Survival of smear-positive multidrug resistant tuberculosis patients in Witbank, South Africa: A retrospective cohort study

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Abstract

Background: A retrospective cohort study was carried out to compare the survival between smear-positive patients and smear-negative multidrug resistant tuberculosis (MDR-TB) patients hospitalised in a specialised TB hospital in Witbank, South Africa.

Methods: A review of medical records of MDR-TB patients treated from 2001 to 2010 was carried out. Survival time was measured from a patient's date of hospitalisation to the date when the patient died, was last treated at the hospital, or the end of the study (whichever came first). All patients who were alive until the end of the study period or lost to follow up were censored and those who died were considered as failures. Survival patterns were estimated using Kaplan Meier plots, log rank tests, and life tables. Cox proportional hazards regression analyses were also conducted.

Results: The mean age of the 442 MDR-TB patients in the study was 37.7 ±11.2 years. The incidence rates of mortality were 13.4 and 43.9 per 1000 person-months for smear-negative and smear-positive MDR-TB patients respectively. Cox proportional hazard regression showed that the predictors of death among MDR-TB patients include HIV co-infection [adjusted Hazard Rate, aHR = 1.89, 95% CI: 1.02-3.52], old age (above 60 years) [aHR =2.05, 95% CI=1.04-3.60], and smear positivity at diagnosis [aHR = 3.29, 95%CI= 2.39-4.64].

Conclusion: The study showed that the probability of survival during the treatment is reduced in MDR-TB patients, who are smear-positive, HIV positive, or older than 60 years. Special care should be given to these patients to improve survival.

Introduction

Drug resistant tuberculosis (DR-TB) is a major challenge to tuberculosis (TB) control throughout the world. Furthermore, South Africa has the fifth largest DR-TB burden worldwide [1]. While the increased numbers of multidrug resistant TB (MDR-TB) patients may be due to concurrent HIV infection and inadequate management of TB, increased case detection may also have contributed to increased incidence of the disease [1].

Smear-positive pulmonary TB has been described as a predictor of mortality among patients with TB [2]. Similarly, MDR-TB has also been shown to be an independent predictor of death among TB patients [3]. However, studies evaluating the effect of smear positivity on the survival outcomes of MDR-TB patients are rare. This study was therefore conducted to assess the effect of smear-positive MDR-TB on the survival of infected patients during hospitalisation.

Materials and methods

Study setting and programme description

This study was conducted in a specialised TB hospital in Witbank, Mpumalanga Province, South Africa. Mpumalanga has a population of about 4.2 million [4]. The prevalence of HIV among pregnant women in this province was 35.6% [5], and the TB incidence was 463 per 100,000 [6].

DR-TB is a disease caused by Mycobacterium tuberculosis strains resistant to one or more anti-TB drugs while MDR-TB can be defined as resistance to rifampicin and isoniazid irrespective of resistance to other first-line anti-TB drugs [1]. Patients are managed at the specialised TB hospital according to guidelines and patients who have clinical features are considered TB suspects. MDR-TB patients are currently being diagnosed using a GeneXpert diagnostic algorithm (Figure 1) [8]. However, at the time when patients in this study were treated (2001 to 2010), only laboratory diagnosis of TB using smear microscopy, TB culture, and drug susceptibility tests (DST) was recommended and only DST result was used for the diagnosis of MDR-TB [7]. MDR-TB patients were treated with either standardized or empirical treatment regimens. Standardized treatment regimen is based on country-specific drug resistance and prior use of second line anti-TB drugs. In South Africa, the standardised treatment for MDR-TB consists of an intensive phase (injectable phase) of five drugs and at least six months duration followed by a continuation phase of 18 months (or less) with four

