Assessment of the Survival Status and Risk Factors for the Mortality of Multidrug Resistant Tuberculosis Patients at Adama and Bishoftu General Hospitals, Oromia, Ethiopia.

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This is to certify that this thesis prepared by Debalke Fantaw, entitled: "Assessment of Survival Status and Risk Factors for Mortality of Multidrug Resistant Tuberculosis Patients at Adama and Bishoftu General Hospitals, Oromia, Ethiopia: Retrospective Cross Sectional Study" and submitted in partial fulfilment of the requirements for the Degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the university and meets the accepted standards with respect to originality and quality.

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Abstract

Assessment of Survival Status and Risk Factors for Mortality of Multidrug Resistant Tuberculosis Patients at Adama and Bishoftu General Hospitals, Oromia, Ethiopia.

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Multi-drug resistant tuberculosis is a wide spreading global problem. The magnitude of this disease varies significantly from country to country and the treatment outcomes are inadequately described in Ethiopia. Hence, this study aims to assess the survival status and risk factors for mortality of multidrug resistant tuberculosis patients at Adama and Bishoftu General Hospitals**.** Retrospective cross-sectional study design was conducted among cohorts of multidrug resistant tuberculosis patients treated from May 2013 to August 2017 at Adama and Bishoftu General Hospitals. Data were collected using data abstraction format from 164 patient cards. All patients were used as study participants. Data were analyzed using STATA Version 13 statistical software. Risks were estimated for the entire follow-up time corresponding to each event occurrence using Kaplan-Meier method and the covariates were fitted to Cox Proportional Hazard Regression Model where 164 patients were followed for a total of 63,141 person-days. The median survival time was 400.5 days or 1.1 year. Among 164 patients, 74 (45.10%) were male and the mean age was 31.5 years. There were 30 (18.30%) known deaths and the survival probability of the study participants at 6, 12, 18 and 24 months of treatment was 84%, 82%, 81% and 72%, respectively. In this study: HIV, co-morbidities and co-infections, low initial body weight, age, occupation and Khat use were identified as risk factors for the death of MDR-TB patients. Comparison of these risk factors showed that there is a significant difference in the probability of survival on MDR-TB patients. Cox Regression analysis Model result showed that factors independently associated with mortality of patients were: HIV (HR=2.75,95%CI(1.23-6.15) &P=0.01); low initial body weight(HR=0.44,95% CI(0.22-0.85) &P=0.02); co-morbidities & co-infections (HR=2.28,95% CI (1.99- 5.26) & P=0.05); age (HR=2.3,95% CI(1.35-3.79) & P=0.00); Khat use (HR=0.41, 95% CI (0.18-0.97) & P=0.04); Occupation (HR=1.31,95% CI (1.06-1.63) & P=0.01). In conclusion, a higher death rate was noted in patients who started MDR-TB treatment with initial low body weight, HIV positive, co-morbidities & co-infections, age and Khat user.

Keywords: Multidrug resistant, Rifampicin resistant, survival status, survival probability, Isoniazid resistant, Tuberculosis, Treatment outcome, risk factors.

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List of Acronyms and Abbreviations

ADR	Adverse Drug Reaction
AFB	Acid Fast Bacilli
ALERT	All African Leprosy and Rehabilitation Treatment Centre
CI	Confidence Interval
DF	Degree of Freedom
DRS	Drug Resistance Surveillance
EFMHACA	Ethiopian Food, Medicine, HealthCare and Administration and Control and Authority
Ho	Null Hypothesis
HIV	Human Immuno Deficiency Virus
HR	Hazard Ratio
K-M	Kaplan Meier
MDR- TB	Multi-Drug Resistant Tuberculosis
PH	Proportional Hazard
RR	Rifampicin Resistant
INH/H	Isoniazid
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis

1. Introduction

1.1 Background of the Study

According to World Health Organization (WHO), Multidrug Resistant Tuberculosis (MDR-TB) is defined as tuberculosis caused by *Mycobacterium tuberculosis* that does not respond at least to the first line oral anti-tuberculosis drugs isoniazid (INH) and rifampicin (R) (WHO, 2016). Tuberculosis typically affects pulmonary but it can also affect extra pulmonary (WHO, 2011). The emergence of drug-resistant tuberculosis is a main hazard to global tuberculosis care and control (WHO, 2014).

About 3.7% of new tuberculosis (TB) patients in the world have multidrug-resistant strains (WHO, 2012). MDR-TB is mostly prevalent in India, China, the Russian Federation, Indonesia and Nigeria (WHO, 2016). The global MDR-TB treatment success rate was 52% (WHO, 2016).

Drug-resistant TB is a continuing threat and 490 000 case of MDR-TB were estimated and from this 13000 cases of MDR-TB were detected and reported in the world. The latest anti-TB drug resistance surveillance data show that 4.1% of new and 19% of previously treated TB cases in the world is estimated to have rifampicin- or multidrug-resistant tuberculosis (MDR/RR-TB) (WHO, 2017).

MDR-TB treatment consists of two phases: Intensive and continuation phase. Intensive phase that refers to the initial period of treatment when maximal bacillary load reduction is aimed and this period is noted by the presence of an injectable drug (WHO, 2011).

The recommended duration of administration of the injectable agent is guided by smear and culture conversion and an intensive phase of 8 months is suggested for most patients and the duration may be modified according to the patient's response to therapy (WHO, 2011).

While Continuation phase refers to the period where the injectable drug is discontinued and patients continue to take oral drugs. The duration of treatment is guided by culture conversion. The injectable should be continued for at least eight months and at least four months after the patient becomes culture-negative (EMOH, 2013).

Although there is a paucity of data on the prevalence of multi-drug resistant tuberculosis, study conducted in south African children revealed that the prevalence of MDR-TB and The isoniazid-resistance TB were 14.2% ,8.8% respectively (Fairlie *et al*., 2011). Moreover, a retrospective study conducted in China from 2006–2015 showed that 6.9% of the study participants had MDR-TB and 18.9% had DR TB (Tao *et al*., 2017). However, in Russia the prevalence of MDR-TB was extremely high: new cases (26.0%) and previously treated cases (72.9%) were resistant to at least INH and R (Makinen *et al*., 2011).

A study conducted in California from 1993–2002 on TB patients demonstrated that 10% were resistant to INH, 1% were resistant to RR and 1% were resistant to both drugs LoBue and Moser (2005). A systematic review done by Biadglegne e*t al* (2014) indicated that the prevalence of MDR-TB in Ethiopia ranges from 3.% - 46.3%.

In Lithuania risk factors related to poor treatment outcome on MDR-TB includes: being younger age, urban living, known TB contact and alcohol abuse (Manissero *et al*., 2010). In Estonia HIV positive and prior history of TB treatment associated with the poor MDR-TB treatment outcomes Kliiman and Altraja (2009). In Oromia Regional State of Ethiopia being farmer, known contact history with TB patients, alcohol use, HIV positive, previous known TB history were significantly associated with MDR-TB treatment outcome (Mulisa *et al*., 2015).

1.2 Statement of the Problem

TB is the 9th leading cause of death worldwide and the leading cause among infectious agents, ranking above HIV/AIDS (WHO, 2017). Ethiopia ranked at 27th among 30 high MDR-TB burdened countries in the world (WHO, 2015). MDR-TB is one of the leading causes of mortality in Ethiopia (EMOH, 2015). The prevalence of MDR-TB in Ethiopia was ranged from 3.3% - 46.3% (Biadglegne *et al*., 2014). A facility based cross-sectional study was conducted in forty three public health facilities in Eastern Amhara Regional state of Ethiopia and the overall prevalence of drug resistance to at least a single drug was 33.5%(Esmael *et al*., 2014).

