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Survival and predictors of mortality from multidrug resistant tuberculosis (MDR-TB) among patients treated at MDR-TB Referal Hospitals in Ethiopia: A retrospective cohort study

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The extent and burden of MDR-TB varies significantly from country to country. In Africa, fewer than half of patients receiving therapy for multidrug-resistant TB (MDR TB) are successfully treated. Even though MDR-TB treatment was started in 2009 survival of MDR-TB treatment particularly of adverse treatment outcome is not studied in national level. Institution based retrospective cohort study was conducted at randomly selected four treatment Initiative Centers (TIC) & referral hospitals in Ethiopia. Data was collected using standardized checklist by trained professionals through reviewing records of all patients ever enrolled. Cox- proportional hazard regression model was built of the 494 records reviewed, 462 met the inclusion criteria. These patients were followed for 202250 person-day of observation; during the follow up period 38 (8.2%) patients were died making overall incidence density rate of 6.79 (95% CI=5.42-8.78) per 100 Person year. Survival at the end of 1st and 4th month was 98.2% and 92.3% respectively, while the overall mean survival time was 24.82(95%CI=22.8-25.72) months. Drugs side effect 3 (95 % CI [2.5-4.3, medical diagnosis other than TB 3.3 (95 % CI [1.7-5.6], HIV sero-status 2.7 (95 % CI [3.4-9.11] and bigger base line body were independently and significantly predicted mortality of MDR-TB patients. The incidence of death and treatment outcomes was in acceptable ranges, yet it needs due attention. Intervention to further reduce deaths has to focus on patients with co-morbidities, HIV, adverse effect and smaller base line body weight.

Key words: 'MDR-TB, Survivable, Mortality, Ethiopia.

INTRODUCTION

Tuberculosis (TB) remains the largest infectious disease killers worldwide. According to the World Health Organization (WHO), in 2015, there were an estimated 10.4 million new TB cases, 1.4 million TB deaths and another 0.4 million deaths among people with TB and HIV. Multidrug-resistant tuberculosis (MDR-TB) is a type of TB that is resistant to at least the first line anti-TB drugs (Rifampicin and Isoniazid) (WHO, 2011). The increasing incidence of MDR-TB and extensively drug-resistant (XDR-TB) tuberculosis is a major concern for TB

control programs worldwide (Zignol et al. 2012). Drug-resistant TB is a man-made problem, largely being the consequence of human error as a result of individual or combination of factors related to management of drug supply, patient management, prescription of chemotherapy, and patient adherence. Poor infection control practice also has been identified as a major contributing factor for the spread of MDR-TB. MDR-TB, like drug susceptible TB, is a droplet infection and is easily transmitted to immune compromised individuals, especially to the HIV infected (FMOH, 2009).

The occurrence of MDR-TB is mainly attributable to human error, although genetic factors are also believed to contribute to a certain extent (Sharma and Mohan, 2006). The principal patient-related factor that predicts the occurrence of MDR-TB is non-adherence to treatment (FMOH, 2011). In 2010, the 27 high MDR-TB burden countries accounted for 85% of all MDR-TB cases. China and India, were the top two countries accounting for 50% MDR-TB cases (WHO, 2010). Of the 27 countries with a high burden of MDR-TB and XDR-TB, 13 countries with data on treatment outcomes for MDR-TB cases reported a success by 25 to 82% among patients that started on treatment in 2007 (WHO, 2008). However, factors associated with the outcomes were shown to be poor or deteriorating TB control, treatment dalliance/early initiation, smoker/substance use, HIV sero-status and patients who develop a clinical complication or not (WHO, 2010).

The treatment of MDR-TB in Ethiopia started recently in TB specialized hospital and expanded to MDR-TB treatment initiation centers (TIC) in selected hospitals of the regions (FMOH, 2009). However, outcomes of the treatment particularly of its adverse outcome and associated factors are not described in Ethiopia. Therefore, examining a cohort who received a standardized second-line therapy and management of MDR-TB to determine the overall survival status has a great importance for proper planning and effective implementation. Therefore, this study aimed at assessing the survival status and identifies predictors of mortality from multidrug resistant tuberculosis (MDR-TB) among patients treated in TB referral hospitals/TIC in Ethiopia.

