Original article

Risk factors of mortality in patients with multi-drug resistant TB

Solomon Molalign[1], Eshetu Wencheko[1]

Abstract

***Background*:** Multi-drug resistant TB (MDR-TB) occurs when the causative agent, *Mycobacterium tuberculosis*, becomes resistant to isonazid and rifampin, the two most effective drugs commonly used to treat TB. Despite high rates of MDR-TB in Ethiopia, little data exist on the prevalence of or risk factors for drug-resistant tuberculosis.

***Objective*:** The aim of the current study was to identify risk factors that are associated with MDR-TB in patients from the All Africa Leprosy, Tuberculosis and Rehabilitation Training Center (ALERT), Addis Ababa, and Gondar University Teaching and Referral Hospital, Gondar, Ethiopia.

***Methods*:** The study included 342 MDR-TB patients (142 from ALERT and 200 from Gondar) who had been under treatment from August 2011 to August 2014 and for whom data for the variables of interest were complete. Descriptive statistics, univariate and multivariate survival analyses were applied. The Kaplan-Meier method was used to estimate overall survival longevity as well as survival levels by covariates. The proportional hazards regression model was employed to identify covariates that have effect on the survival of MDR-TB patients.

***Results*:** Out of the total 342 subjects, 37(10.8%) died before the end of the follow-up period (August 2011 to September 2014); 11 and 12 deaths occurred in the first and second three-months of MDR-TB treatment follow-up, respectively. The median survival for MDR-TB patients was 16 months. Covariates associated with increased risk of mortality were: having clinical complications, resistance to Isoniazid (INH), Rifampicin (RIF) and at least one of other drugs (Ethambutol (E), Streptomysin (STM), Kanamycin (KAN), Amikacin (AMK) & Capreomycin (CPM)), smoking, body weight and age.

***Conclusion*:** The mortality rate of patients was high at the earlier stages of treatment. The three laboratory and clinical factors (complication, resistance to drugs, smoking) were found to have significant association with increased risk of mortality. [*Ethiop. J. Health Dev.* 2015;29(2):82-89]

Introduction

About one-thirds of the world population has latent Tuberculosis (TB), which means people have been infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease. People infected with TB bacteria have a lifetime risk of falling ill with TB. However, persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a much higher risk of falling ill. Multi-drug resistant TB (MDR-TB) occurs when the causative agent, *Mycobacterium tuberculosis*, becomes resistant to isonazid and rifampin, the two most effective drugs commonly used to treat TB. MDR-TB results from either infection with organisms which are already drug-resistant or may develop in the course of a patient's treatment MDR-TB patients who respond poorly to short course chemotherapy and need to be treated intensively for up to 24 months with a regimen based on reserve anti-TB drugs (1).

Isoniazid, the most powerful mycobactericidal drug available, ensures early sputum conversion and helps in decreasing the transmission of TB. Rifampicin, by its mycobactericidal and sterilizing activities is crucial for preventing relapses. Thus, isoniazid and rifampicin are important drugs in the management of TB. While resistance to either isoniazid or rifampicin may be managed with other first-line drugs, resistance to both isoniazid and rifampicin (MDR-TB) demands treatment with second-line drugs. These drugs have limited sterilizing capacity and are not suitable for short course treatment. Thus, patients with MDR-TB require prolonged treatment with drugs that are less effective and more toxic (2).

By September 2013 a total of 92 countries had reported at least one XDR-TB case; in this period about 480, 000 people developed MDR-TB. More than half of these cases were in India, China and the Russian Federation. About 170,000 MDR-TB deaths occurred in 2012. Almost 84,000 patients with MDR-TB were identified by WHO globally in 2012; the estimate in 2011 was 62,000. The biggest increases were in India, South Africa and Ukraine (1). Asia bears the burden of the epidemic as almost 50% of MDR-TB cases worldwide are estimated to occur in China and India (3).

The Global Plan to Stop TB 2011-2015 envisages that, in order to progress towards universal access, about one million MDR-TB patients need to be placed on treatment between 2011 and 2015. The Plan also aims to have at least 75% of MDR-TB patients completing their treatment successfully by 2015. Among MDR cases that started treatment in 2010, the 75% treatment success threshold was achieved by 34 of the 107 countries reporting outcomes (1).