A cross-sectional study done at West Armachiho and Metema districts of Amhara Region showed that the overall prevalence of MDR-TB was 5.7 % (Mekonnen *et al*., 2015). A study conducted by Getachew *et al* (2013) at St. Petros Hospital, the survival probability of MDR-TB patients at 6, 12, 18 and 24 months of treatment was 88.5%, 85.8%, 82.7% and 79%, respectively. In this study : HIV positive, smoking behaviours, co-morbidities and clinical complication as the main factors for difference in the probability of surviving during treatment (Getachew *et al*., 2013).

Another study conducted in Ethiopia at ALERT centre and Gondar University Hospital revealed that 37(10.8%) were died before the end of the follow-up period and the median survival for MDR-TB patients was 16 months and in this study: presence of clinical complications; resistance to INH, R, Ethambutol, streptomycin, kanamycin, Amikacin and Capreomycin; smoking; body weight and age were significant risk factors for mortality Molalign and Woncheko (2015). In North west Ethiopia non-adherence to the first line anti-TB treatment was significantly associated with MDR-TB (Adane *et al*., 2013).

According to the Federal Ministry of Health and WHO annual report, the occurrence and poor treatment outcome of MDR-TB in Ethiopia is very high and it has significant influence on productivity (EMOH, 2015).

Although the Government of Ethiopia and different stakeholders were working on reduction of MDR-TB, it is still burning public health concern in Ethiopia. Hence, this study aimed to assess the survival time and risk factors for mortality in multidrug resistance tuberculosis patients at Adama and Bishoftu general hospitals, Oromia, Ethiopia.

1.3. Literature Review

1.3.1 The Epidemiology of Multidrug Resistant Tuberculosis

The WHO report showed that 170,000 deaths due to MDR-TB occurred globally (WHO, 2014).The occurrence of MDR-TB in Switzerland was 33.8% among new case-patient (Sanchez-Padilla *et al*., 2012). MDR-TB case in Nigeria among new and previously treated cases was 6.0% and 32.0% respectively (Onyedum *et al*., 2017). Similar study done in Nigeria on MDR-TB and resistant to R, INH , 6.6%, 2.7% ,were respectively (Uzoewulu *et al*., 2014). The highest MDR-TB rate among urban settings, namely, Addis Ababa (7.1%) and Hariri (6.8%) (EMOH, 2015).

In a cross-sectional study conducted in West Armachiho and Metema Amhara Regional State in 2014 showed that the overall prevalence of MDR-TB was 5.7% and the prevalence of MDR-TB among new and previously treated cases was 2.3% and 13.9%, respectively (Mekonnen *et al.*, 2015).

1.3.2 Risk Factors for Multidrug Resistant Tuberculosis

In one study conducted in Thailand by Chuchottaworn *et al* (2015) being more than two episodes of earlier TB history, duration of illness more than two month, AFB more than three times, presence of lung cavities and presence of pleural effusion identified as risk factors for poor treatment outcome of MDR-TB .Another study done in chain showed that active TB treatment more than 8 months , greater than three prior anti-TB treatment and more than three TB foci in the lung were identified as risk factors (Chen, *et al*., 2013).

A study done in Oromia Regional State in Ethiopia indicated that an occupation of farming, known TB contact history, alcohol use, exposed to HIV infection, previous known TB history were risk factor for MDR-TB (Mulisa *et al*., 2015).

1.3.3 The Treatment Outcome of Multidrug Resistant Tuberculosis

MDR-TB treatment requires prolonged use of multiple second-line anti-TB drugs, which are more expensive and toxic than first-line drugs, nonetheless less efficacious Leimane and Leimans(2006). The treatment outcome of MDR-TB patients in South Africa with HIV had a higher hazard of death (HR: 2.33, P<0.0001) and Low baseline weight was also associated with a higher hazard of death (HR: 2.52, P<0.0001) (Farley *et al*., 2011).

The proportion of MDR-TB patients who successfully completed treatment varied from 44% in Eastern Mediterranean Region to 58% in South East Asia Region. The Global Plan's target for 2015 of achieving at least 75% treatment success in MDR-TB patients was only reached by 30 out of 107 countries (WHO, 2012).

Previous study in Portugal showed that the treatment outcomes of patients with MDR-TB and XDR-TB was 66% and 52%, respectively (Oliveira *et al*., 2013). Systematic review and meta-analysis conducted in 21 countries on MDR-TB and the treatment outcome was poor as compared to drug sensitive TB patients (Johnston *et al*., 2009).

One study in India on MDR-TB patients showed that 43(29.7%), 48 (33.10%), 8(5.5%) cured, completed their treatment and died respectively(Patel *et al*., 2016).Systematic review and Meta analysis was done on primary research and the percentage of successful treatment outcome was reported for 81.9 % Harris (2016). Study conducted in France on MDR-TB patients showed that the median survival time was 31 months Flament-Saillour(1999). In another study in UK discovered that median survival time was 46 months (Drobniewski *et al*., 2002).

1.3.4 Drug Susceptibility Testing service in Ethiopia

Different WHO-approved DST techniques are recommended to be used for Screening of drug resistant strains from samples of drug resistant -TB cases. However, the choice of the DST technique in field depends on the simplicity and applicability of the procedure, infection control precaution level and result turn-around time (EMOH, 2013). The Gene- Xpert/ MTB/ RIF assay, which enables simultaneous detection of Mycobacterium tuberculosis (MTB) and rifampicin (RIF) resistance, was endorsed by WHO in December, 2010.This assay was specifically recommended for use as the initial diagnostic test for suspected drug-resistant or HIV-associated pulmonary tuberculosis(Lawn *et al*.,2013).

In Ethiopian context, Gene Xpert for Mycobacterium tuberculosis with 2 hours and rifampicin resistant also detected with 2 hours and the preferred method considering the suitability for use at health facility level, the rapid turnover time of results, and minimal need for expertise & infection control precautions. However, Line probe Assays and conventional DST techniques will continue to be used at reference laboratory (EMOH, 2013).Another method for drug susceptibility testing and mycobacterium detection that is available in Ethiopia called line probe assay and Line probe Assay(LPA) is preferred diagnostic test for reference laboratory At reference laboratory, direct smear microscopy must be done from

samples to decide whether to directly perform LPA, in case of positive smear results, Do the LPA indirectly if MTB grows on culture after negative smear result and If the LPA result shows resistant to R and H, or R only, patient must be treated with second line drug (EMOH, 2013).

2. Objective

2.1 General Objective

- Assessment of survival status and risk factors for mortality of multidrug resistant tuberculosis patients at Adama and Bishoftu General Hospitals, Oromia, Ethiopia.

2.2 Specific Objectives

1. To compare survival risk of MDR-TB patients between different exposures.
2. To determine the hazard rate among patients under MDR-TB treatment.
3. To investigate risk factors for lower survival probability of patients under MDR-TB treatment.

3. Methodology

3.1 Study Setting

Adama and Bishiftu General Hospitals are the two additional hospitals in Oromia Regional State that provide MDR-TB treatment. MDR-TB treatment started at the study settings on May 2013. At the two hospitals, no study was previously conducted to assess the survival time of MDR-TB patients and associated risk factors for their mortality.