METHODOLOGY

Study setting and design

Ethiopia is the second populous country in Africa with estimated total population of 100 million by the year 2016. Ethiopia ranks eighth in the global list of high-burden countries with an estimated 210,000 incident cases of TB (224 per 100,000) and fifteenth from high MDR-TB burden countries. MDR-TB treatment was started in St. Piter TB Specialized Hospital at the end of 2009. Then the service was expanded to selected regional referral hospitals; Gondar University Referral Hospital started in 2011, Dilchora Hospital at the middle of 2011 and Bishoftu in 2014. In Ethiopian Fiscal Year (EFY) 2006, additional 13 MDR TB centers started treatment services, increasing the total number of MDR treatment centers to 32 country-wide in September 2014, while a total of 332 health institutions were providing follow-up services. In addition, there are functioning TIC in each selected geographical areas including Arba Minch, Yirgalem and Queen Eleni Mohamed Memorial Hospitals in SNNPR. Since 2001, a cumulative total of 1,559 MDR TB patients were enrolled in second line drug (SLD) treatment. Institution based retrospective cohort study was carried out in tuberculosis referral centers/TIC in Ethiopia; Dile Chora, Yirgalem, Queen Eleni Mohamed Memorial and Shene Gibe Hospitals [9].

Study population and sampling technique

All patients MDR-TB who were treated in randomly selected MDR-TB referral centers in Ethiopia were included in this study. The sample size needed to identify predictors of mortality from MDR-TB is calculated based on, sample size estimation for the assessment of survival time under the Cox proportional hazards model by using the STATA Version 11.0 Statistical package computer program considering the following assumptions: a 1.9 hazard ratio (effect size) associated with a one-unit increase in covariate of interest which is the presence of clinical complication when other covariates were held constant, the default 0.5 standard deviation of covariate of interest, the probability of failure (death) observed is 0.1543 [10], with 5% marginal error and 95% confidence interval of certainty (α = 0.05). The number of subjects needed to achieve a power of 80% and assuming no subjects anticipated to withdrawal from the follow up was 494. Of the 32 referral/treatment initiation centers, four were selected by simple random sampling. Sample was allocated proportion to the population and records were reviewed continually; which were Dile Choral, Negest Eline Mohammod, Yergalem, and Shenen Gibe Hospital, However, St. Peter's Hospital was excluded in the study because of refusal to participate in the study.

Data collection procedure and quality control

Patients record documents including registers and monitoring cards were used as sources of data. Data was collected by using structured checklist. The checklist was developed from standard treatment protocol for the management of MDR-TB, registration log book, monitoring chart and reviewing related literatures to collect the required individual information from the relevant documents. The checklist sought information on: patient related data (age, sex, residence), anthropometric measurements (height, weight, body mass index, BMI), co-morbidities, types/category of MDR-TB, medication given, end status and dates of admission and events. Four data collectors and two supervisors who have a bachelor degree in health science and been trained with MDR-TB management and/or are working in TB clinics were used for data collection. To keep data quality supervisor and data collectors were

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oriented on how and what information they should collect from the targeted data sources. The prepared checklist was pretested on the actual site before actual date of data collection and any correction was made based on the finding. Proper categorization and coding of the data completeness and consistency of the collected data was checked on daily bases during data collection by supervisor and the principal investigator. Whenever there appears incompleteness and ambiguity of recording, the filled information formats were crosschecked with source data. An individual record with incomplete data was excluded. Double entry and data cleaning were also considered.

Data analysis

After data collection, each questionnaire was checked for completeness and consistency by the principal investigator and supervisors. Data was cleaned, coded and entered into Epi-info version 7 and exported to STATA version 11, then exploratory data analysis was carried out to check the levels of missing values, presence of influential outliers, multi-collinearity, normality and proportionality of hazards over time.

Bivariate analysis was done to identify associations between dependent and independent variables. Hazard ratio with 95%CI and P-value was used to assess the strength of association and statistical significance. Life table was constructed to estimate probabilities of becoming death for categorical variables at different time intervals. Kaplan Meier survival curve together with log rank test was fit to test for the presence of difference in incidence of death among the groups. Variables significant at P<0.25 level in the bivariate analysis and variables which have medical/public health significance were included in the final Cox- regression analysis, to identify independent predictors of successful treatment outcomes.