[1]Department of Statistics, College of Natural Sciences, Addis Ababa University, Addis Ababa, Ethiopia

Of the 27 countries with a high burden of MDR-TB and extensively drug resistant TB (XDR-TB), 13 countries with data on treatment outcomes for MDR-TB cases reported a success of 25% to 82% among patients who started treatment in 2007. However, it should be remembered that increases in the prevalence of resistance can be caused by poor or deteriorating TB control, immigration of patients from areas of higher resistance, outbreaks of drug-resistant disease, and variations in surveillance methodologies (4). MDR-TB occurs mostly in relation to improper treatment of drug-susceptible TB. In countries like Ethiopia MDR-TB is becoming a challenge because of poor adherence to treatment and an increase in the use of illegal and use of unapproved treatment regimens for MDR-TB (5).

According to the 2011 health and health-related report of the Federal Ministry of Health of Ethiopia, TB is the third leading cause of death in Ethiopia. During the year 2010/11, a total of 159,017 TB cases were identified in Ethiopia; among these 151,866 (95.5%) were new cases with all forms of TB (6). The proportion of new smear-positive, smear-negative and extra-pulmonary TB among all new cases were 32.7%, 34.8%, and 32.5%, respectively. Re-treatment (after failure or relapse of first treatment) cases represented about 2.9% of all TB cases. According to the anti-TB drug resistance survey conducted in Ethiopia in 2012/13, among 804 newly diagnosed TB cases, 13 (1.6%) were found to be infected with MDR-TB. The rate of MDR-TB among specimens from 76 previously treated TB cases was 11.8%. According to WHO 2012 report, there were an estimated 1,700 and 550 MDR-TB cases among new and re-treatment pulmonary TB cases in 2011, respectively, in Ethiopia (1).

Global Health Committee (GHC) reached a significant milestone about Ethiopia by initiating lifesaving therapy with 787 patients for drug-resistant TB since the program began in 2009. GHC initiated the countrywide program for drug-resistant TB in Addis Ababa at St Peter's Hospital in 2009 and in Gondar at the Gondar University Teaching and Referral Hospital in 2010 in partnership with the Ministry of Health of Ethiopia using approaches developed in Cambodia.

Given the fact that, so far, outcomes of MDR-TB treatment have not been adequately described in Ethiopia, this study aims to identify risk factors leading to death by examining data about subjects who received a standardized second-line therapy at ALERT and Gondar medical facilities.

Method

Study sites: This study used data from two sites. All Africa Leprosy, Tuberculosis and Rehabilitation Training Center (ALERT) is a medical facility in Addis Ababa. The Teaching Referral Hospital of University of Gondar is located in Gondar town, 741 km northwest of Addis Ababa. A total of 400 patients with MDR-TB were treated in ALERT and Gondar Hospital during the study period from August 2011 to September 2014.

Data collection: This study was based on data from a cohort of 342 MDR-TB patients (142 in Addis Ababa and 200 in Gondar) enrolled for treatment during the period from August 2011 to August 2014. Data about patients who were diagnosed with a first MDR-TB episode, i.e. patients whose status have changed from TB to MDR-TB or were infected with MDR-TB without having had TB before were collected. The data were taken from the medical records of patients by health professionals (trained to extract the necessary data) from the respective centers through a uniform checklist containing some socio-demographic factors, clinical factors and length of time patients have been in treatment. They were then entered into a password-protected computer by data clerks to maintain confidentiality after checking for completeness and coding. Approval to access the records of patients and use the same for the current research was obtained from the respective managements of the two health facilities.

In line with the objective set, the study used a semi-parametric survival analysis method, namely proportional hazards regression. The response/outcome variable is "survival longevity" of patients in months (status coded: death = 1, censored = 0). Considering their potential importance a list of socio-demographic and clinical factors found in the medical records of the patients have been included. These are sex (male, female); age (years); baseline body weight (kilograms); marital status (single, married, others, i.e. widowed/divorced/separated); level of education (illiterate, primary, secondary and above); HIV co-infection (positive, negative); clinical complication (no, yes); co-morbidities (no, yes); drug susceptibility test results (INH & RIF only, INH, RIF and at least one of other drugs (E, STM, KAN, AMK & CPM); therapeutic delay (less than one month, over a month); and smoking status (yes, no). The study also took into account all possible first-order interactions. The two statistical packages employed for data analyses were SPSS and Stata.