In Adama Hospiatal one medical doctor and two nurses provided MDR-TB treatment. Similarly, two medical doctors and three nurses were also provided MDRTB treatment at Bishoftu General Hospital.

3.2 Study Design and Period

Retrospective cross-sectional study design was conducted among cohorts of MDR-TB patients under second- line treatments that were started treatment from May 2013 up to August 2017.

3.3 Population

3.3.1 Source population and Study participants

The source population were all MDR-TB patients who started at Adama and Bishoftu General Hospitals. When the study populations are confirmed with MDR-TB at the two hospitals and started treatment with second- line drugs in these hospitals and fulfil inclusion criteria.

3.3.2 Inclusion and Exclusion Criteria

Inclusion Criteria includes:

- ✓Patients who were confirmed MDR-TB by smear microscopy and culture, and started treatment
- ✓Patients who have clinical sign and symptom of MDR-TB and started treatment

Exclusion Criteria:

- ✓Patients not started second line MDR-TB treatment
- ✓XDR-TB patients

3.3.3 Sample Size and Sampling Procedures

The numbers of patients in the two hospitals were small as a result; all the patients who started MDR-TB treatment were included in the study to increase the precision of the result. Thus, among 168 MDR-TB patients at both hospitals, only 164 study participants were eligible: 145 from Adama and 19 from Bishoftu Hospital. Based on this assumption, all of 164 patients, who were on treatment with second line anti-tuberculosis drugs were used as a sample for this study.

3.4 Study Variables

Outcome Variable:

- The outcome variable in the study was time to death.

Independent variables

- **Socio-demographic Factors**: Age, sex, religion, occupational status, initials weight of the patients, educational status, marital status, smoking, khat and alcohol use status;
- **Clinical Variables**: Tuberculosis treatment history, site of tuberculosis (pulmonary and extra pulmonary or both, HIV co-infection and other co morbidities and the type of drug resistance at baseline, the types of adverse drug reaction occurred after treatment.

3.5 Data Collection

Data were extracted from the patient follow up records using the structured data extraction format. Five percents of the data collection format were pretested at the study setting and some data were not correctly recorded on the patient's card and the data collection formats were modified, only full data was taken from the patient's card. Data were extracted from the patient's card using three nurses who were working in MDR -TB centres and supervised by principal investigator. Variables with socio-demographic characters, clinical factors, treatment outcome event started and event occurrence time were recorded on the questionnaires from the patients' card.

3.6 Data Quality Assurance

Training was given by principal investigator for data collectors on how to collect data. On-site supervision and feedback was given on daily basis for data collectors by principal investigator. The data were checked on daily basis for consistency, completeness, clarity and accuracy. Five percent of the total checklist was refilled and ten percent of the data was

double-entered to check for its accuracy. The data was entered in to a computer protected by password to maintain the confidentiality, checking for completeness and coding was done.

3.7 Data Management and Data Analysis

Time to death was the outcome variable that was measured and coded as 1 for dying and 0 for censored. The patients surviving till the end of the cohort study contributed a censored case. Censorship includes cured, treatment completed, treatment failure, and transfer out/in, lost to follow up and study time completion.

Time to event data (survival probability) was calculated by subtracting date of event occurred from date of treatment started. Some of the continuous variables were categorized for the ease of Cox-proportional hazard regression model and age was considered as time dependent covariate.

Data was analysed using STATA Statistical package, Version 13.0. Hazard ratio with 95% CI and two-sided test of significance were used to measure the association of dependent and independent variables. Survival express over the follow up time was described using the Kaplan- Meier (KM) survival curve and life table. The covariates were fitted to Cox proportional hazard regression model.

Risk on survival curve was estimated for the entire follow-up time corresponding to each event occurrence using Kaplan-Meier survival and life table estimate method. Survival curves were compared between different exposure groups using log-rank test (Chi-square test with 1df under Ho).

To track survival patterns of the patients, a Cox proportional hazard regression model which is the most commonly used multivariable approach for analysing of survival time data was used. In real life, the rate or risks of death or events are often not constant but change over time; 'robust' so that closely approximates parametric model. This method estimates semi-parametrically the distribution of exposure time (months lived) to the likelihood of a patient dying at time t. Covariates were then allowed to shift this baseline proportionally:

h (t) = h o (t) Expo (βiXi), where, ho (t) is the baseline hazard function, Xi is a vector of covariates, and Expo βi is the relative risk(hazard rate) associated with the i^{th} explanatory variable.

This model was chosen because it can handle censored such as cases with incomplete exposure i.e. alive patients Gogtay and Thatte (2017). Model selection was based on

Collette's Model selection approach. This approach assumes that all variables are considered being on an equal footing and there is no a priori reason to include any specific variables.

Approach:

1. Fit univariant model for each covariate and identified the predictor significant at 0.2 levels.
2. Fit a multivariable model with all significant Univariant predictors and use backward selection to eliminate non significant variables at 0.1 levels.
3. Starting with final model step (2), consider each of the non significant variables from step (1) using forward selection, with significance level 0.1.
4. Do final extract of main effects model (omit variables that are non significant, add any that are significant), using stepwise regression with significance level 0.05. At this stage, it also considers adding interactions between any of the main effects currently in the model, under the hierarchical principle.

3.8 Operational Definitions

Multi-drug-resistant Tuberculosis: - Multidrug-resistant TB (MDR-TB) is caused by Mycobacterium tuberculosis organisms that are resistant to the most effective anti-TB drugs called isoniazid and rifampicin (WHO, 2012)

Extensively drug resistant TB: - is a form of TB caused by organisms that are resistant to isoniazid and rifampicin (i.e. MDR-TB) as well as any fluoroquinolone and any of the second–line anti-TB injectable drugs such as Amikacin, kanamycin or capreomycin (WHO, 2012)

Primary drug resistance:-Primary or initial drug resistance means that a person has been infected with a drug-resistant TB strain(WHO,2014).

Pulmonary drug resistant TB: Drug resistant tuberculosis involving the lung parenchyma.(EFMOH,2013)

Extra pulmonary TB: Drug resistant tuberculosis involving organs other than the lungs(EFMOH,2013).

New MDR-TB: A patient who has received no or less than one month of anti-tuberculosis treatment(EFMOH,2013).

Transfer in: A patient who has been transferred from another treatment site to continue MDR-TB treatment(EMOH,2013).

Sputum conversion: is defined as two sets of consecutive negative smears and Cultures, from samples collected at least 30 days apart. The date of collection for the first sample is considered as the date of conversion(EMOH,2013).

Acquired drug resistance: Acquired drug resistance is the result of inadequate, incomplete or poor treatment quality that allows the selection of mutant resistant strains(WHO,2014).

Died: A patient who dies for any reason during the course of treatment(WHO,2014).

Censored: When the outcome of interest has not been observed for an individual this includes:

Cured: Treatment completed according to Ethiopian Ministry of Health (national) recommendation without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase(EMOH,2013).

Treatment Completed: Treatment completed according to national recommendation without evidence of failure but no record that three or more consecutive cultures taken at least 30 Days apart are negative after the intensive phase (EMOH, 2013).

Treatment success: The sum of cured and treatment completed(WHO,2014).

Treatment Failure: Patient who is sputum smear/culture positive at end of the treatment (18 – 24 months)

Transfer Out: Patient who has been transferred to another referral centre and for whom the treatment outcome is not known.