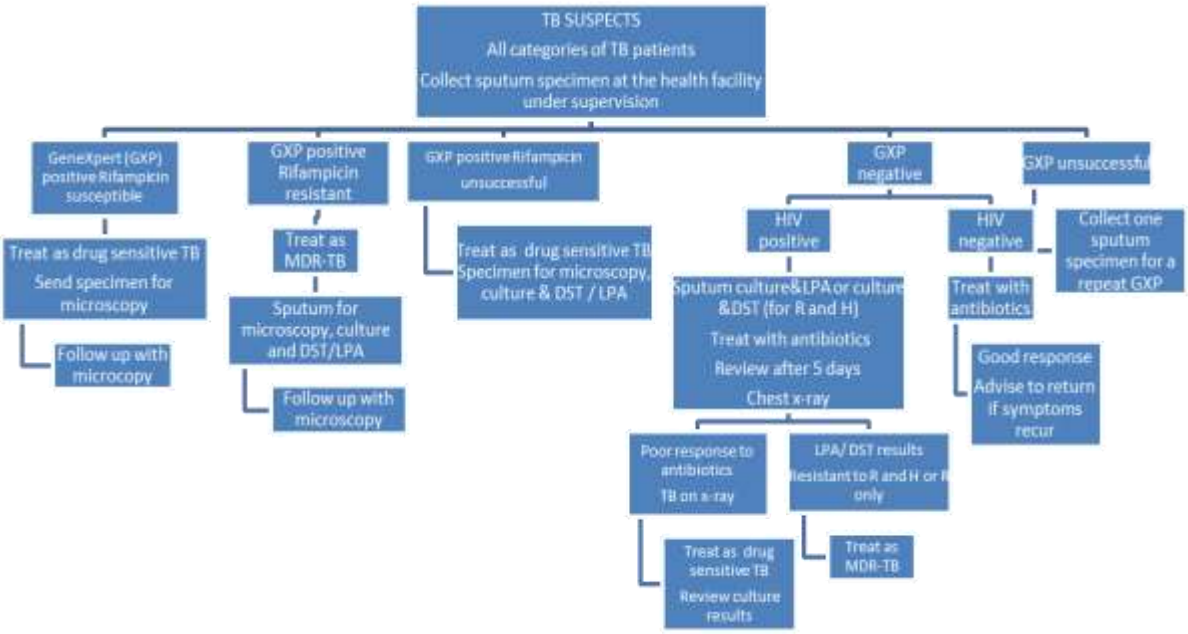

Figure 1: Diagnostic algorithm for MDR-TB

drugs. The duration of MDR-TB treatment is related to the TB conversion date ("date of collection of the first sputum that turned TB culture negative"). While the injectable phase is determined by adding four months to the TB culture conversion date (usually not less than six months), duration of treatment usually determined by adding 18 months to the TB culture conversion date [1]. Patients are sometimes treated with empirical treatment regimen based on drug sensitivity [9]. TB patients are hospitalised if they have: MDR-TB; Extrapulmonary TB; Disseminated or miliary TB; Severe haemoptysis; Severe debilitation; AIDS; Social considerations or; Co-morbid conditions necessitating hospital treatment [7-10]. Patients with MDR-TB are usually discharged after two consecutive TB negative smear microscopy results [11]. Although there were few changes in guidelines for MDR-TB during the index period, they were not as significant as to make the patients treated during this period incomparable [7, 8, 10].

Study design

We conducted a retrospective cohort study of hospitalised MDR-TB patients and analysed the survival of patients treated over a ten-year period (2001-2010). All patients hospitalised aged 15 years or older treated for pulmonary MDR-TB at the hospital during the index period were included in the study. Patients who had only extra pulmonary TB and period of hospital admission less than 24 hours were excluded to ensure findings of the present study can be compared to other studies. A systematically selected sample of 442 MDR-TB patients was used for the study. Every second MDR-TB patient hospitalised from January 1, 2001 to December 31, 2010 was selected.

Data abstraction

Patients' treatment cards were the main data sources. A structured format was created for uniform data abstraction. The data collection instrument included variables including gender

(male, female), date of birth, marital status (single, married), place of residence (within province, outside province), HIV co-infection (positive, negative, not tested), previous TB treatment (yes, no), sputum smear result before commence of treatment (positive, negative), diabetes comorbidity (yes, no), outcome at the end of follow-up (censored or dead), date when patient was hospitalised, and the date when the patient died, was last treated at the hospital, or the end of the study whichever came first.

A TB case is said to be smear-positive if at the start of treatment, acid fast bacilli (AFB) can be demonstrated in one or more sputum smear specimens in a country where there is a "functional external quality assurance system with blind rechecking" [12].

The primary analysis was the survival time measured from a patient's date of hospitalisation for MDR-TB treatment to the date when the patient died, was last treated at the hospital, or the end of the study whichever came first. While individuals who died were considered as failures, those who were alive until the end of the study period or lost to follow up were censored. All selected patients were followed up for 24 months from the date of hospitalisation. All patients who were alive at the end of the study period were censored.