Result

Descriptive Analysis: From the total of 400 MDR-TB patients the study included 342 MDR-TB patients for whom full records about the variables of interest were complete. Of these 37 subjects (10.8%) died in the study period; 305 subjects (89.2%) were censored. The population consisted of 195(57%) males and 147(43%) females. Nine out of 71 (13%) were HIV-positive while 28 out of 271 (about 10%) were HIV-negative. Summary statistics of the demographic and health factors and of the continuous variables included in this study are given in Tables 1 and 2, respectively.

Table 1: **Summary results of death and censored events versus demographic and health factors (*n* = 342)**

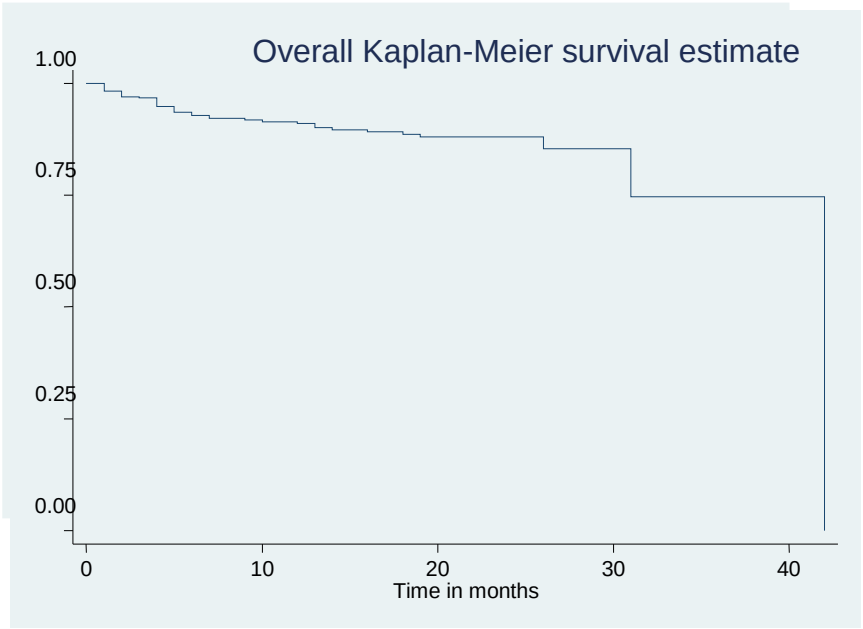
Demographic and Health Factors		Summary of the number of deaths and censored values			
		Total (%)	Death	Censored	Death %
Sex	Male	195(57)	21	174	10.8
	Female	147(43)	16	131	10.9
Marital Status	Single	158(46.2)	14	144	8.9
	Married	155(45.3)	18	137	11.6
	Others (widowed/divorced)	29(8.5)	5	24	17.2
Educational	Illiterate	123(36)	16	107	13.0
Level	Primary	100(29.2)	9	91	9.0
	Secondary and above	119(34.8)	12	107	10.1
HIV Status	Negative	271(79.2)	28	243	10.3
	Positive	71(20.8)	9	62	12.7
Co-morbidities	No	325(95)	34	291	10.5
	Yes	17(5.0)	3	14	17.6
Clinical	No complication	313(91.5)	25	288	8.0
Complication	Yes	29(8.5)	12	17	41.4
Drug	INH & RIF only	269(78.7)	24	245	8.9
Susceptibility test	INH, RIF and at least one of other drugs (E, STM, KAN, AMK & CMP)	73(21.3)	13	60	17.8
Therapeutic	Less than one month	239(69.9)	23	216	9.6
Delay	Over one month	103(30.1)	14	89	13.6
Smoking	Yes	38(11.1)	8	30	21.1
	No	304(88.9)	29	275	9.5

During the first and the second three-months of MDR-TB treatment 11 and 12 deaths occurred, respectively. The median survival time of patients was 16 months; the minimum and maximum follow-up time, respectively, were 1 month and 42 months. Males had relatively lower survival longevity (14.55 months) than females (16.8 months). The median weight of patients was 50.5 kg. Nearly 90% were non-smokers. About 8.5% had clinical complications: 7, 3, 3, 8 and 8 subjects, respectively, due to pneumothorax, pneumonia, hemoptysis, cor-pulmonale and others. About 95% of the patients had no medical diagnosis other than TB; 5% had co-morbidities such as diabetes (3.5%) and others (myocardial infarction or asthma (1.5%)) other than HIV. Drug susceptibility test showed that 269(78.7%) were found to be resistant only to rifampicin and isonizid; the remaining were resistant to RIF, INH and at least one of other drugs (E, STM, KAN, AMK & CMP). The length of time from MDR-TB confirmation to start of treatment (therapeutic delay) was less than one month in 239(69.9%) patients and longer in 103(30.1%) patients.