Lost to follow-up: A patient whose treatment was interrupted for two consecutive months or more and disappear from the treatment site (WHO,2014).

Cohort: Group of patients diagnosed and registered for MDR-TB treatment.

Mono drug resistant: Resistant to one first-line anti-TB drug only.

Rifampicin-resistant TB (RR-TB): Refers to TB strains that are considered eligible for treatment with MDR-TB regimens(WHO, 2016).

Poly-drug resistance: resistance to more than one first-line anti-TB drug (other than both Isoniazid and Rifampicin).

Drug-susceptibility testing (DST): Refers to in vitro testing using either phenotypic methods to determine susceptibility or molecular techniques to detect resistance-conferring mutations to a particular medicine(WHO, 2016).

Bacteriological confirmed TB : is one from whom a biological specimen is positive by smear microscopy, culture or (such as Gene X-pert MTB/RR)(EMOH, 2013).

Clinically diagnosed/suspected MDR-TB: is one who does not fulfil the criteria for bacteriological confirmation MDR-TB but has been diagnosed with MDR-TB by a clinician or other medical practitioner who has decided to give the patient a full course of MDR-TB treatment(WHO, 2014).

3.9 Ethical Consideration

The Ethical clearance was obtained from School of Pharmacy Ethical Review committee, Addis Ababa University. The permission to conduct research was also obtained from Adama and Bishoftu General Hospitals. Neither photocopied nor removed documents from the patients card at the hospitals; hence, the privacy and confidentiality of individual patient/and document was maintained absolutely.

4.Results

4.1 Socio-demographic Characteristics

As shown in Table 4.1, among 164 study participants, most of them 90(54.90%) were females and 113(68.90%) were between 18-43 years of age. The mean age of the study participants was 31.5 years and majority 88(53.70%) were urban residents. In terms of the educational classification of the study participants: 77(47.00%), 76(46.30%), 11(6.70%) were illiterate, read and write; elementary, junior and high school; diploma and degree level, respectively. In terms of occupational also, 34(20.70%) were employed. On the other hand, 31(18.95%), 22(13.41%), 36(21.95%), 26(15.85%) were daily labours, farmers, students and housewives, respectively. Regarding to social drug use, 33(20.10%) and 16(9.80%) patients were Khat and alcohol users, respectively.

Table 4.1:The Socio-demographic Characteristics of MDR-TB Patients at Adama and Bishoftu General Hospitals.

Socio-demographic Characteristics		Numbers (%)
Gender	Male	74 (45.10)
	Female	90(54.90)
Marital status	Ever married	94(57.30)
	Never married	70(42.70)
Age in years	Below 18	18(11.00)
	18-30	76(46.30)
	31-43	37 (22..60)
	>=44	33(20.10)
Educational Status	Illiterate ,read and write	77(47.00)
	Elementary, Junior &High school	76(46.30)
	Diploma and Degree level	11(6.70)
Residence	Urban	88(53.70)
	Rural	76(46.30)
Occupational status	Employed	34(20.70)
	Daily labours	31(18.95)
	Farmers	22(13.41)
	Students	36(21.95)
	House Wives	26(15.85)
	Others	15(9.14)
Social drug use	Non user	103(62.80)
	Khat	33(20.10)
	Alcohol	16(9.80)
	Smoker	12(7.30)

4.2 Clinical Characteristics of the Study Participants

As shown in Table 4.2 below, among the total study participants at base- line RR were 126 (77.00%) While resistant to R and H were 35(21.30%) and 137(83.50%) were treated active TB before MDR-TB treatment started; although 27(16.50%) patients were no previous tuberculosis treatment history. From 164 study participants 157(95.70%) were diagnosed and treated for pulmonary MDR-TB; 39(23.78%) patients were HIV positive.

Table 4.2: The Clinical Characteristics of MDR-TB Patients at Adama and Bishoftu General Hospitals.

Clinical Characteristics	Numbers (%)
Types of MDR-TB	
Pulmonary	157(95.70)
Extra pulmonary	7(4.30)
History of TB treatment	
Treated before	137(83.50)
Not treated before	27(16.50)
Method of drug resistant detected	
Genexpert	133(81.10)
Line Probe Assay	30(18.30)
Clinical suspected	1(0.60)
Type of drug resistant	
R	126(77.00)
H and R	35(21.30)
RHE/S	2(1.10)
HIV status	
Negative	125 (76.22)
Positive	39(23.78)

RR=Rifampicin Resistant, H=Isoniazid Resistant, E=Ethambutol, S=streptomycin.

As showed in Table 4.3, MDR-TB patients mostly exposed for co-morbidities and co-infections were identified. Of the total 164, 39(23.78%) were HIV positive while 11(6.71%) study participants were exposed for both HIV and other co-morbidities and co-infections. Co-morbidities and co-infections other than HIV were type II diabetics and hypertension and pneumonia were 12(7.31%) and 6(3.66%), respectively.

Table 4.3: The type of Co- morbidities and co-infections on MDR-TB patients at Adama and Bishoftu General Hospitals .

		HIV		
Co-morbidities and co-infections		Negative	Positive	**Total**
Negative		110	28	138
Positive		15	11	26
Total		125	39	**164**
Type of co-morbidities and confection	**Numbers (%)**			
Type II diabetes and Hypertension	12(7.31)			
Pneumonia	6(3.66)			
Anemia	4(2.44)			
Congestive heart failure and Cor-pulmonal	4(2.44)			
Total	26(15.85)			

4.3 Types of Adverse Drug Reaction Occurrences

As shown in Table 4.4 below, 53(32.31%), 20 (12.19%), 6(3.64%) and 3(1.82%) patients developed drug induced gastric manifestation, hypo-kalmia, peripheral neuropathy, hearing impairment and respectively.

Table 4.4: The type of adverse drug reaction occurred on MDR-TB patients at Adama and Bishoftu General Hospitals.

Types of adverse drug reactions occurred	**Numbers(%)**
Drug induced gastric manifestation	53(32.31)
Hypo kalmia	20(12.19)
Drug induced psychosis	3(1.82)
Hearing impairment	3(1.82)
Peripheral Neuropathy	6(3.64)
Renal toxicity	3(1.82)
Drug induced hepatitis	2(1.22)
Hypothyroidism	1(0.61)

4.4 Treatment Outcomes of the Study Participants

Treatment outcome of the study participants as shown in Figure 4.1,30(18.30%), 103(62.80%), 22(13.41), 4(2.44%) and 5(3.05%) patients were died, cured, transferred out, treatment completed and lost to follow-up, respectively.