Statistical analysis

Abstracted data was entered into electronic format and cleaned for errors and outliers. Initial analysis was carried out using Pearson's chi square test or Fisher's exact test for categorical variables, and two-tailed t test for continuous variables.

The Kaplan Meier (KM) method was used to obtain univariate descriptive statistics including median survival time, survival experience of patients in the study, and graph of survival probabilities as a function of time. Incidence rates in person-months were calculated. Probability of survival of hospitalised MDR-TB patients was also estimated using Life table. Furthermore, log rank test was used to assess observed difference in survival time between smear-positive MDR-TB patients and smear-negative patients.

Association between baseline variables and mortality was tested using the Cox proportional hazard regression model. We tested non-violation of the assumptions of Cox proportional hazards model and each baseline variable that did not violate the assumptions was entered into a separate Cox proportional hazards model. A multivariate Cox proportional hazards model was then fitted with the predictors that have $P \leq 0.30$ in the bivariate model and variables that remained significant in the final model were retained as independent predictors of survival. Attributable Risk Percent (AR %) and Population Attributable Risk Percent (PAR %) were also calculated. A two-tailed α level of 0.05 and confidence level of 95% were considered to be statistically significant.

Violation of proportional hazard assumptions was checked by procedures: Log (−log (st) plots, Schoenfeld residual plots and by regressing Schoenfeld residuals against time to test for independence between time and residuals. Statistical analysis was performed using Stata version 12 [13].

Ethics

The study protocol was approved by the Institutional Review Board (IRB) of the Faculty of Health Sciences, University of Pretoria (IRB approval number: S153/2012), and Ethics Committee of the Department of Health, Mpumalanga Province. The present study was a review of hospital records. Hence, informed consent was not taken from patients. However, consent and approval of the management of the Witbank Specialised TB Hospital was obtained. Furthermore, collected information was protected and analysed such that no unique sociodemographic information could potentially identify any particular patient.

Results

Description of the study cohort

Among MDR-TB patients hospitalised at the study site from 2001 to 2010, medical records of 442 patients retrieved from admission logbook of the hospital were accessed. Almost half of the patients in the study lived in Mpumalanga Province (Table 1). The minimum and maximum ages of patients in the study were 16 and 68 years respectively while the mean age was 37.7 (SD=11.2) years. More than half (252) of the study patients were males. Information on marital status was recorded for only 144 (32.6%) of patients and 87 (60.4%) were single. Regarding the type of TB, 247 (57.4%) of patients had smear-positive MDR-TB

Table 1 Survival MDR TB

Covariate	Number at risk	Number of deaths	Hazard Ratio	95% CI	P value
Age categories					
15-60	431	144	1.00		
61-68	11	7	2.64	1.24-5.64	**0.012**
Gender					
Male	252	79	0.84	0.61-1.16	**0.286**
Female	190	72	1.00		
Place of Residence					
Mpumalanga province	196	19	1.00		
Other province/country	214	13	1.01	0.84-1.22	0.879
Employment status					
Unemployed	278	94	1.00		
Employed	164	57	1.00	0.72-1.39	0.988
Marital status					
Unmarried	87	22	1.00		
Married	57	31	1.13	0.66-1.96	0.652
Previous TB treatment					
No	89	26	1.00		
Yes	345	123	1.23	0.80-1.87	0.346
HIV status					
Negative	43	13	1.00		
Positive	172	68	1.48	0.82-2.68	**0.195**
Not tested	227	70	1.38	0.76-2.50	**0.289**
HIV positive, on antiretroviral drugs					
No	22	7	1.00		
Yes	136	53	1.32	0.60-2.90	0.490
Smear status					
Negative	247	53	1.00		
Positive	183	90	3.05	2.17-4.29	0.000

(Table 1). The mean ages of HIV positive and HIV negative patients were 38.3 (SD=9.90) and 40.6 (SD=16.26) years respectively. Among HIV positive patients, 136 (86.1%) were known to have started anti-retroviral treatment (ART) initiation (Table 1).

Occurrence of death

Of 442 MDR-TB patients in the study observed over a 24-month period (intensive and continuation phases for most patients), 183 (42.6%) had smear-positive TB infection. While 151 (34.2%) patients who died were treated as failures in the study, 291 (65.8%) patients were censored. Furthermore, the total time of follow up for all patients in the study was 6154 person-months while the incidence rate of mortality was 24.9 per 1000 person-months.