The overall Kaplan-Meier survival estimate (see Figure below) reveals that most of the deaths occurred in the first quarter of MDR-TB treatment initiation. A manifestation of this feature has been given above, i.e. 11 and 12 deaths occurred in the first and the second three-months, respectively. Additional estimates of the Kaplan-Meier survivor functions (not included in this paper) have been constructed to check for possible existence of differences in survival experience by categories of variables. A confirmation of differences in survival experience among groups of clinical complication(s) and smoking status at 0.05 level of significance is provided by the log-rank test (see Table 3).

Table 2: **Summary results of death and censored events versus time, age and body weight (*n* = 342)**

Patient Status	Variable	Mean	SE	Min.	Max.	Median	Q_1	Q_3
Censored	Time	16.37	8.311	1	40	18	9	23
	Age	30.59	12.134	1	72	28	22	38
	Body weight	50.71	9.710	7	88	51	46	56
Death	Time	8.38	9.13	1	42	5	2	12.5
	Age	36.19	12.789	16	76	36	26.5	43.5
	Body weight	44.77	7.347	32	60	47	40	50.5
Overall	Time	15.51	8.750	1	42	16	8	23
	Age	31.19	12.311	1	76	28	22	40
	Body weight	50.07	9.652	7	88	50.5	45	55



On the other hand, there are no indications of significant differences in survival/death experience among the groups of the remaining categorical covariates, namely gender, marital status, educational level, HIV status, drug susceptibility test, co-morbidities and therapeutic delay.

Table 3: **Results of the log-rank test for detecting differences in survival experience among groups of clinical complication(s) and smoking status (*n* = 342)**

Covariates	chi-Square	d.f.	p-value
Sex	0.22	1	0.6372
Marital status	2.12	2	0.3470
Educational level	1.72	2	0.4236
HIV status	0.86	1	0.3525
Co-morbidities	0.03	1	0.8548
Clinical complication(s)	42.56	1	0.0000*
Drug susceptibility	1.31	1	0.2526
Therapeutic delay	0.03	1	0.8694
Smoking status	5.76	1	0.0164*

*significant at 0.05 level

Results of the Cox Proportional Hazards Regression Analysis: The multivariable Cox regression analysis showed that the covariate weight was found to be insignificant. However, we decided not to discard weight right away without looking at a possible interaction effect with age; this is clinically meaningful. Even though the interaction of age with weight had a significant effect on the mortality of MDR-TB patients, the estimated adjusted hazard ratio was found to be close to unity (0.9963) implying that the inclusion of the interaction does not contribute to the improvement of the model. On this ground and also in the interest of having a parsimonious model, the interaction term has been left out. Consequently the preliminary final model contained the five main covariates, namely age, weight, clinical complication, drug susceptibility test and smoking status. The results based on the main covariates are displayed in Table 4.

Table 4: **The *final* Cox model for the data (with only main covariates (*n* = 342).**

Covariate	$\hat{\beta}$	s.e.	Wald χ^2	d.f.	Sig.	Est. aHR exp($\hat{\beta}$)	95% CI for HR Lower	Upper
Body weight	-0.0950	0.0190	24.82	1	0.0000	0.39*	0.3726	0.4014
Age	0.0366	0.0132	7.59	1	0.0059	1.20**	1. 1701	1.2323
Clinical complication(s) (*ref*. = no complications)	1.6341	0.3901	17.55	1	0.0000	5.13	2.3860	11.0090
Drug susceptibility (*ref*. = resistance to at least three anti-TB drugs)	0.8447	0.3732	5.12	1	0.0236	2.33	1.1199	4.8367
Smoking status (*ref*. = smokers)	0.8790	0.4328	4.13	1	0.0422	2.41	1.0313	5.6251

*computed for a 10-kg body weight difference. **computed for a 5-year age difference.

We have made routine checks of model diagnostics before concluding that the model with the five main predictors in Table 4 is taken as the final model. It was found that the model satisfies the assumption of proportional hazards; there were no serious problems with regard to influence and outliers; and it was confirmed that the model fits the data very well. As a consequence of such positive confirmations, the model can be taken as the final model. The subsequent interpretations of results given below are, therefore, based on aHR (estimated adjusted hazards ratio) and the respective 95% confidence intervals. In using estimated aHR for interpretation we understand that all other variables in the model, except the one about which we are making inference(s), are kept constant.