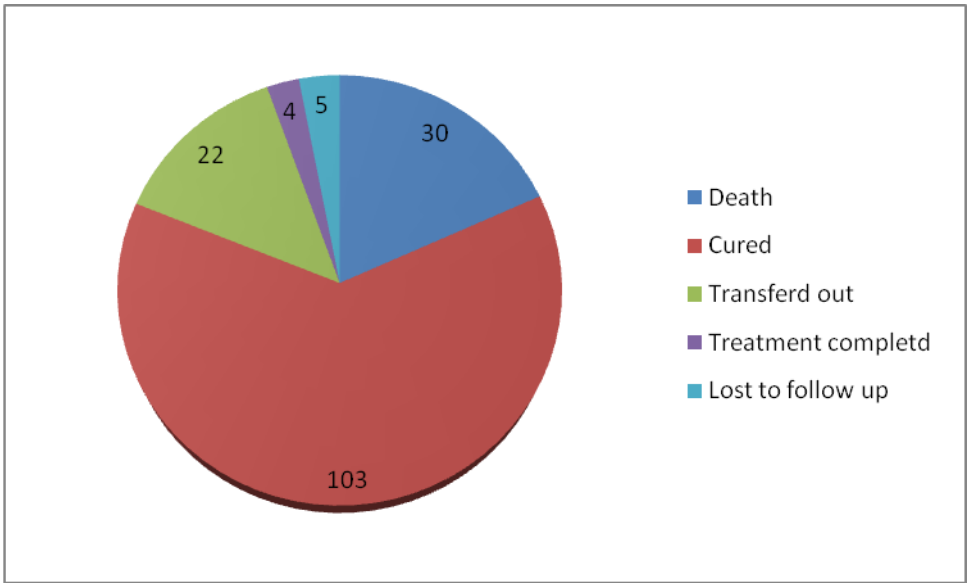

Figure 4.1: The treatment outcome of the MDR-TB patients at Adama and Bishoftu General Hospitals .

4.5 Univariate analyses of Independent Variables

Table 4.5 shows the covariates or explanatory variables. The Table indicates that HIV positive patients were 216% times more likely to die than other patients during MDR-TB treatment (HR=3.16, 95% CI (1.22-8.22) & P=0.02). Co-morbidities and co-infections were also identified as risk factors for poor treatment outcome. In this study, MDR-TB patients who had been exposed to low initial body weight were 60% times more likely to die than other study participants with evidence of (HR=0.40, 95%(0.19-0.79) &P=0.01).

Table 4.5: Analysis of covariates or predictors variables associated with risk of death during MDR-TB treatment at Adama and Bishoftu General Hospitals.

	P-value	CHR	95% CI for CHR	
			Lower	Upper
Sex	0.35	0.68	0.29	1.54
Residence	0.2	1.79	0.74	4.35
Tobacco	0.29	0.42	0.08	2.09
Alcohol	0.10	3.70	0.77	17.89
Khat	0.1	0.39	0.13	1.19
Site of Tuberculosis	0.98	0.00	0.00	.
Treated for active TB	0.24	1.88	0.66	5.33
First line drug resistant	0.90	0.95	0.44	2.07
HIV	0.02	3.16	1.22	8.22
Co-morbidities &co-infections	0.14	1.91	0.81	4.51
occupation	0.07	1.25	0.98	1.60
Education	0.61	0.83	0.40	1.72
Adverse drug effect	0.36	0.67	0.29	1.57
Age of patients	0.01	2.03	1.17	3.53
Initial weight of the patients	0.01	0.40	0.19	0.79

CHR= Crude Hazard rate, 95% CI (confidence interval)

In Figure 4.2 x-axis shows HIV status and y-axis shows survival probability of MDR-TB patients. As depicted in the figure, MDR-TB with HIV positive patients has less survival probability in time as compared to HIV negative MDR-TB patients. However, both MDR-TB with HIV negative and positive patients' survival probability decreases as days of treatment increases and beyond about 600 days it becomes flat.

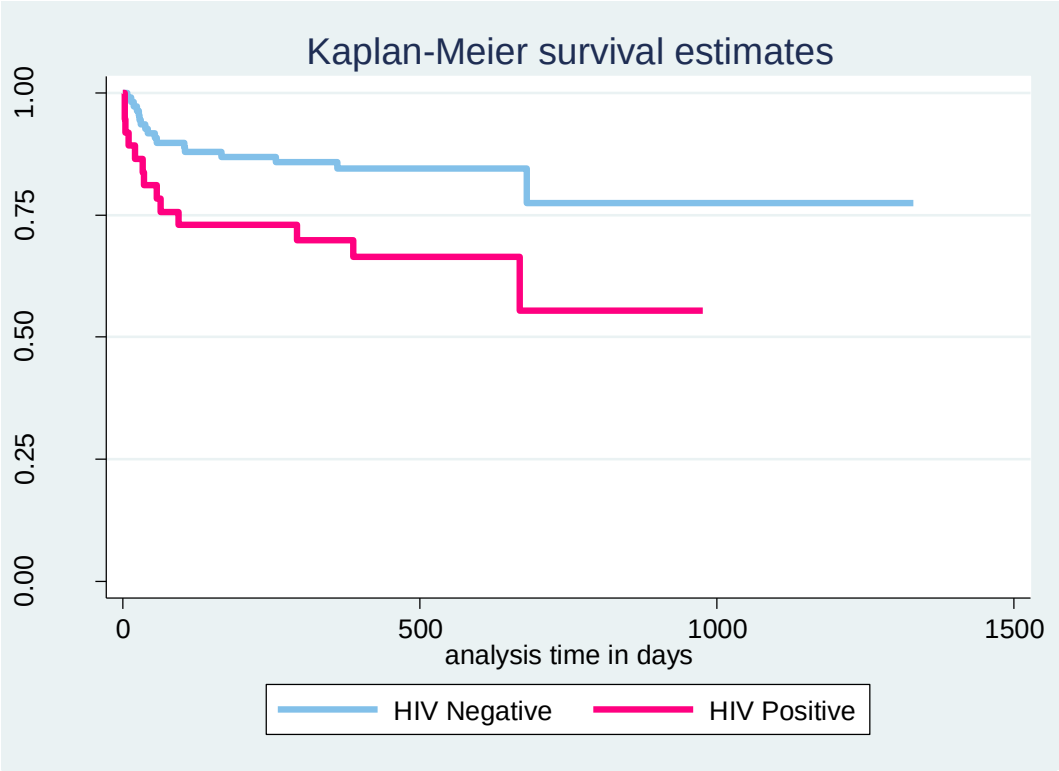

Figure 4.2: Kaplan-Meier survival estimate among HIV sero-positive and sero-negative MDR-TB patients at Adama and Bishoftu General Hospitals.

As shown in the Figure 4.3 below, x-axis shows the Khat used status and y-axis shows survival probably of MDR-TB patients, there was high death of MDR-TB patients that used Khat when compared with not Khat users. The incidence of death on used Khat and not used Khat was 7.1 and 4.2 per 10,000 populations, respectively.

