Original Article

Factors Predicting Mortality in Multidrug-resistant Tuberculosis Patients Treated Under Programmatic Conditions

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Abstract

Background. Current multidrug-resistant tuberculosis (MDR-TB) management is associated with significant mortality which is deterrent for effective TB control worldwide. Knowledge of risk factors that predict mortality in MDR-TB is required to formulate measures to improve treatment outcomes. There is lack of data on the independent predictive factors of mortality among Indian patients being treated under programmatic conditions.

Objectives. To evaluate factors predicting mortality in MDR-TB patients being treated under programmatic management of drug-resistant tuberculosis.

Methods. Medical records of all MDR-TB patients who were initiated on Category IV anti-TB regimen between January 2012 and December 2014 and had declared outcome were retrospectively analysed. Information on different demographic, clinical and treatment (past and present) related parameters was retrieved. Relevant factors were analysed for their possible association with mortality using univariate and multivariate Cox regression analysis.

Results. Out of total 278 patients, 61 (21.9%) died during two years of their treatment duration. The median time to death was seven months. Out of 61, 40 patients (65.5%) died during the first nine months of their treatment. On multivariate Cox regression analysis, high age, low body mass index, previous anti-TB treatment, low serum albumin levels and presence of adverse drug reactions during MDR-TB treatment were found as independent factors predicting mortality ($p<0.05$).

Conclusions. Mortality in MDR-TB is associated with certain modifiable and non-modifiable risk factors. Appropriate knowledge and timely intervention to manage these, especially the nutritional status, may help to decrease the mortality associated with MDR-TB. **[Indian J Chest Dis Allied Sci 2018;60:227-232]**

Key words: Treatment outcome, DOTS-Plus, Death, Tuberculosis control.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a serious global public health threat that is associated with poor outcome. As per recent World Health Organization (WHO) statistics, only 52% of the MDR-TB patients, who were put on treatment in 2013, achieved successful outcome.[1] Long duration of treatment, unavailability of free drugs, drugs related side effects and treatment non-adherence are the major hurdles in its successful management. Even after incorporation of management of MDR-TB in the National TB Control Programme,[2] the success rates have not shown consistent improvement. The scenario is no better in India where the treatment success rate has remained below 60% in the surveillance studies.[3,4] As per WHO, only 46% of the MDR-TB patients who were started on treatment in 2013 in India achieved successful outcome.[1] High death and default rate seen among these patients is an important factor for poor outcome that needs to be tackled in a stringent manner.

Recent evidence from studies conducted in India have shown a high mortality rate of 14% to 29% in MDR-TB patients being treated under programmatic conditions.[3-5] In the light of these facts, knowledge of risk factors that predict mortality in MDR-TB become essential to formulate corrective measures to control the death rate. Few studies done under different geographical areas and designs have suggested age, human immunodeficiency virus (HIV) positivity, history of MDR-TB and previous multiple courses of anti-TB therapy, etc as potential predictors of mortality.[6-8] However, there is paucity of data about the risk factors of mortality in Indian patients. In

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view of different genetic and geographic environment with different treatment practices, the predictors of mortality found elsewhere may not be applicable to Indian patients. Hence, we planned to analyse data of our registered MDR-TB patients, treated under programmatic conditions, to find out independent factors predicting mortality in these patients.

Material and Methods

Study Design

This was a retrospective study conducted in the department of Pulmonary Medicine, Government Medical College and Hospital (GMCH), Chandigarh. All diagnosed pulmonary MDR-TB patients (residents of Chandigarh and five districts of Haryana) who were initiated on Category IV anti-TB regimen at drug resistant-TB (DR-TB) centre, GMCH between January, 2012 and December, 2014 and had achieved an outcome were recruited in the study. The diagnosis of MDR-TB was done at Revised National TB Control Programme (RNTCP) accredited Intermediate Reference Laboratory (IRL) using liquid culture, line probe assay or cartridge based nucleic acid amplification test (CBNAAT) following standard guidelines.[2] The study was approved by Institutional Ethics Committee of GMCH. Informed consent was not required as whole data was retrieved from the medical records of patients who had already completed treatment or had a declared outcome.