The total time at risk of death for smear-negative MDR-TB was 4023.0 person-months and the incidence rate of mortality was 13.4 per 1000 person-months. Similarly, the total time at risk of death for smear-positive patients was 2072.2 person-months with an incidence rate of 43.9 per 1000 person-months. The 25^{th} percentiles of survival time among smear-negative and smear-positive patients were 20.3 months and 3.8 months respectively. The median survival time for smear-positive MDR-TB patients was 16.3 months. However, less than 50% of the smear-negative MDR-TB patients died before the end of the study.

More than 70% of the deaths among MDR-TB patients were attributable to smear-positive TB infection: Attributable Risk Percent (AR %, 95% CI) - 71.7[56.1-81.8]. The Population Attributable Risk Percent (PAR %) was 45.0%.

Survival status of patients in the study

Life table analysis showed that more than half of the deaths - 80 (53.0%) [59 in smear-positive patients and 21 in smear-negative patients] occurred during the first six months (intensive phase) of treatment while 71 (47.0%) died within the following 18 months (continuation phase). Overall, the survival rates of all patients in the study after the intensive phase and at the end of the study period were 70.3% and 59.6% respectively. Furthermore, smear-positive MDR-TB patients had lower rate of survival compared to smear-negative patients (Table 2).

Table 2 Survival Table

		Smear Negative				Smear Positive			
Interval (months)		**N**	**Deaths**	**Lost**	**Survival (%)**	**N**	**Deaths**	**Lost**	**Survival (%)**
0	2	247	7	7	97.1	183	26	2	85.7
2	4	233	12	5	92.1	155	22	5	73.4
4	6	216	2	16	91.2	128	11	11	66.8
6	8	198	3	18	89.7	106	4	9	64.1
8	10	177	8	7	85.6	93	7	4	59.2
10	12	162	6	2	82.4	82	3	3	57.0
12	14	154	1	4	81.9	76	4	7	53.9
14	16	149	5	2	79.1	65	4	1	50.5
16	18	142	3	5	77.4	60	3	2	47.9
18	20	134	3	6	75.6	55	1	1	47.1
20	22	125	1	2	75.0	53	3	4	44.3
22	24	122	2	9	73.7	46	2	2	42.3
24	26	111	0	111	73.7	42	0	42	42.3

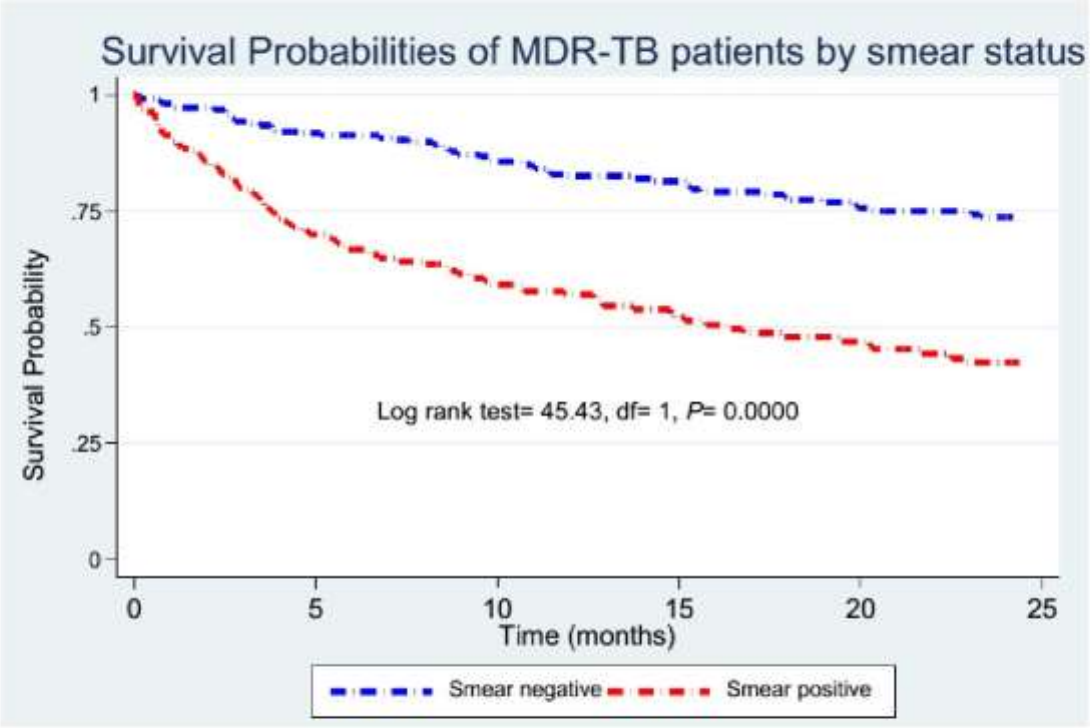
Survival Probabilities of MDR-TB patients by smear status
Survival Probability
1
.75
.5
.25
0
0
5
10
15
20
25
Time (months)
Log rank test= 45.43, df= 1, P= 0.0000
Smear negative
Smear positive