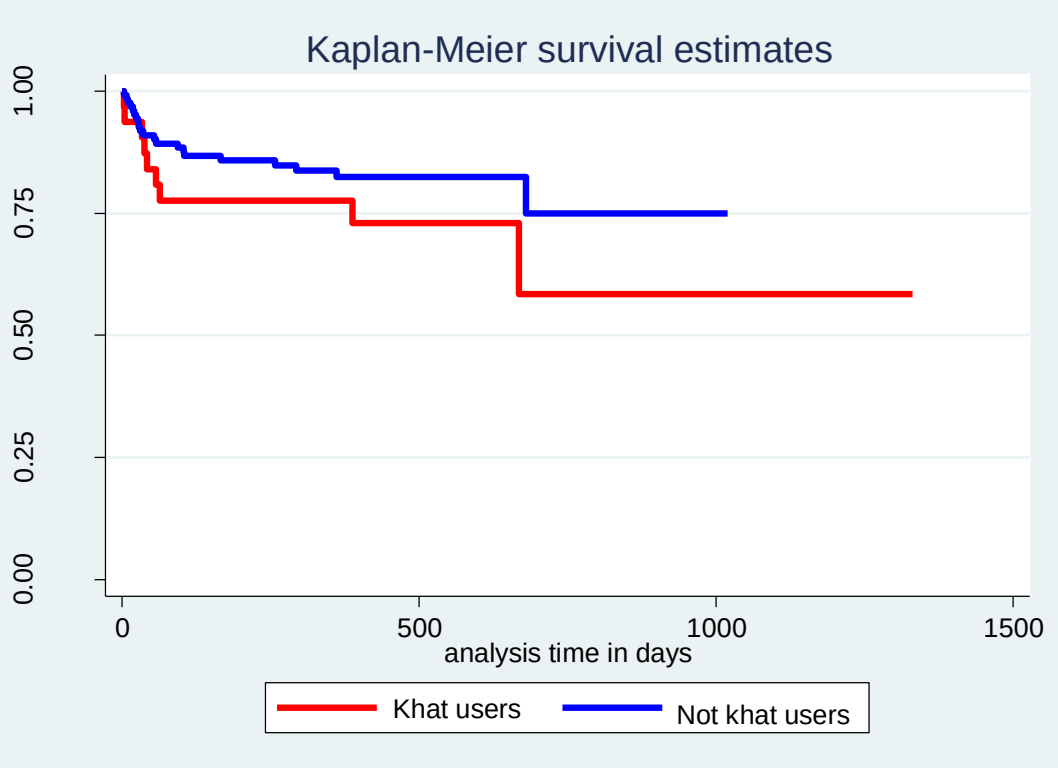

Figure 4.3: Kaplan-Meier survival estimate among MDR-TB patients who used Khat and not used Khat at Adama and Bishoftu General Hospitals.

Figure 4.4 x-axis shows age of MDR-TB and y-axis also survival probability of patients based on their age. Patients between 31-43 years of age die more than below 18 years because the incidence of death less than 18 years, 18-30 years, 31-43 years and >=44 years of age is 3.3, 3.8, 5.2 and 7.03 per 10,000 population, respectively and age of the patients was increase, the likely to die also proportionally increases.

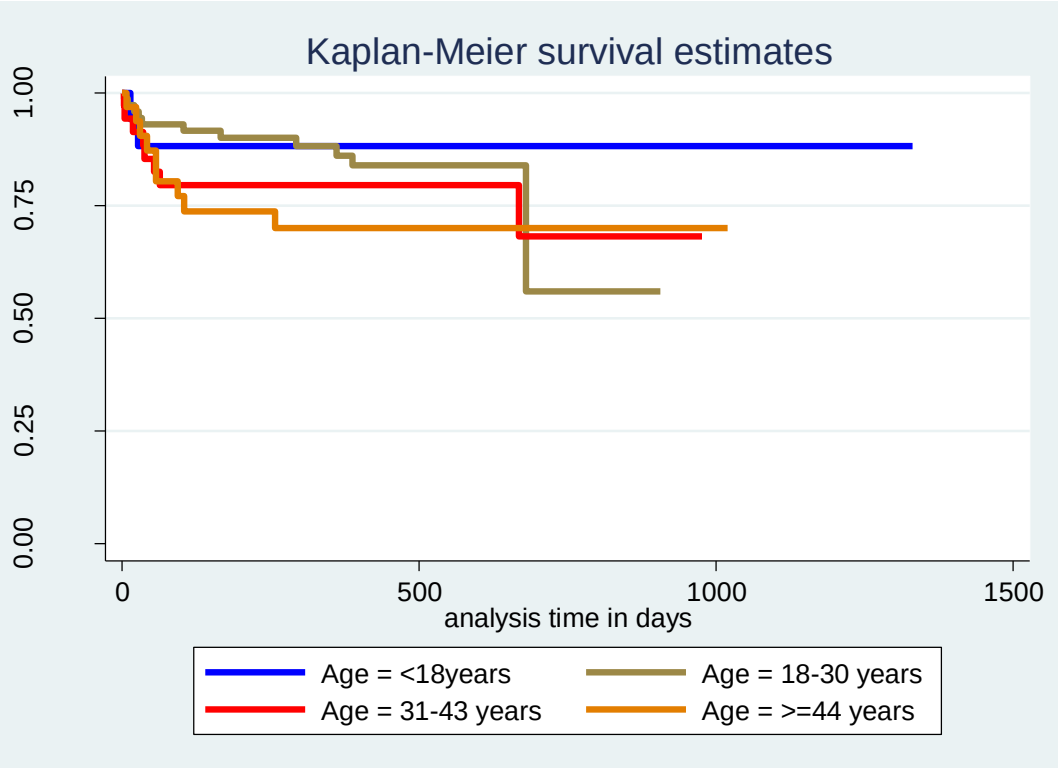

Figure 4.4: Kaplan-Meier survival estimates of MDR-TB patients based on age at Adama and Bishoftu General Hospital.

Figure 4.5 shows the survival probability of MDR-TB patients based on initial body weight. The initial mean body weight of the study participants was 45.85kg. The incidence of death weight less than 30kg, between 30-45 kg and 46-60kg and greater than 60kg were 3.2, 8.2, 2.5 and 1.6 per 10,000 populations, respectively. Study participants whose weight was more than 46kg had been survived more than others; on the other hand, high death was available between 30-45 kg.

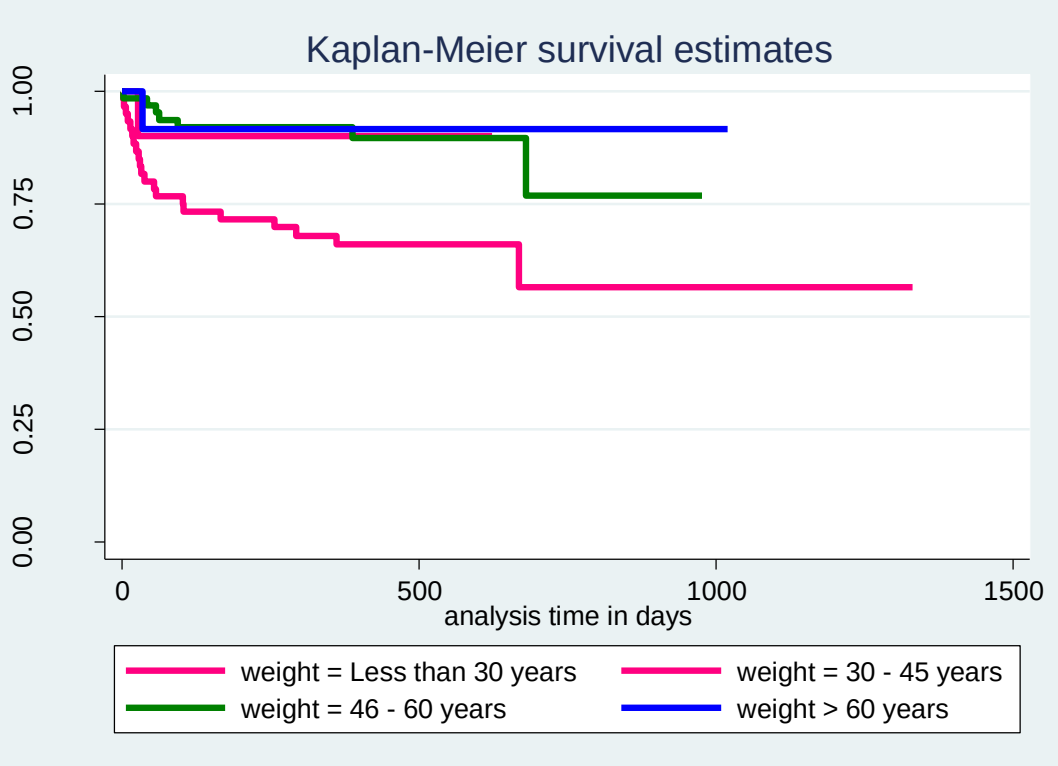

Figure 4.5: Kaplan-Meier survival estimates of MDR-TB patients based on initial body weight of MDRTB patients at Adama and Bishoftu General Hospitals.