Operational Definitions

Multidrug resistant TB was defined as isolates of *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin. Different outcomes to Category IV treatment, viz cure, treatment default, treatment completed, death and treatment failure were defined as per recent RNTCP-PMDT (patients treated under programmatic management of drug-resistant TB) guidelines.[2] In the past history, one anti-TB treatment course was defined when the patient had taken the drugs for >1 month. For the purpose of analysis, default and treatment failure in the previous anti-TB course was labelled as an adverse outcome. A patient was described as non-adherent to Category IV anti-TB treatment when he had missed ≥10% of the total prescribed dose of anti-TB treatment.[9]

Methods

Medical records of patients available at the drug resistant-TB (DR-TB) Centre, office of State TB Officer and at GMCH were scrutinised to retrieve information on demographic and clinical parameters including addictions, co-morbidities, like diabetes mellitus and HIV status and history of previous anti-TB treatment. Routine investigations done as a part of pre-treatment evaluation were noted. Further, details about current Category IV anti-TB treatment, particularly any interruption in the treatment, adverse drug reactions (ADRs), time of culture conversion, total weight gain, etc, were also retrieved. Final treatment outcome of all enrolled patients was recorded. Thereafter, patient-related factors, like age, gender, body mass index (BMI), haemoglobin, smoking status, alcohol use, etc, disease-related factors, like number of previous anti-TB treatment courses, outcome etc, and therapy-related factors, like treatment adherence, ADRs, final outcome, etc, were selected from previous studies done in India[3,4] and outside[6-8,10] as well as on the basis of our knowledge and experience. These were evaluated for their possible association with all cause mortality in MDR-TB patients undergoing treatment using appropriate statistical tests.

Statistical Analysis

Quantitative variables are summarised as mean±SD and qualitative variables are presented as percentages. Chi-square test was performed to compare categorical variables, and Student's t-test was used to compare continuous variables. We used Cox proportional hazards regression analysis with forward inclusion approach to find association between potential risk factors and mortality. Univariate and multivariate models were used to measure crude and adjusted hazard ratios (aHR), respectively, with their 95% confidence intervals (95% CI), for different factors predicting mortality. Mortality curves were obtained through Kaplan-Meier method to verify the potential association of variables with mortality. A p-value <0.05 was considered statistically significant. All statistical calculations were done using Statistical Package for the Social Sciences (SPSS, version 21.0).

Results

Three hundred and one DR-TB patients were registered at the DR-TB Centre Chandigarh during the specified time period. Out of them, 11 patients, registered as extensively drug-resistant TB (XDR-TB) and 12 MDR-TB patients, transferred out after initiation of treatment, were excluded. Remaining 278 registered MDR-TB patients were considered for final analysis. Majority of the patients were young males with a mean age of 35.1±14.7 years and a male:female ratio of 2:1. Demographic and clinical characteristics of the patients are presented in table 1.

Table 1. Baseline characteristics of MDR-TB patients

Parameter	Value Mean (SD)
Age (years) (mean±SD)	35.1 (14.7)
Gender (Male:female)	183:95 (2:1)
BMI (kg/m^2)	16.0 (3.5)
Diabetes mellitus	27 (9.7)*
Smoker	72 (25.8)*
Alcoholism	56 (20.1)*
Haemoglobin (g/dL)	11.3 (2.1)

*expressed as No. (%)

Definition of abbreviations: SD=Standard deviation; BMI=Body mass index

Out of 278 patients, 154 (55.3%) had a successful outcome (130 cured and 24 treatment completed). Table 2 shows different treatment outcomes of 278 MDR-TB patients after Category IV treatment. Of the total patients, 182 (65%) achieved culture conversion at three months. Treatment adherence was seen in 65.7% patients, whereas, 74 patients had history of missing ≥10% of the total prescribed dose of anti-TB treatment. Previous history of TB was scrutinised to calculate the number of previous anti-TB treatment courses taken by the patient as well as adverse outcome (default or treatment failure) in them. It was found that out of 278 patients, 179 (64%) had taken >1 courses of anti-TB treatment, out of which 97 (34.8%) also had an adverse outcome in any of them.