Interpretation of the analytic results based on the final model: *Weight*: Since an increase in body weight by a 1-kilogram does not make sense clinically, we opted to take comparisons based on a 10-kg differential. Hence, the estimated adjusted hazards ratio for a 10-kg difference in initial weight is about 0.39 with 95% CI (0.3726, 0.4014). The interpretation is that the rate of death is estimated to decrease by 61% for every increase of 10-kg of body weight independent of the weight at which the increase is calculated; that is, body weight increase has a beneficiary effect. A decrease of between 60 and 63 percent is consistent with the data with 95 percent level of confidence.

Age: For exactly the same reason with weight, a 1-year age differential does not make sense. Instead a 5-year differential of age has been used in this study. Associated with this is aHR =1.20 and a 95% CI (1.1701, 1.2323). This means the hazard increases by 20% for every 5-year increase in age (negative effect) and is independent of the age at which the increase is calculated. The confidence interval estimate suggests that an increase in the hazard rate of between 17 and 23 percent is consistent with the data with 95 percent level of confidence.

***Clinical complication*:** Patients with clinical complications experienced nearly fivefold risk of death compared to those without clinical complications; the risk could be as low as 2.4 times or as high as 11 times larger with 95% confidence compared with patients who did not experience any clinical complications.

***Drug susceptibility*:** Patients who were resistant to at least three anti-TB drugs, including INH and RIF are 2.3 times more likely to die than patients with only INH and RIF; the risk could be as low as 1.12 times or as high as 4.8 times larger with 95% confidence compared with patients without experience of drug susceptibility.

***Smoking*:** The rate of dying among smokers is 2.4 times higher than that of non-smokers; the rate could be as low as 1.03 times or as high as 5.63 times larger with 95% confidence compared with non-smoker patients.

Discussion

This discussion section has two parts – one providing findings from the literature on the same issue and a second part where comparisons of the findings of the current study and earlier studies.

General discussion

A study that aimed at describing the clinical, microbiological, molecular epidemiology and treatment of 90 MDR-TB cases in the United Kingdom included gender, age at diagnosis, ethnicity, country of birth, year of entry into the UK, history of prior TB, and immune-compromised status as potential predictors of the outcome. Clinical and radiological details were also considered. The results showed that immune-compromised status, appropriate utilization of three drug treatment and age were associated with survival (7).

A retrospective study conducted in the National Jewish Medical and Research Center by reviewing the records of 205 MDR-TB patients who were treated in the in-patient service and discharged between January 1, 1984 and December 31, 1998. The predictors considered were age, gender, racial and ethnic distributions, number of drugs resistant, time with TB before first visit to the center, users of flouroquinolone drug, extent of illness and surgery. It was found that clinical complications due to pneumonectomy and lobectomy and fluoroquinolone therapy were associated with improved microbiological and clinical outcomes in all 205 patients (8).

A prospective epidemiological case control study undertaken in four European Union countries (France, Germany, Italy, and Spain) with the aim of identifying risk factors of multidrug resistance in patients with pulmonary TB. A total of 414 subjects of whom 138 cases have been resistant to both isoniazid and rifampicin and 276 controls (either not resistant to anti-TB drugs or resistant to only one anti-TB drug) were included in the study. The covariates included were: age, gender, birthplace, TB contacts, previous tuberculosis, intravenous drug use, income, living situation, co-morbidity other than HIV, and HIV status. The study identified age, known TB contacts, previous TB, income and intravenous drug use as risk factors associated with MDR-TB (9).

A retrospective study conducted in South Korea to assess clinical characteristics, treatment outcomes, and long-term survival rate of patients with XDR-TB in a cohort of HIV-negative patients (10). A total of 1,407 patients with culture-proven MDR-TB were enrolled from all national TB hospitals, all Korean National Tuberculosis Association chest clinics, and eight randomly selected university hospitals near Seoul. Medical records were reviewed for patients' demographics, TB treatment history, co-morbidities, acid-fast bacilli culture and drug susceptibility test (DST) results, chest radiographs, and treatment modalities and outcomes. The result of the study showed that age, BMI and DST results were

statistically significant predictors. Mortality was approximately three to four times more likely in patients with XDR-TB than in patients with MDR-TB. The overall treatment success rate was less than 50 percent, while the success rate in patients with XDR-TB treatment was 29 percent.