As shown in Table 4.7. The survival probability of MDR-TB patients decreased when the treatment time increased. The survival probability at 6, 12, 18, 24 month was 84%, 82%, 81% and 72%, respectively.

Table 4.7: Overall survival estimate from life table on MDR-TB patients at Adama and Bishoftu Hospitals.

Time interval based on date	Cumulative proportion surviving at the end of interval (100%)
180	84%
360	82%
540	81%
720	72%

4.6 The Types of Risk factors for the Mortality of the Study Participants

According to Cox-regression analysis results, initial body weight of the study participants was the predictor for death and it was statistically significant (P=0.02). HIV sero-positive study participants had less survival probability and approximately three times likely to die as compared to HIV sero-negative study participants as shown in Table 4.6 below:

Table 4.6: The type of risk factors for the mortality of MDR-TB patients at Adama and Bishoftu General Hospitals.

			95.0% CI for AHR	
	P-value	AHR	Lower	Upper
Initial weight	0.02	0.44	0.22	0.85
Age of patients	0.00	2.26	1.35	3.79
occupation	0.01	1.31	1.06	1.63
Co -morbidities &co-infection	0.05	2.28	1.99	5.26
HIV status	0.01	2.75	1.23	6.15
Khat	0.04	0.41	0.18	0.97

AHR: Adjusted Hazard rate & 95% confidence intervals (CI)

5. Discussion

The objective of this study was to evaluate the survival status and identify risk factors for the mortality of MDR-TB patients at Adama and Bishoftu General Hospitals. The mean age of the study participants was 31.5 years which is younger than other cross-sectional study conducted in Tanzania with mean age was 39.5 years Mollel and Chilongola (2017). This study revels similar result to previous study in Egypt whose mean age was 30.4 years (Ahmad *et al*., 2016).

Of the total 164 study participants, students were more exposed to MDR-TB with 21.95% followed by employed (20.7%), daily labors (19.6%) and farmers (13.1%). In contrast, a study in Tanzania showed that farmers (37.04%) and students (6.88%) were more exposed to MDR-TB Mollel and Chilongola (2017).

Regarding to social drug use status, 7.3% and 20.1% of the study participants were smokers and Khat users, respectively. The study result is comparable with other study done in St.Peter TB Specialized Hospital where smoker study participants were 5.32% (Getachew *et al*., 2013). This study's finding is also similar to the study conducted in Tanzania and cigarette smoking were 5% and alcohol users were 18% (Nyaki *et al.*, 2016).

In this study, 83.5% MDR-TB patients were treated for active tuberculosis infection before while 16.5% MDR-TB patients were newly started MDR-TB treatment for developing primary MDR-TB resistant. This study's result is different from study conducted by Getachew *et al* (2013) where 92.3% MDR-TB patients were treated for active tuberculosis although only new 3.7% MDR-TB patients developed primary resistant.

Another study conducted in Egypt showed that acquired resistance and primary resistance were 95.3%, 4.7%, respectively *El Di et al (2015)*. Hence, looking to the findings of this study and other studies indicate that new MDR-TB exists without any prior history of exposed and treated to active TB. The probable reason might be transmission of MDR-TB from MDR-TB patients to care giver, family member, friends or people in contact with the patient.

In this study, participants were developed R (77%) and H and R (21.3%) which was similar to study conducted in South Africa 21% study participants were resistance to both INH and R (Gandhi *et al*., 2012). In general, in this study primary resistant for MDR-TB was more prevalent than the previous study by Musa *et al* (2017) where prevalence of MDR-TB in new cases was 2.1% (95% CI:1.7–2.5%).

Based on the this study finding, types of ADR occurred on the study participants were renal toxicity and hearing impairment with percentage of 1.8% and 1.8%, respectively. The occurrence of ADR is smaller when compared with other study which reported that 3.8% and 14.5% of study participants were developed renal toxicity and hearing impairments, respectively (Sagwa *et al*., 2013). Drug induced psychosis and peripheral neuropathy or other unwanted ADR occurred with 1.8% and 3.6% correspondingly.

When compared this study's finding on ADR with a study conducted by *El Di et al (2015)* is smaller since the later has drug induced depression of 3.70%. In addition this study identified drug induced gastric manifestation and hypo-kalmia with prevalence of 31.50%, 11.90%, respectively and this is in contrast with the same study conducted by El Di *et al* (2015) where gastrointestinal tract manifestation and hypo-kalmia were 57.00% and 26.20%, correspondingly. The probable justification for small occurrence of ADR in this study might be the health provider could not identify the ADR and even the patient could not recognize.

In this study, 18.30% patients died regardless of MDR-TB treatment which is higher when compared with the study conducted at St. Peter TB Specialized Hospital in 2012 on 188 study participants, where 15.43% patients were died (Getachew *et al.,* 2013). The occurrence of death in this study is higher than similar study conducted at ALERT and Gondar University Hospital in 2016, where 10.80% of the study participants were died (Molalign and Woncheko, 2016). However, death in this study is smaller than study conducted by Ramaswamy and Musser (1998) which was 55% and from other study done by Aibana *et al* (2017) in Ukraine which was 36.4%.

The Government of Ethiopian is working to screen and treat MDR-TB; nevertheless, the study finding showed that there was high death rate relative to the previous studies finding. On the other hand, cured and completed their treatment were 62.80%, 2.44%, respectively, which is slightly higher than a retrospective study conducted in China with finding of 54.00%, 9.00%, respectively (Alene *et al.*,2017).

The survival probability of study participants at 6, 12, 18, 24 month was 84.00%, 82.00%, 81.00% and 72.00%, respectively. This is lower than other study conducted at St. Peter TB Specialized Hospital, where 6, 12, 18 and 24 months was 88.53%, 85.83%, 82.71 % and 78.95 % survival time, respectively (Getachew *et al*.,2013). Another study conducted by

Alene *et al* (2017) showed that survival probability of the patients at the end of treatment at 24 months was 80%.

In addition, the overall incidence of death in the current study was 4.852 per 10,000 populations which was higher compared with study conducted at St. Peter Hospital, where 3.6 per 10,000 population (Getachew *et al*., 2013).

The total follow up time for the study participants was 63,141 person-days or 1.1 years and the median survival time was 400.5 days or 13.35 months which was smaller than study conducted in France, where median survival probability was 31 months used (Flament-Saillour *et al.*,1999). In this study finding also contradicted with other study done by Molalign and Wencheko(2016) in Ethiopia with the median survival probability of the MDR-TB patients was 16 month. Other study done in Lithuanian also different from this study finding the median survival time for MDR-TB patients was 4.1 (95% CI 3.7 to 4.4) years (Balabanova *et al*., 2011).