Table 2. Treatment outcomes among MDR-TB patients

Treatment Outcome	No. (%)
Cure/treatment completed	154 (55.3)
Treatment failure	1 (<1)
Treatment default	43 (15.4)
Died	61 (21.9)
Switched to treatment for XDR-TB	17 (6.1)
Treatment stopped due to ADRs	2 (<1)
TOTAL	278 (100)

Definition of abbreviations: MDR-TB=Multidrug-resistant tuberculosis; XDR-TB=Extensively drug-resistant tuberculosis; ADRs=Adverse drug reactions

Out of total 278 patients, 61 (21.9%) died during the course of their treatment. The median time to death for the patients was seven months. Twenty-nine patients expired within six months of the treatment initiation and 40 (65.5%) died prior to nine months (Figure 1). Mean age of patients with fatal outcome was 39.4±16.7 years with a male predominance (M:F= 5:3). Fifty-two (85%) patients were malnourished with a mean BMI of 14.2±3.35 kg/m^2. Most of the patients were also anaemic with a mean haemoglobin of 9.9±1.9 g/dL. Forty-four patients out of 61 had taken >1 anti-TB treatment courses in the past, out of which 25 (41%) also had an adverse outcome during that treatment.

Cox regression analysis was performed to evaluate pre-defined parameters for their possible role as predictors of mortality in MDR-TB. On univariate analysis, age, BMI, diabetes, haemoglobin, albumin level, treatment adherence to Category IV anti-TB course and ADRs had significant association with

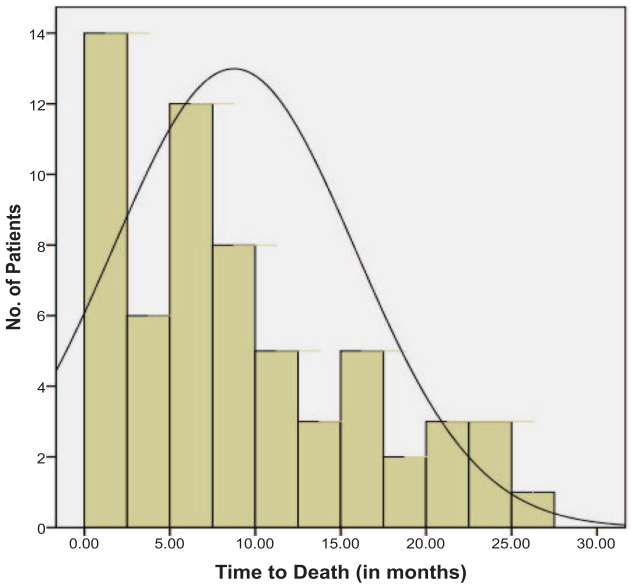

Figure 1. Histogram showing distribution of number of patient's deaths in relation to time after treatment initiation.

mortality. All factors found significant on univariate analysis (p<0.2) were included in the multivariate model. On regression analysis, age, low BMI, number of previous anti-TB treatment courses, low serum albumin level and ADRs were found as independent factors predicting mortality in patient with MDR-TB (p<0.05) (Table 3).

On Kaplan-Meier survival analysis, there was a significant difference in the survival between patients above (n=75) and below a BMI of 18.5 kg/m^2 (n=203) (Figure 2A). It was seen that higher number of previous anti-TB treatment courses was a more significant predictor of mortality (aHR 2.35; 95% CI 1.18-4.68; p=0.01) than their adverse outcome. Our results demonstrated a borderline association between occurrence of ADRs and mortality risk (aHR 2.33; 95% CI 1.4-3.9; p=0.046). (Figure 2B).

Discussion

The present study was sought to identify the risk factors of mortality in patients with MDR-TB during two year– course of anti-TB treatment. The results showed that high age, low BMI, low serum albumin

Table 3. Association of different parameters with mortality on univariate and multivariate Cox regression analysis in MDR-TB patients