Model was built by forward step wise procedure and compared by likelihood ratio test and Harrell's concordance statistics test. Interactions and confounders were tested using cutoff point beta change greater than 20%. Proportionality assumption was tested by global test based on Scheonfeld residuals. Instability of parameter estimate among variables in the final fitted model was checked by using variance inflation factor (VIF). Goodness of fit of the final model was checked by Nelson Aalen cumulative hazard function against Cox Snell residual. Association was summarized by using adjusted hazard ratio and statistical significances tested with 95% confidence interval.

RESULTS

Characteristics of participants' admission

A total of 494 consecutively selected records of MDR-TB patients in the four randomly selected MDR-TB referral hospitals and treatment initiation center were reviewed. Of these, 32 records have missing data on treatment outcome or date of the treatment outcome and/or missing major variables which were important in the evaluation of treatment outcome and determinants. Therefore, 462 records with full information on treatment outcome and its date were included in the study from the selected MDR-TB referral hospitals and treatment initiation centers in Ethiopia. More than half (57%) of the patients enrolled into the study were males and the median age was 27.5 (IQR = 23-35.5) year, while the median BMI was 15.7 (IQR=12-18.8). Most prevalent one was pulmonary tuberculosis, which is prevalent among 430 (93%) patients and both extra pulmonary and mixed infection was prevalent among 3.5% of patients. Also, higher proportion of patients (418/462 or 90.5% of patients) had been previously treated for TB, with a median of two episodes. While, significant proportion of patients has even three episodes of treatment (Table 1).

Larger proportions of patients, 462 (92%) were diagnosed by phenotypic or genotypic drug and sensitivity testing (DST), while only 7.7% were confirmed through line probe assay (LPA). According to the DST result, 407 (88%) of patients had developed resistance to rifampicin (RIF) only or with others, while 268 (58%) patients have resistance to isoniazid (INH) only or with other drug resistance. Still, a significant proportion of patients initiated a treatment with a medical professionals decision. In addition, two third (69.6%) of patients had radiologic finding suggestive of tuberculosis. Opacity, previous TB scar, cavitation/cavitary lesion, infiltration, infusion and atelectasis were the most prevalent findings.

Clinical and medical conditions of patients enrolled in the study

All patients enrolled in the MDR-TB treatment program were tested for HIV infection and 36 (7.8%) were found to have HIV. It is more prevalent in Dile Chora Hospital of Dire Dawa District. Of the positive cases, 24 (63.2%) were diagnosed during their previous TB treatment program and the rest were newly diagnosed. ART regimen was also initiated for all of the cases (66.6%) according to the National Ethiopian HIV treatment guidelines, whereas 4 (10.8%) patients information about ART treatment is missed from the card. Regarding to other medical condition, significant proportion 78 (16.8%) of patients also had at least one medical diagnosis other than MDR; mostly, disseminated TB and diabetes mellitus (DM) were diagnosed individually or together. For instant, diabetic mellitus were 46 (9.9%).

As to the national MDR-TB treatment protocol, patients were treated with the standard second-line drugs (SLDs) regimen with a median of five drugs. Concerning the treatment given for patients, Capreomycin (81.5%) was the most common injectable used and the median duration of injectable drug depends on duration of smear or culture conversion and other factors which delay the conversion like missing of treatments. It was 8.3 months (IQR 7.1-11.5 months). The most common oral agents used as treatment were ethionamide (98%), levofloxacin (96.7%) and cycloserine (97%).

Most patients, 314 (68%) experienced at least one side effect in the course of treatment, which happened mostly during the first month. However, most of the side effects do not lead the patient to terminate the treatment or

Table 1. Socio-demographic and clinical characteristic of MDR-TB patients in TIC of Ethiopia, 2009-2016.

Variable	Frequency	Percent
Sex		
Male	263	57
Female	199	43
Infection site of TB		
Pulmonary	430	93
Extra pulm	16	3.5
Both	16	3.5
Treatment history of TB		
Yes	418	90.5
No	44	9.5
Number of episodes (n=418)		
Once	154	37
Twice	251	60
Three times	13	3
HIV Sero status		
Reactive	36	7.8
Non-reactive	426 (92.9)	92.9
Resistance to		
RIF and/or other	407	88
INH and/or other	268	58
+Substance use		
Yes	38	8.2
No	424	91.8
Have comorbidity		
Yes	78	16.8
No	384	83.1
Drugs adverse effect		
Yes	431	68
No	31	32

change a regimen. Of them, the most prevalent side effects were nausea or vomiting and gastritis or gastric disturbance in 32 and 24% of patients, respectively. The rest were hypokalemia (10%), renal toxicity (7.3%), blurring of vision (4.4%), RBS disturbance (4.4%) and significant proportion of other side effects were also recorded.

