% of the participants from twenty-five countries were found to have successful outcome.[15] The researchers also noted that using capreomycin and kanamycin had inadequate results. Our study, on the other hand, was descriptive and cross-sectional, and the data came from only one Centre. Recent Indian research that was released said that 52% (n=415) of the patients receiving treatment for MDRTB had a cure. Remarkably, 16% of research participants passed away during therapy, and 24% of patients were lost to follow-up.[16] The cure rates for MDR-tuberculosis patients remained high at 73.55%, and comparable outcomes were reported from the Republic of South Africa, where 72.9% of MDRTB patients experienced a positive outcome following therapy.[17] According to the study's findings, 38.44% of patients in Pakistan had a positive outcome in terms of successful therapy.[18] Nevertheless, the study's sample size was just 36 patients, and those people were monitored for four years. Different countries have different treatment success rates for drug-resistant TB. Patients with XDR-TB were the greatest indicator of failure of therapy in this study. Outcomes that contradict a previous study's claim that MDR-TB patients' unmarried status was related to mortality.[19] One explanation might be that patients find it challenging to systematically monitor their prescription

regimens since providing for their families and making a living come before taking care of themselves. Still, this conclusion requires additional studies.

The study investigated numerous predictors of poor treatment outcomes using both univariate and multivariate analyses. In the univariate analysis, variables such as gender, weight, previous TB treatment, duration of illness, and resistance to first-line drugs were examined. However, these factors did not show a significant influence on treatment outcomes. In contrast, certain factors such as age, place of residence, presence of lung cavitation, resistance to second-line drugs (SLDs), and resistance to ofloxacin were identified as associated with poor treatment outcomes. These findings align with results reported in other studies. In accordance with our study, another study also reported that gender and age are not significantly associated with treatment outcomes while BMI, alcohol, Diabetic Mellitus, and Cavitary lesions on the Chest x and Tobacco are significantly associated with treatment outcomes.[12] Another study done by Javaid et al. reported some predictors by using logistic regression. They reported that being married, resistance to second-line drugs, and the presence of drug resistance to TB were significantly associated with treatment outcomes.[20]

Conclusion

This study unveiled a cure rate of 68.69% for DR-TB treatment regimens, alongside a death rate of 18.6%. Several factors, including age, place of residence, presence of lung cavitation, resistance to second-line drugs (SLDs), and resistance to ofloxacin, were pinpointed as correlates of unfavorable treatment outcomes. Implementing strategies aimed at early diagnosis and the effective management of MDR-TB holds promise in enhancing treatment outcomes, thereby mitigating mortality rates and halting the further spread of the disease.

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