	Univariate Analysis		Multivariate Analysis	
	Crude HR (95% CI)	**p-value**	**Adjusted HR (95% CI)**	**p value**
Age	1.024 (1.008-1.04)	0.003	1.05 (1.02-1.07)	<0.001
Female	1.04 (0.62-1.74)	0.88		
BMI (kg/m^2)	0.81 (0.74-0.89)	<0.001	0.79 (0.66-0.96)	0.01
Tobacco smoking	1.4 (0.82-2.46)	0.22		
Alcoholism	1.25 (0.68-2.28)	0.46		
Diabetes mellitus	2.02 (1.0-4.1)	0.05		
Haemoglobin	0.66 (0.57-0.77)	0.001		
Serum albumin	0.39 (0.27-0.58)	<0.001	0.43 (0.25-0.71)	0.001
Culture conversion at >3 months	1.27 (0.55-2.9)	0.56		
Adverse outcome in previous anti-TB treatment	1.6 (0.87- 3.03)	0.13		
No of anti-TB treatment courses	1.37 (0.95-1.96)	0.08	2.35 (1.18-4.68)	0.01
Treatment adherence	0.42 (0.25- 0.72)	0.002		
Adverse drug reaction	1.88 (1.01- 3.5)	0.047	2.33 (1.4-3.9)	0.046

Definition of abbreviations: MDR-TB=Multi-drug resistant tuberculosis; HR=Hazard ratio; CI=Confidence interval; BMI=Body mass index; TB=Tuberculosis

level, previous anti-TB courses and ADRs during current Category IV therapy were independent predictors of mortality.

Sixty-one MDR-TB patients (21.9%) died during the course of TB treatment in the present study which is comparable to similarly designed previous studies.[3,4] Overall, mortality rates in MDR-TB cases have been highly variable, ranging from 4.5% to 63%[8,10-12] in different studies. This variability could be due to differences in the study design, management protocol or may reflect quality of the TB control programme. Mortality seen in MDR-TB patients is multi-factorial in nature with interplay of different patients, disease and treatment related risk factors. Knowledge of these factors can guide us to plan corrective measures to decrease the mortality rate. In the present study, we found five factors as significant predictors of mortality out of which three were modifiable and hence amenable to corrective action.

In the present study, 29 patients (47.5%) died within first six months of start of treatment. This early phase mortality might be the result of drug-related toxic/side effects and/or baseline severity of the disease. On statistical analysis, there was no difference in demographic and clinical parameters between those who died in the first six months *versus* after six months.

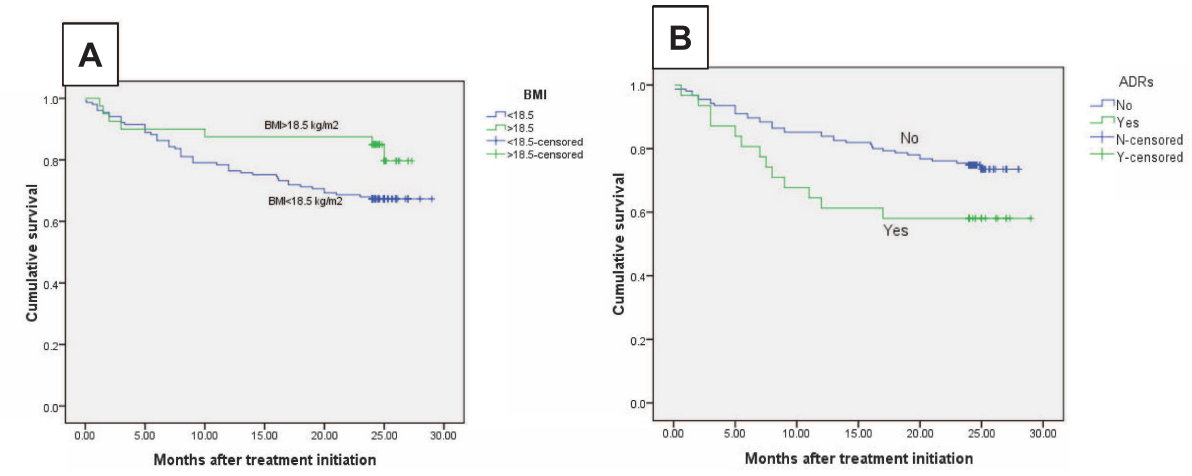

Figure 2. Kaplan-Meier estimates of survival for MDR-TB patients showing (A) all-cause mortality according to BMI and (B) all-cause mortality according to adverse drug reactions.