Assessment of treatment outcome of MDR-TB/XDR-TB in Latvia from 2000 to 2004 compared demographic, clinical and treatment characteristics with the outcomes MDR-TB and XDR-TB and has revealed that XDR-TB resistance and having bilateral cavitations were associated with risk of death; retirees and students were the most affected social groups. It was also observed that HIV infection has no association with MDR-TB (11).

A retrospective national cohort study about MDR-TB/XDR-TB was done in Lithuania based on 1,809 cases reported from 2002 to 2008. The objective of the study was to identify risk factors associated with survival of patients with MDR-TB/XDR-TB. It was found that age, rural residence, alcohol use, employment status, lower level of education, positive or unknown HIV status, cavity disease and being smear-positive at the time of MDR-TB/XDR-TB diagnosis were associated with survival. There was no difference in survival of patients with primary MDR-TB or XDR-TB compared with those who developed drug resistance during the treatment period. There was no association of survival either with acquired TB before versus primary or with XDR-TB versus MDR-TB (12).

A prospective cohort study based on data collected from 2000 to 2004 in South Africa documented that the factors associated with a significantly increased hazard of death were: HIV infection, drug susceptibility, treatment regime, body weight and therapeutic delay longer than two months (13).

A retrospective study about treatment outcome of MDR-TB was undertaken in the United Kingdom. The study included 204 patients diagnosed with MDR-TB between 2004 and 2007. The findings suggested that having any co-morbidity, particularly HIV and diabetes, were strongly associated with death of patients. Also, use of a fluoroquinolone or a bacteriostatic drug was more likely to have a successful treatment outcome. Treatment with an injectable agent (Streptomycin, Amikacin, Capreomycin and Kanamycin) did not have a significant effect on treatment outcome (14).

A study was done to ascertain social determinants of MDR-TB in the US based on data gathered in the years 2005 to 2009. The study population was the US population (all 50 States and the District of Columbia). As database it used the Disease Control and Prevention Online Tuberculosis Information System. Variables considered were: whether or not the patient lived in a correctional facility at the time of diagnosis; HIV status; homelessness; whether or not the patient had an occupation; and place of birth (US-born or foreign born). The study identified living in a correctional facility and place of birth to be strongly related with MDR-TB (15).

Another study conducted in Tanzania (16) showed that HIV status was not found to be a risk factor of death among MDR-TB patients. The two studies (9, 14) came to the conclusion that HIV-seropositivity was not a significant risk factor of death during MDR-TB treatment period. However, the risk of death among immune-compromised patients was high.

A case control study that was conducted in Addis Ababa, Ethiopia, between November 1, 2011 and February 28, 2012 found that interruption of first-line anti-TB treatment, educational status, gender, number of rooms in a patient's house, TB site, drug side effects during first-line treatment, lack of direct observation by health workers, and first-line anti-TB treatment were associated with developing MDR-TB. On the other hand, HIV status, history of smoking and family size was not significantly associated with developing MDR-TB (17).

Yet another study in St. Peter TB Specialized Hospital in Addis Ababa, Ethiopia (18) attempted to identify predictors of survival time and assess survival among patients receiving MDR-TB treatment based on data gathered from October 2011 to May 2012. A cohort of 188 patients who started treatment in February 2009 was followed up for a total of 79,600 person-days. The median follow-up time was 466.5 days (1.28 years). While smoking, therapeutic delay of at least one month, HIV seropositivity, and clinical complication were found to be significantly associated with survival, no statistically significant association was found with age, gender, baseline weight, radiological findings, previous TB treatment, number of first line resistant drugs and co-morbidity.

B. ***Comparisons of findings of the current study with findings in other studies***:

Median survival: The current study showed that the median survival of MDR-TB patients was about 16 months (1.25 years); (12) and (7), respectively, found median survival of 4 and 3.78 years for patients in Lithuania and the United Kingdom.

Death rate: In the current study total death rate for the cohort was estimated at about 10.8 percent; this rate is similar to that in another study where the death rate for pooled data from 21 countries was 11 percent (19). Death rates of 7, 15 and 23.4 percent, respectively, had been reported for Latvia (11), Uzbekistan (20) and South Africa (13).