Of the total participants, 157 (34%) of patients were enrolled after failure of re-treatment and 158 (25%) of them were enrolled after relapse (Figure 1).

Treatment outcome and survival status

A total of 462 MDR-TB patients were followed for different duration until they experience the outcome of interest or the due date of follow up ends; for a minimum of 3 day and a maximum of 780 days with median follow

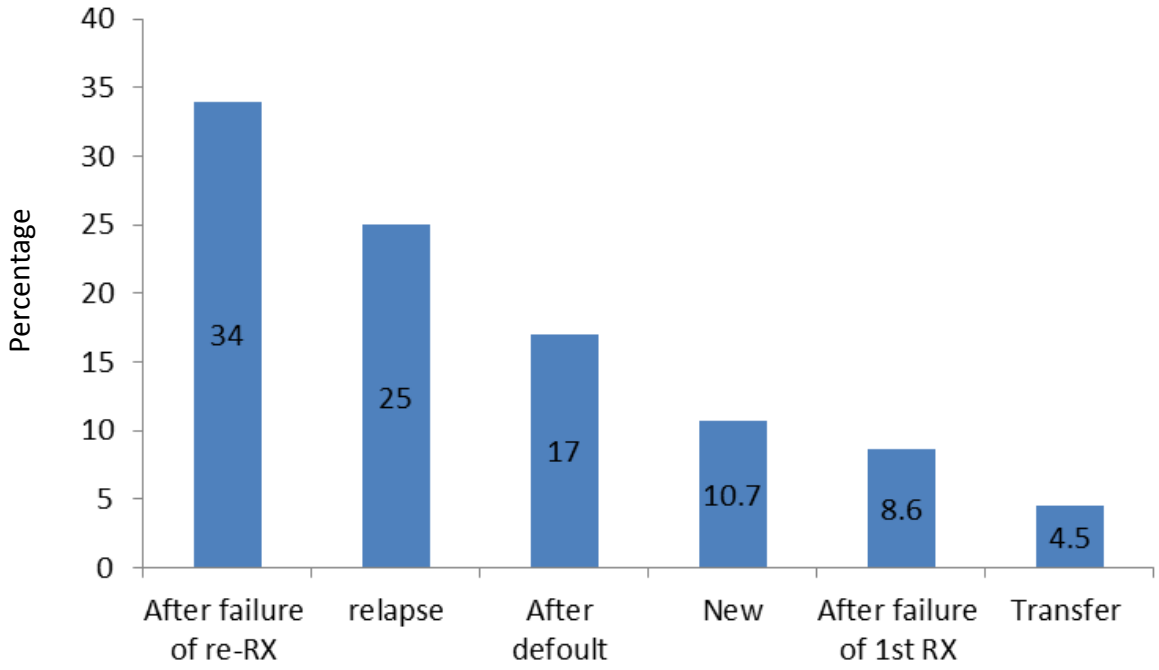

Figure 1. Participant's category of MDR-TB patients in TIC of Ethiopia, 2009-2016.

Table 2. The outcome of Multi-drug resistance treatment in Ethiopia, 2009-2016.

Treatment outcome	Proportion	Percent
Cured	236	51
Completed	70	15.2
Died	38	8.2
Defaulted	60	13
Transferred out	16	3.5
On treatment	42	9.1

up period of 500 (IQR: 211-683) days which give 204,250 person-day of observation or 6808 person month of follow up. Based on this, incidence of death was calculated using person-day of follow up as a denominator for the entire cohort and for particular groups. Within the follow up period, 38 deaths were recorded. Hence, the overall incidence density (IDR) of death in the cohort was 6.79 (95% CI=5.42-8.78) per 100 person year and it was significantly different for categories of predictors. The highest incidence of death was observed in the first five months of treatment and it decreases subsequently.