Definition of abbreviations: MDR-TB=Multidrug-resistant tuberculosis; BMI=Body mass index; ADRs=Adverse drug reactions

Similar to previous studies,[7,8,13] age was found to have a positive association with mortality in the present study. The association remained significant even after adjusting for age-related co-morbidities, like diabetes and smoking. Another important finding of the study was a strong association of mortality with the nutritional parameters, BMI and serum albumin. On Kaplan-Meier survival analysis, there was a significant difference in the survival between patients above and below a BMI of 18.5 kg/m^2. The negative association between nutritional status and mortality has been seen in previous studies done outside India.[7,10,14,15] The results from the present study confirm a similar association in Indian patients and highlight the need to strengthen the measures for nutritional management of MDR-TB patients under PMDT.

In contrast to previous studies[3,4], factors pertaining to previous TB treatment were also evaluated as predictors of mortality in the present study. It was seen that higher number of previous anti-TB treatment courses was a more significant predictor of mortality (aHR 2.35; 95% CI 1.18-4.68; p=0.01) than their adverse outcome. The finding is in coherence with the previous studies that also demonstrated a positive association between the number of previous TB episodes and the risk of death.[6,16] More previous anti-TB treatment courses reflect a longer course of active and severe disease that might contribute to a higher mortality risk.

Treatment of MDR-TB is punctuated by a variety of ADRs whose incidence may go up to 75%-80%.[17-19] In the present study, we experienced ADRs in around 21% patients which are apparently low probably due to under-reporting of such events (especially at the periphery level). Common adverse events in order of their relative incidence were gastro intestinal disturbances, hearing impairment, joint pains, renal dysfunctions, skin lesions and neuro-psychiatric disturbances. Ironically, ADRs have been associated with good treatment outcome in a previous study[19] which needs further evaluation. Our results demonstrated a borderline association between occurrence of ADRs and mortality risk (aHR 2.33; 95% CI 1.4-3.9; p=0.046). However due to under-reporting, the association between the two need further confirmation. Apart from ADRs, non-adherence to anti-TB treatment course was also associated with an increased risk of death on univariate analysis in the present study; however, it did not remain significant after adjusting for other factors. Besides medical causes, non-adherence largely reflects lack of knowledge and awareness on the part of the patient,[9] and hence, can be prevented through active involvement of the health care/Directly Observed Treatment provider.

Diabetes mellitus, a debilitating co-morbidity, reduces cellular immunity, thus increasing the risk of developing MDR-TB.[20] However, it has not been conclusively proven to affect mortality in previous studies and meta-analysis.[10] In the present study a borderline association with mortality on univariate analysis was noted but was not significant after adjustment for confounders. It is well established that smoking and alcohol abuse are significant risk factors for TB disease as well as for poor outcome.[3,10] Even though smoking and/or alcohol abuse might have contributed to increased morbidity (chronic obstructive pulmonary diseases, coronary artery disease, etc) but it did not predispose to increased mortality in our study. Nevertheless, the harmful effects of these substances can not be under-estimated and need to be universally addressed.

Apart from these, there were certain other factors which could not be evaluated as predictors in the study. HIV infection has been consistently associated with increased mortality in MDR-TB patients[6,7,16] but it could not be analysed on account of low HIV positivity rate (n=4) in our study population. Baseline resistance to other 1st and 2nd line drugs,[7,12] extra-pulmonary TB[16] and patient education status[6,21] are few other risk factors linked with increased mortality that could not be evaluated due to inherent design of the study.

The major strength of our study was the quality and reliability of the results. A sample size of 280 patients, who received MDR-TB treatment under TB control programme of Government of India, helped to evaluate the real-life picture of the disease management. The study evaluated the predictive power of a wide variety of patients, disease and therapy related parameters in MDR-TB that probably has not been assessed earlier in Indian patients. However, there were few limitations also. It was retrospective study based on scrutiny of the past medical records, as a result, certain variables, like resistance to other 1st and 2nd line anti-TB drugs and patient education level could not be evaluated as mortality predictors. Objective assessment of chest radiograph was not available which could have been important variable predicting disease severity and death. The study did not elaborate the causes of death among the TB patients, that might have added more relevance to the results.

Conclusions

The present study concluded five important parameters which predict mortality in MDR-TB patients during their course of treatment. Knowledge of these, especially the modifiable factors, like BMI, serum albumin and ADRs can guide us to take appropriate corrective

measures, that in turn, can improve treatment success in patients with MDR-TB. It also emphasises the need to ensure proper reporting and recording of patient information, especially ADRs and death details that will improve the quality of future analysis.

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