Clinical complications**:** Clinical complications due to pneumonectomy and lobectomy had been found to be associated with survival outcome of MDR-TB patients (8). A study conducted in Uzbekistan (20) indicated that clinical complication is a risk factor of mortality and treatment failure. A retrospective cohort study

conducted in St. Peter TB specialized hospital, Addis Ababa, Ethiopia (18) showed that patients with clinical complications had a higher hazard of mortality than those who did not have any complications. The finding of the current study agrees with the above cited findings with respect to complications.

***Co-morbidities*:** A study (21) in New Delhi, India suggested that co-morbidities did not influence the outcome of MDR-TB treatment. A finding in (18) came up with a conclusion that co-morbidities had no significant influence on the risk of mortality associated with MDR-TB. The current study also showed that co-morbidities were not identified as risk factors of mortality. In contrast, studies done in Rawalpindi, Pakistan (22) and in Estonia (23) identified co-morbidities as risk factors for treatment failure and concluded that they had an impact on mortality among MDR-TB patients.

***Resistance to anti-TB drugs*:** According to (21) over 70 percent of patients were resistant to three or more anti-TB drugs. Resistance to more than two drugs was found to be a risk factor of mortality among MDR-TB patients in Pakistan (22). The finding of the current study in this regard agrees with the above findings.

***Body weight*:** A retrospective study conducted in South Africa (13) showed that patients in the weight group below 45kgs and the intermediate weight group (46-60kg) experienced higher rates of death relative to the weight group 60kgs and above. The finding in (21) suggested that baseline weight predicts poor outcome of MDR-TB. The current study also identifies low weight as a risk factor.

Age: The results from Tanzania (16) and Nigeria (24) showed that age was not a risk factor of poor outcome among MDR-TB patients. Higher age is associated with poor outcome of MDR-TB in four European Union countries (France, Germany, Italy, and Spain) (9). The current study found that advanced age is associated with high mortality rate in MDR-TB patients concurring with the conclusions in (16) and (24).

***Smoking*:** According to (17) smoking status was not significantly associated with MDR-TB development while (18) concluded the opposite. The current study asserted that smoking is a risk factor of mortality among MDR-TB patients agreeing with the latter of the two findings above.

Conclusion:
Mortality rate was high in the first quarter of MDR-TB treatment initiation and stabilized in later stages; 11 and 12 deaths occurred in the first and second three months of MDR-TB treatment initiation, respectively. Five main factors that are identified to significantly affect survival of the patients were age, baseline weight, clinical complication, drug susceptibility and smoking status.

Finally we would like to point out that the current study was carried out under the following limitations: (*i*) data were extracted from medical records; (*ii*) it was presumed that all deaths were caused by MDR-TB; (*iii*) the data records in both study sites (Addis Ababa and Gondar) did not provide information about other social determinants such as socioeconomic status, alcohol abuse, etc. and clinical factors such as MDR-TB category, adverse effects, mode of care, radiological findings, CD4 count etc. that would have been helpful in explaining MDR-TB rates; and (*iv*) the analyses were based on baseline values of the explanatory variables considered.

Acknowledgements
The authors would like to thank the All Africa Leprosy, Tuberculosis and Rehabilitation Training Center, Addis Ababa, and Gondar University Teaching and Referral Hospital for making the data for this research undertaking available. We also acknowledge the insight and contribution provided by the anonymous reviewers.

References

1. World Health Organization. Global Tuberculosis Control Report; 2013 *tuberculosis global facts www.who.int/tb/data.* (accessed on March, 2015).
2. Sharma SK, Mohan A, Kadhiravan T. HIV-TB co-infection: Epidemiology, diagnosis and management. *Indian J Med Res*. 2005; 121: 550-567.
3. Zignol M. Incidence of multidrug-resistant tuberculosis: 2003 global estimates; 2003. Available at: http://www.stoptb.org/wg/dots_plus/meetings.asp (accessed on June 5, 2014).
4. World Health Organization. Global Tuberculosis Control Report; 2010 tuberculosis.
5. World Health Organization. Guidelines for the programmatic management of drug-resistance tuberculosis. Geneva, Switzerland; WHO; 2008.
6. Federal Ministry of Health of Ethiopia. Guidelines for clinical and programmatic management of TB, TB/HIV and leprosy in Ethiopia (fifth edition). March, 2013, Addis Ababa
7. Drobniewski F, I Eltringham, C Graham, J G Magee, E G Smith, B Watt. A national study of clinical and laboratory factors affecting the survival of patients with multiple drug resistant tuberculosis in the UK. *Thorax* 2002; 57: 810-816.
8. Chan E. D., Valerie L, Matthew J. S, Julanie F. C, Mai-Lan N. H, Marian G, Michael D. I. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 2004; 169: 1103-1109.
9. Casal M., M. Vaquero, H. Rinder, E. Tortoli, J. Grosset, S. Rusch-Gerdes, J. Gutierrez, and V.