Figure 2

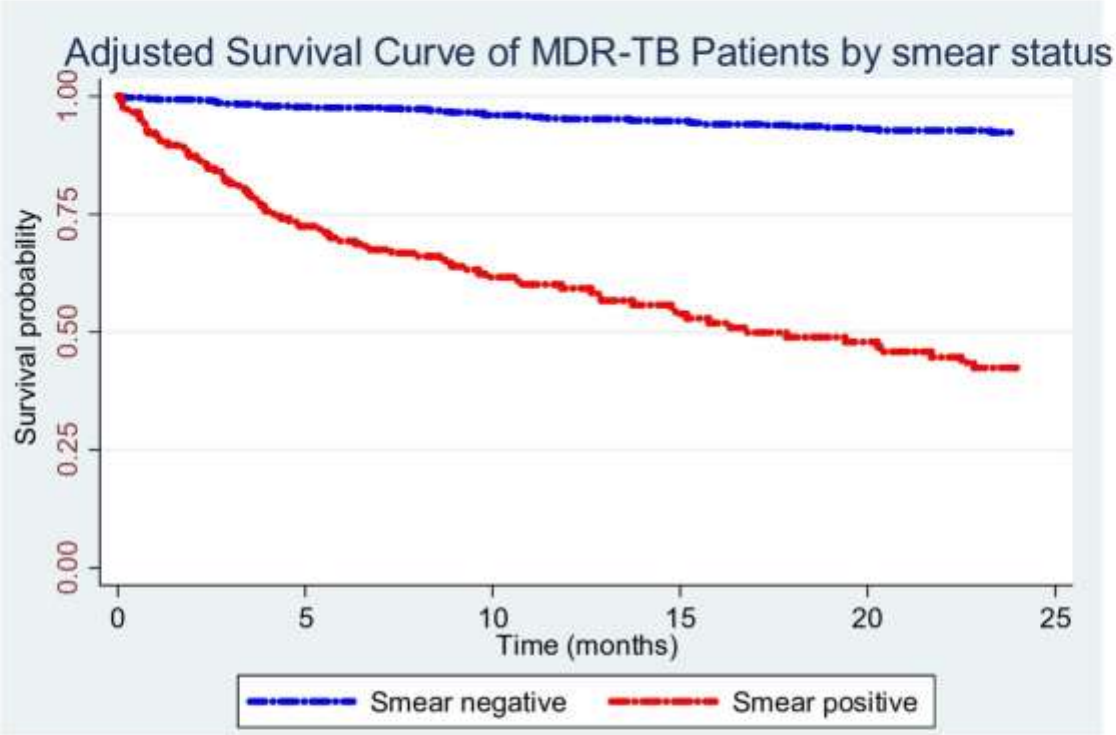
Adjusted Survival Curve of MDR-TB Patients by smear status
Survival probability
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
25
Time (months)
Smear negative
Smear positive

Figure 3

The Kaplan Meier survival curve (Figures 2,3) in keeping with life table results, showed that smear-positive MDR-TB patients have lower survival compared smear-negative patients (log rank statistic= 45.43, df= 1, P= 0.0000).

Factors affecting the survival of hospitalised MDR-TB patients

The initial Cox proportional hazard regression showed that four covariates including being HIV positive, smear-positive, gender, and old age had p values lower than 0.3 (Table 3). However, the final model using the multivariate Cox proportional hazard regression showed that only three covariates including being HIV positive, smear-positive, old age (above 60 years) were independent predictors of death (Table 3). The risk of dying among hospitalised MDR-TB patients increased significantly by almost 200% if HIV positive [adjusted Hazard Ratio, aHR = 1.89, 95% CI: 1.02-3.52]. Similarly, for older patients above 60 years, the risk of dying from MDR-TB also doubles [aHR =2.05, 95% CI=1.04-3.60]. Mortality risk also increases by about 300% if a patient is smear-positive [aHR = 3.29, 95% CI= 2.39-4.64] (Table 3).