Of all patients, 306 (66.2%) were successfully treated (either cured or treatment completed), that is, 236 (51%) patients get cured and 70 (15.2%) completed their treatment, while 38 (8.2%) of patients died during treatment (Table 2). Patients were followed for a median of 500 (IQR: 210-683) days on treatment.

The cumulative probability of survival at the end of 1st, 2nd, 3rd, and 4th month was 98.2, 97.3, 95 and 92.2%, respectively with significant difference between categories of variables, while the overall mean survival time was 24.82 (95%CI=22.8-25.72) months. The mean survival time was also significantly different for predictor variables. While the median survival time was undetermined because the largest observed analysis time was censored, the survivor function does not go to zero; in this case the mean is thebest estimate of survival time (Figure 2).

The difference in hazard of death among variables during the course of intervention period was estimated from Kaplan Meier survival curves with log-rank test and significant difference was observed. The survival of

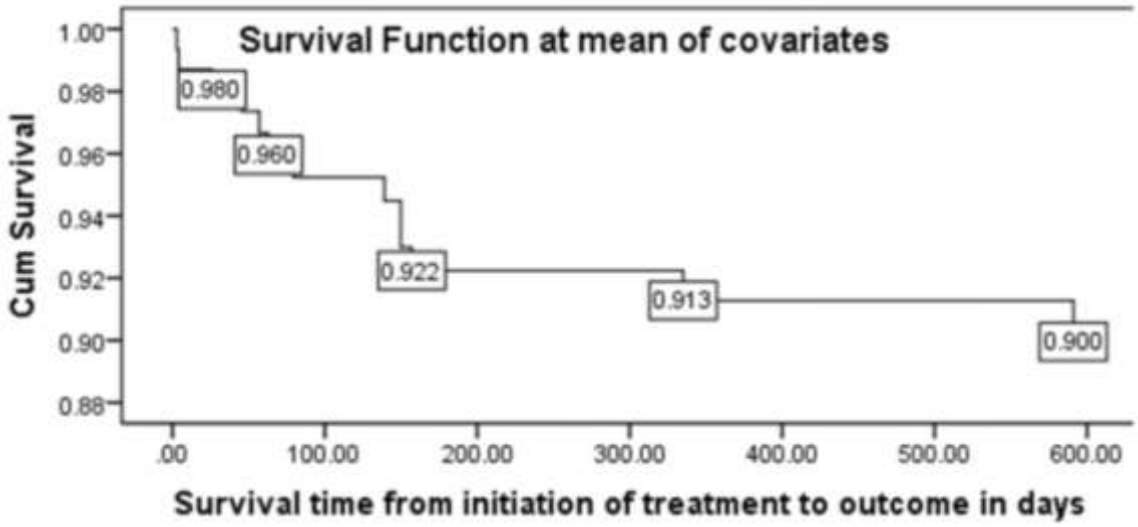

Figure 2. Survival estimate among MDR-TB patients, Ethiopia, 2009-2016.