Jarlier. A Case-Control Study for Multidrug-Resistant Tuberculosis: Risk Factors in Four European Countries. *Microb Drug Resist*. 2005;1: 62-9.

10. Hyung K, et al. Treatment Outcomes and Long-term Survival in Patients with Extensively Drug-resistant Tuberculosis. *Am J Respir Crit Care Med*. 2008; 178:1075-1082.
11. Holtz TH, V. Leimane, G. Dravniece, V. Riekstina, I. Sture, S. Kammerer, M.P. Chen, G. Skenders. Treatment outcome of multidrug/extensively drug-resistant tuberculosis in Latvia, 2000–2004. *European Respiratory Journal* 2010. Print ISSN 0903-1936.
12. Balabanova Y, Radiulyte B, Davidaviciene E,et al. Survival of drug resistant tuberculosis patients in Lithuania: a retrospective national cohort study. *BMJ* Open 2011;1:e000351. doi:10.1136/bmjopen-2011-000351.
13. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, et al. Outcomes of Multi-Drug Resistant Tuberculosis (MDR-TB) among a Cohort of South African Patients with High HIV Prevalence. *PLoS* ONE 2011; 6(7): e20436. doi:10.1371/journal.pone.0020436
14. Anderson L F, S Tamne, J P Watson, T Cohen, C Mitnick, T Brown, F Drobniewski, I Abubakar. Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: a retrospective-prospective cohort study from 2004 to 2007. (Euro Surveill. 2013;18 (40):pii=20601).
15. Khan, R. The Social Determinants of Multidrug Resistant Tuberculosis in the United States between 2005 and 2009. Public Health Thesis 2013; Georgia State University.
16. Range N., Friis H., Mfaume S., Magnussen P., Changalucha J., Kilale A., Mugomela A. Andersen A. B. Anti-tuberculosis drug resistance pattern among pulmonary tuberculosis patients with or without HIV infection in Mwanza, Tanzania. *Tanzania Journal of Health Research*, 2012.
17. Hirpa S, Medhin G, Girma B, Melese M, Mekonen A, Suarez P, Ameni G. Determinants of multidrug-resistant tuberculosis in patients who underwent first-line treatment in Addis Ababa: a case control study. *BMC Public Health* 2013; 13:782.
18. Getachew T, Bayray A, Weldearegay B. Survival and predictors of mortality among patients under multi-drug resistant tuberculosis treatment in Ethiopia: St. Peter's Specialized Tuberculosis Hospital, Ethiopia. *International Journal of Pharmaceutical Sciences and Research*, January, 2013.
19. 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. doi:10.1371/journal.pone.0006914.
20. Cox HS, Kalon S, Allamuratova S, Sizaire V, Tigay Z. N, et al. Multidrug-Resistant Tuberculosis Treatment Outcomes in Karakalpakstan, Uzbekistan: Treatment Complexity and XDR-TB among Treatment Failures. *PLoS* ONE 2007; 2(11): e1126. doi:10.1371/journal.pone.0001126.
21. Dhingra V. K, Rajpal S., Mittal A and M. Hanif. Outcome of Multi-Drug Resistant Tuberculosis cases treated by individualized regimens at A Tertiary Level Clinic. *Indian J Tuberc*. 2008; 55:15-21.
22. Khurram M., Hamama Tul Bushra Khaar, Fahim M. Multidrug-resistant tuberculosis in Rawalpindi, Pakistan. *J Infect Dev Countries* 2012; 6(1): 29-32.
23. Kim HR, Hwang SS, Kim HJ, Lee SM, Yoo CG et al. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. *Clin Infect Dis*. 2007;45:1290-1295. doi:10.1086/522537. PubMed: 17968823.
24. Oladimeji O, Isaakidis P, Obasanya OJ, Eltayeb O, Khogali M, et al. Intensive-Phase Treatment Outcomes among Hospitalized Multidrug-Resistant Tuberculosis Patients: Results from a Nationwide Cohort in Nigeria. *PLoS* ONE 2014; 9(4):e94393. doi:10.1371/journal.pone.0094393.