In this study the major risk factors for mortality of MDR-TB patient were identified and the Cox proportional hazard regression analysis showed that being HIV positive was statistically significant risk factors for the death of MDR-TB patients (HR=2.75,95% CI(1.23-6.15) & P=0.021). In this regard, this study's finding is similar with study a conducted in Ukraine, where HIV infection is the strongest baseline risk factor of poor outcome (Aibana *et al.*,2017). An additional study conducted in Malaysia also supports this study (Elmi *et al*.,2016).

In the present study, study participants who had exposed to co-morbidities and co-infections during and after their MDR-TB treatment die more likely than without it and this was supported by study done at ALERT and Gonder University Hospital Molalign and Wencheko (2016). Therefore, in this study the risk factors for mortality of MDR-TB patients at Adama and Bishoftu general hospitals were identified. These include: age, HIV positive, others co-morbidities and co-infections in addition to HIV, initial body weight, occupation and Khat use.

Based on Cox proportional hazard regression analysis, age is one of the risk factors for mortality. Age of the study participants is very significant for low survival probability of the patients with (HR=2.26, 95% CI (1.35-3.79) & P=0.00). This is supported with a study done by Molalign and Wencheko (2016) with (HR=1.20, 95% CI (1.17-1.23) & P=0.006).The

present study also supported study done by Balabanova *et al* (2011) where (HR=4.80, 95 % CI (3.16 - 7.29) for greater than 60 years and less than 30 years of age.

Other risk factor is lower initial body weight of the study participants. The mean initial body weight of the study participants were 45.67kg. In this study, the status of initial body weight during treatment starting time is one of the predictors for mortality with (HR=0.44, 95% CI (0.22-0.85) & P=0.02. This result was also supported by Molalign and Wencheko(2016).This finding is supported by other study (FarleyE *etal*.,2011) and study in Tanzania (Nyaki *et al*.,2016).

Khat use is one of the risk factors for mortality of study participants in this study and with evidence of (HR=0.41, 95%CI (0.18-0.97) & P=0.04) and this is supported study conducted by(Ageely, 2008) and because the effects of Khat chewing in humans elevated blood pressure and heart rate and this may lead to MDR-TB patients aggravated their mortality. Being HIV postive was one of another risk factors for dying with (HR=2.75,95% CI(1.23-6.15) & P=0.01.Even the incidences of death in HIV positive patients were 8.35 persons per 10,000 populations and this results supported by study conducted by Farley *et al* (2011), where patients with HIV had a higher hazard of death (HR: 2.33, P<0.0001).

In the present study co-morbidties and co-infections were risk factors for mortalityof the study participants . The types of co-morbidites and co-infections were type II diabetics and hypertention, pnemonia, anemia, congstive hearfailure and corpulmonal. This groups of patients had hazared rate of (HR=2.28, 95% CI (0.99-5.26) and P=0.05). MDR-TB patients exposed to co-morbidities and co-infections in addition to HIV 2.3 times more likely to die than without and other risk factors. This finding is supported with study conducted by Getachew *et al* (2013), where patients who have clinical complication had a higher hazard of mortality (HR =1.90, 95% CI (1.52 - 2.39) $P < 0.001$) than who do not have the complication.

6. Limitation of the Study

1. The design of this study is a retrospective cross-sectional on MDR-TB patients and even if all 164 MDR-TB patients were used as total sample and not representative to all MDR-TB patients in Ethiopia and difficult to generalized the survival status and risk factors for the mortality of the MDRTB patients.
2. Some data not recorded properly on the patients card such as : Radiological finding; Laboratory investigation serum electrolyte; Organ function test (ALT and AST); Body weight after initiation of MDR-TB treatment; Height of the patients and body mass index and difficult to incorporate for analysis purpose in this study.

7. Conclusion

In this study the major risk factors for mortality of MDR-TB patients identified are: Initial low body weight, HIV positive, co-morbidities and co-infections, age, Khat use and occupation of the study participants. The survival probability of MDR-TB patients at 6, 12, 18, 24 months was 84%, 82%, 81% and 72%, respectively and the treatment outcomes of those patients includes: death(18.30%); cured(62.80%); treatment completed (2.44%); transferred to other treatment site (13.4%) and lost to follow up(3.05%) MDR-TB patients. Even though survival is poor, promotion of the existing treatment program will further improve patients' survival at the study setting.

8. Recommendation

- For good treatment outcome of MDR-TB patients special attention is required. Based on current study finding the following recommendations are given.
  - The hospital administrative should be support MDR-TB patients by nutritional. Because, initial body weight of the study participants was identified as risk factors for their mortality.
  - The survival probability of the MDR-TB patients was low and further research should be done to identify the cause of the death by hospitals.
  - Co-morbidities and co-infections on MDR-TB patients at the study setting were identified as risk factors of mortality and proper management of these risk factors should be implementing by health care providers.
  - MDR-TB patients in the study setting were used Khat and this also identified as risk factors for mortality. This may be affecting the treatment outcome of the study participants and the healthcare providers should be work on adherence not used Khat by the patients.

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Annex I: Data abstraction format

Name of the variables

Code No. _____

1. Type of events.

1.1 Death

1.2 Censored (Cured, Treatment Failure, Treatment Stopped ,Transfer Out, Treatment Completed, Lost to follow up)

1.3 Date of treatment started dd/mm/yy----------

1.4 Date of event occurrence dd/mm/yy----------

2. Age of patients in year ----------

3. Sex 1. M ( ) 2. F( )

4. Occupational status of the patient

1. Governmental employee 2. Non-governmental employee 3. Daily labour 4. Owner private

5. Farmer 6. Prostitute 7. Student 8. House wife 9 .Others ----------

5. Residence 1. Urban ( ) 2. Rural( )

6.Weight of the MDR-TB patients before treatment started ---------- in kg

7.Educational status of MDR-TB the patients

1. Illiterate 2. Read and write 3. Elementary school 4. Junior high school 5. High school 6. College diploma and above; Key: 1<0 class, 2.Grade (1-3), 3.Grade (4-6); 4. Grade (7-8) 5. Grade (9-12) and 6. Diploma and Degree Graduated

8. Marital status (please circle it)

Married

Never married

Divorced

Widow

9.Religious of MDR-TB patients

Orthodox

Muslim

Catholic

Protestant

Others.....

10. Social drug use characteristics of MDR-TB patients. Please circle.

10.1 Did she/he smoke tobacco: 1. Yes 2.No ,

10.2 Did she /he drink alcohols: 1. Yes 2.No

10.3 Did she /he chewing Khat: 1.Yes 2.No

10.4 Did she / he other drug user: 1.Yes 2.No

11.Site of Tuberculosis and TB treatment history

1. Pulmonary only

2. Extra pulmonary only

3. Pulmonary and extra pulmonary

12. Did she / he treated for active TB before 1.Yes 2. No

13. The type of drug resistance before MDR-TB treatment stared.....

14. Which methods were used to detected drug resistant?

1.Gene-x pert

2.Line probe assay

3. Solid culture

4. Liquid culture

5. Others

15. Is there HIV co-infection 1. Yes 2. No

16. Presence of other chronic disease 1.Yes 2.No 3. Unknown

If yes please write the type of chronic diseased----------

17. Radiological finding

1.Bilateral cavitations

2. unilateral cavitations

3. Abnormal x-ray without cavitations

4. Normal x-ray

18. Sputum smear microscopy at base line 1. Positive 2.Negative

19. Culture result at base line 1. Positive 2. Negative

20. Is there a serious adverse event (SAE) during MDRTB treatment 1. No 2. Yes

If the answer is yes for question 19, what is the serious adverse drug reaction?

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