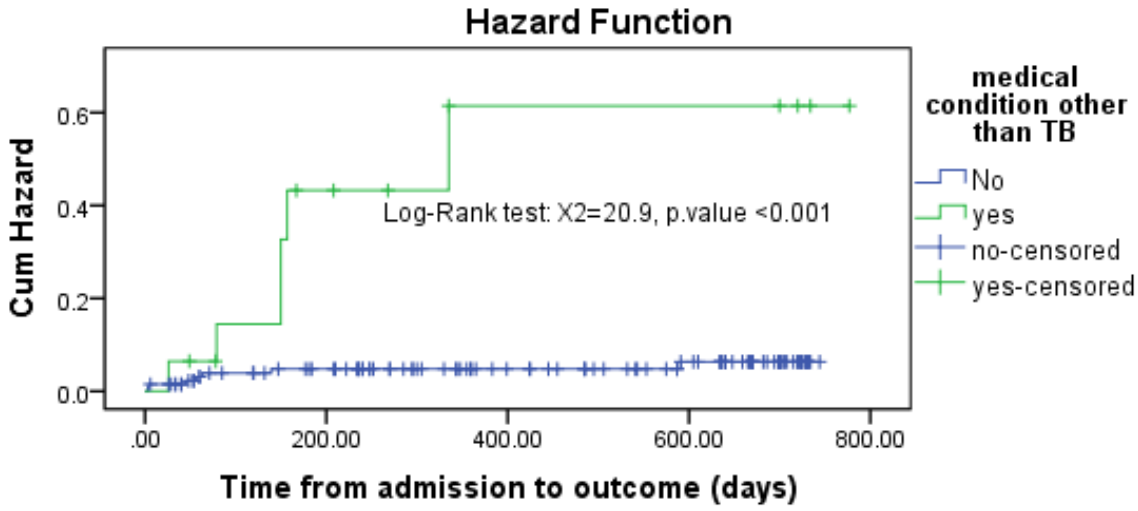

Figure 3. Hazard of death between patients with medical complication and without complication in Ethiopia from 2009-2016.

patients with medical complication was significantly shorter (Figure 3).

Determinants of death (failure)

In bivariate analysis, a significant difference was observed between predictors; Table 3 demonstrates that base line weight (CHR = 0.55, 95% CI = 0.75, 0.88), number of previous treatment episode (CHR = 1.68, 95% CI = 2.5, 5.7), medical condition or complication other than TB and HIV (CHR = 3.1, 95% CI = 1.76, 9.9), HIV sero-positivity (CHR = 2.4, 95% CI = 4.2, 11.6) and presence of side effect (CHR = 2.8, 95% CI = 2.24, 6.15) were associated with mortality. While for multiple Cox regression variables which have p-value of <0.25 in the bivariate analysis, multiple Cox regression was fitted with forward stepwise method. Hence, the following variables were identified as significantly associated with death, death was 3 (95% CI [2.5-4.3]) times higher among patients who developed drug side effect than those who do not have developed side effect. Regarding to patients with medical diagnosis other than TB and HIV were 3.3 (95% CI [1.7-5.6]) times more likely to die than patients without any additional

Table 3. Factors those were significantly associated with death in multiple cox-regression analysis.

Predictor	CHR (95%CI)	AHR (95%CI)	p-value
Sex (male)	1.2 (1.11-5.8)	1.7 (2.2-8.7)	0.04
Drug adverse effect	2.8 (2.24- 6.15)	3 (2.5-4.3)	0.001
Medical diagnosis other than TB/co-morbidity	3.1 (1.76, 9.9)	3.3 (1.7-5.6)	0.001
Baseline Weight	0.55 (0.75-0.88)	0.18 (0.81-0.97)	0.001
HIV sero-positivity	2.4 (4.2- 11.6)	2.7 (3.4-9.11)	0.03

medical diagnosis. Concerning HIV sero-status, the risk of death was 2.7 (95% CI [3.4-9.11]), times higher for HIV sero-positive patients than HIV sero-negative patients. Bigger base line body weight favored the prevention of mortality. Final, body weight increase by 1 kg likelihood of mortality was reduced by 18%.

DISCUSSION

This study has summarized survival status and treatment outcomes from a cohort of multi-drug resistance tuberculosis patients who initiated a treatment in multi-drug resistance tuberculosis patients' referral hospitals and treatment initiation centers of Ethiopia from 2009 to 2016. The overall rate of treatment success was 66.1%. The result is higher than global report (50%) (WHO, 2015; Dennis et al, 2015) study conducted in SNNPR (25.5%) (Girum et al, 2017). But, the study is in line with the MDR-TB treatment success rate recorded in another study conducted in patients from St. Peter Referral Hospitals (Getachew et al, 2013). However, the rate is still far short of the WHO target of 75% treatment success (The Global Planto Stop, 2010).

Accordingly, the probability of survival at the end of the second years in this study was 90%, which is similar to study conducted in Ethiopia (Girum et al, 2017), whereas, higher than a study conducted in Ethiopia, South Africa and Lithuania (Getachew et al, 2013; Hussein et al, 2013; Nkhoma et al, 2012; Ulmasova et al, 2012). This may be due to the fact that in the present study subjects, there were less HIV-infected patients. This study reported that HIV infection is a risk factor for development of MDR-TB. In a previous study, mean survival time was different in different researches due to use of different technique. In this case, extended mean 20 years and restricted mean 2 years were used to describe the mean survival time; however, in others, the extended mean which is appropriate to estimate when larger proportion of population are censored was used.