Table 3

Covariate	Number at risk	Number of deaths	Adjusted Hazard Ratio	95% CI	P value
Age categories					
15-60	431	144	1.00		
61-75	11	7	2.05	1.24-5.64	**0.033**
Gender					
Female	190	72	1.00		
Male	252	79	1.31	0.83-2.06	0.242
HIV status					
Negative	43	13	1.00		
Positive	172	68	1.89	1.02-3.52	**0.043**
Not tested	227	70	1.93	1.04-3.60	**0.037**
Smear status					
Negative	247	53	1.00		
Positive	183	90	3.29	2.11-5.57	**0.000**

Discussion

The effect of smear-positive MDR-TB on the survival of infected patients during hospital treatment has been described in this study. The present study also showed that the survival rates of smear-positive MDR-TB patients at the end of 12- and 24-month periods were 57.0% and 42.3% respectively. These contrast with the survival rates of 82.3% and 73.7% found respectively among smear-negative MDR-TB patients after 12- and 24-month periods. Furthermore, smear-positive AFB, old age (above 60 years), and HIV positive status were shown as independent predictors of death among hospitalised MDR-TB patients.

A study in Russia showed that 50% of patients with MDR-TB were still alive five years after treatment [14]. This compares with present study which showed that more than two thirds of the MDR-TB patients were alive after two years of treatment initiation. Patients were followed up for two years in the present study. Hence, a higher rate of survival was found compared to the study in Russia [14]. Although survival studies restricted to MDR-TB patients are few, a study reported an all-cause mortality rate of 31.2% among a group of MDR-TB patients in Korea [15]. This is similar to the mortality rate of 34.2% shown in the present study.

The proportions of patients who survived after one- and two-year periods after treatment initiation were smaller among smear-positive MDR-TB patients. Similarly, patients who had smear-positive MDR-TB were three times more likely to die. A study in Lithuania reported that smear-positivity at diagnosis was associated with about 1.5 times increase in the risk of death among MDR-TB patients [16]. Furthermore, smear positivity at diagnosis was also associated with a five-fold increase in the risk of death among MDR-TB patients in a recent study in Bulgaria [17]. The influence of smear positivity at diagnosis on the survival of MDR-TB patients reported in this study is consistent with the findings of previous studies.

A study reported that HIV co-infection doubles the risk of death among MDR-TB patients [18]. The finding of the current study is also consistent with those of previous studies [18-20], having shown that the risk of death among those who had HIV co-infection increased by two. This underscores the need to give priority attention to MDR-TB patients with HIV co-infection.

Kurbatova et al [20] reported a two-fold death risk among MDR-TB patients who were older than 45 years in a DOTS-plus projects in Estonia, Latvia, Philippines, Russia, and Peru. The current study also found that patients who were older than 60 years were two times more likely to die from MDR-TB than younger patients in keeping with a previous study [20]. The higher risk of death among elderly patients could be a result of reduced immunity and increased susceptibility to severe infections often found among them [21].

Evidence from literature suggests that male gender is associated with higher risk of mortality among MDR-TB patients [20]. Similarly, male gender also increases the risk of death by two times among MDR-TB patients in South Africa [22]. However, the present study found no significant association between gender and survival among patients with MDR-TB.

Missing data was a major limitation of this study. The extent of completeness in the dataset varied among different variables. Marital status, alcohol use, and smoking status were missing in the records of many of the study patients. Hence, we could not test the association of these variables with mortality. Although HIV status of patients were considered, other details including WHO clinical staging and CD4 count of patients were not taken into account. Furthermore, the findings of the study can only be generalized to similar settings where MDR-TB patients are usually managed by hospitalisation.

The current study has shown substantially reduced probability of survival for smear-positive MDR-TB patients throughout the period of treatment. The study showed that the probability

of survival during the treatment of MDR-TB patients is reduced if a patient is smear-positive, HIV positive, or older than 60 years. Therefore, health workers should give special care to these groups of patients to improve survival among them.

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