In this study, the incidence mortality was lower than the report of St. Peter TB Referral Hospital which was 13.3 patients per 100 person year of observation (Getachew et al, 2013). In addition to that, it is lower than many other studies (Macarthur et al, 2014; Isaakidis et al, 2015); however, it is similar with other study finding (WHO, 2003). This may be as a result of difference in the service areas and the time that the care was initiated. Unlike the present case, the first treatment initiation centers which served as a referral centers for long period, during the first phase of management in the first generation hospitals. A larger proportion of patients were dead. But in the second and third generation hospitals, where less complicated cases are managed and treatment program has been simplified; the rate of mortality is also reduced. Such that in the current study, mortality may be less reported. In Ethiopia, treatment success rate was higher (Dennis et al, 2015) than in the present finding. It may be due to higher loss to follow up rate, in which 13% of patients were either lost to follow up or defaulter which markedly reduces the proportion of successful treatments.

Similarly, the risk of death among MDR-TB patients who developed drug side effect in the course of treatment was 3 (2.5-4.3) times higher than those who did not develop any adverse effect. In case of severe complication like toxicity, electrolyte disturbance and RBS disturbance patients may experience fatal outcome and also obliged to withhold the treatment or change regimen which further increase hazard of mortality. It is consistent with several study findings (Farley et al, 2011; Balabanova et al, 2011) in which mortality increases as severe adverse outcomes encountered during treatment.

The risk of mortality among multi-drugs resistance tuberculosis patients was also higher when they have co-morbidities or medical complication other than tuberculosis (Sharma and Mohan, 2006; Meressa et al, 2015). In the current study, the hazard rate of death among patients with co-morbidities or medical complication was 3.3 times higher than patients who have no medical co-morbidity. The national finding indicating the risk of death among co-infection patients was high (Getachew et al, 2013; Meressa et al, 2015). In addition, death was high among patients with adverse outcomes (Cox et al, 2007). The reason might be due to low compliance, lack of intensive care facility and acute adverse outcomes (Girum et al, 2017).

One of the effects of MDR-TB is causing appetite loss which is prone to mal-nutrition and contributing to mortality (WHO, 2011; Orenstein et al, 2009; Farley et al, 2011). In this study as the base line weight increased by

a kilogram, mortality is reduced by 18%, which is consistent with several research findings (Balabanova et al, 2011; Farley et al, 2011; Tang et al, 2013). The reason may be due to comorbidity, which is leading to under nutrition that can affect the body disease resistance and immune system. Finally, it is prone to death.

In line with previous reports, mortality in the course of multi-drugs resistance tuberculosis treatment is largely contributed by co-infection of HIV (Getachew et al, 2013; Dennis et al, 2015; Meressa et al, 2015). Patients who were HIV sero-positive were 2.7 times more likely to die than patients who were sero-negative. Also, this has been evidenced from most recent studies (Getachew et al, 2013; Dennis et al, 2015; Anderson et al, 2013). It might be due incompliance and drug side which increase the hazard of mortality.

The data has been collected by primary trained on MDR-TB treatment professional and who were familiar with treatment guideline and record of treatment. In addition, the collected variables were not biased by knowledge of the subjects' outcomes because predictors were collected at admission, before the discharge outcome was known guaranteeing that the measurement of predictor. However, in this study, one of the primary treatment imitative centers (St. Peter's) refuse to participate. It might affect exact estimation of survival time and treatment outcome because at the beginning survival might be affected by service quality, availability of professional and on time presentation to treatment.

CONCLUSION AND RECOMMENDATIONS

The overall incidence density of death in this study was 8.2% which is lower than several national and international studies' findings. The probability of mean survival time was also comparable with other researches. And also, the probability of survival was consistent with many study finding whereas, outcome of death in early months was high in this study. After controlling the effect of other variables, the presence of drug side effect, medical complication, baseline weight and sero-positivity was predicted mortality from MDR TB during the course of treatment.

Therefore, health professional should establish treatment of all medical co-morbidity early on time. Professional should strengthen patient adherences to ART treatment and hospital principally strengthens professional adherence to MDR-TB treatment guideline. Federal Ministries of Health should establish strategies to avert poor treatment outcome among male group, which might be due to abuse of substance by those group. In addition, health professionals should monitor and report drugs adverse effect early and managing it accordingly. Finally, researcher should conduct others researches on variables not included in this study and prospective design giving policy level recommendations.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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