

**ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF PUBLIC HEALTH**



**SURVIVAL AND ITS DETERMINANT OF MULTIDRUG-RESISTANT
TUBERCULOSIS PATIENTS WITH HIV CO-INFECTION: St. PETER
TUBERCULOSIS SPECIALIZED HOSPITAL ADDIS ABABA, ETHIOPIA**

BY: YEMARWUHA ABEBE

**A THESIS SUBMITTED TO THE SCHOOL OF GRADUATE
STUDIES IN ADDIS ABABA UNIVERSITY FOR THE PARTIAL
FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF PUBLIC HEALTH**

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December, 2016
Addis Ababa, Ethiopia

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Abstract

Back ground

According to World Health Organization (WHO) 2015 report globally 480 000 new cases and 190,000 estimated deaths occurred in 2014 due to MDR TB. Ethiopia ranked 7th from top 22 highest TB-burden and 15th from 27 highest MDR-TB burden countries; and one of high HIV/AIDS prevalent in Sub-Sahara African countries. Nevertheless, a little known about Survival of Multidrug-resistant Tuberculosis patients with HIV/AIDS co-infection in Ethiopia. Hence, this study is to determine the Survival and their determinants in MDR TB patients co-infected with HIV/AIDS Addis Ababa, Ethiopia

Method

A retrospective cohort study design was conduct at St. Peter TB specialized hospital Addis Ababa, Ethiopia; from February to March 2016. Survival of exposed and non-exposed groups was compared by Kaplan-Meier survival functions by using log-rank test. Factors that associated with outcome variables at 20 % ($p < 0.2$) significant level in the bivariate analysis was included in the final Multivariable analysis. Cox proportional hazards regression model was used to determine factors associated with risk of death by controlling confounding and effect modifier.

Result

Out of 93 expose groups 48 (51.61%) were female and the rest 45 (48.39%) were male. Ninety three exposed study subjects were survive for a total of 26,581 person per 10000 days, and 213 non-exposed study subjects were survive for a total of 63,782 person per 10000 days. Median survival time of exposed study subjects was 269 person days and for non-exposed study subjects had 254 person days median survival time. Kaplan Meier survival curve shows lower survival (long-rank test, $P < 0.010$) was seen in exposed groups compared to non-exposed group throughout the follow up time with parallel survival estimate curve. Independently associated factors for increasing risk of death was hospitalization at the time of treatment initiation (HR: 8.64; [1.11 - 67.00]), presence of HIV co-infection (HR: 2.15; [1.04 - 4.46] and age greater than or equal to 65 (HR: 10.07; [1.80 - 56.29]).

Conclusion

This study find out MDR TB patients without HIV had better survival than those MDR TB patients with HIV co-infection. Hospitalization at the time of treatment initiation, presence of HIV co-infection and age greater than or equal to 65 years of age increase the risk of death.

Recommendations

Early detection (diagnosis) and treatment for MDR TB for HIV positive patients; regular medical check-up for MDR TB to aged people; decrease hospitalization by early diagnosis and treatment and further studies on MDR TB and survival of older population.

Acronyms

AFB	Acid Fast Bacilli
ART	Antiretro-viral therapy
Cm	Capreomycin
CD4	Cluster of Differentiation 4
CI-95% -	Confidence Interval at 95%
CPT	Cotrimoxazole preventive therapy
Cs	Cycloserine
DM	Diabetes Mellitus
DST	Drug Sensitivity Test
ETM	Ethambutol
Eto	Ethionamide
GHC	Global Health Committee
HBC	High Burden Country
HIV	Human Immunodeficiency Virus
INH	Isoniazid
IPT	Isoniazid preventive therapy
Lfx	Levofloxacin
MDR	TB Multidrug-resistant tuberculosis
TB	Tuberculosis
RIF	Rifampicin
STM	Streptomycin
WHO	World Health Organization
XDR TB	Extensive-drug resistance tuberculosis
Z	Pyrazinamide

1. Introduction

1.1 Background

Mycobacterium tuberculosis is a main causative agent to develop TB infection. The disease is transmitted through air during inhalation and mainly affects the lung (pulmonary TB) but it can also affect any organ of body in addition to the lung^[1]. Tuberculosis can be effectively treated with first line drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) for six months. But when this first line drugs are not properly used (erratically used, poor quality of drugs, poor clinical practice and low completion rate) this leads to Multidrug-resistant Tuberculosis (MDR TB) (1, 3). MDR TB is resistance to isoniazid and rifampicin (back bones of first line anti-TB drugs) (1-4). MDR TB is treated with second line drugs which needs longer treatment (18-24 months); toxic and complication prone; highly Costy; lower cure rate; higher death rate; difficult to control co-infection (MDR TB+HIV=disaster)^[2].

According to World Health Organization (WHO) 2015 report globally 480 000 new cases and 190,000 estimated deaths occurred in 2014 due to MDR TB^[1, 4]. Among pulmonary TB patients notified in 2013, around 300 000 had MDR TB. India, China and the Russian Federation contributes more than half of patients^[1, 4].

MDR TB patients enrolled for treatment were 111000 in 2014 which was 97000 up from 2013. while between 2013 and 2014 MDR TB patient enrollment increased by 13% in top 27 MDR TB high burden countries (HBC) (1). But 39 000 confirmed MDR TB patients and unknown number detected in previous years were waiting for treatment^[4].

According WHO 2015 report worldwide Treatment outcome of MDR TB patients in 2012 cohort is 50% were treated successfully, 16% were died, 16% were lost follow up, 10% were treatment failed and 8% were had no outcome information^[1].

Ethiopia has 15th rank of top 27 MDR TB high burden country (HBC) ^[1, 4-5], and it also one of the 5 HBC MDR TB that can achieve treatment successes rate greater than 70% (1). Among 9 million TB patients an estimated of 13% people were HIV- positive. Of these African region accounted 78% HIV-positive TB cases ^[1]. Ethiopia has 20% HIV/AIDS prevalence among 85% TB patients tested for it in 2013 ^[6]. The diagnosis of TB (including MDR-TB and XDR-TB) is very difficult in HIV/AIDS patients compare with non-infected one, this leads to increase morbidity and mortality in those co-infected patients. But treatment of MDR-TB co-infected with HIV/AIDS similar to MDR-TB patients not infected by HIV/AIDS ^[7].

1.2. Statement of the problem

Africa contributes 79% of all TB/HIV cases and 23% (2 million deaths) due to TB out of the world, according to WHO the stop TB department, 2011 ^[8]. The new emerging of MDR-TB create difficulty to control (eradicate) TB ^[1, 4]. The presence of MDR-TB co-infected with HIV/AIDS makes things more complicated; increase morbidity and mortality^[1, 4, 5]. Ethiopia ranked 7th from top 22 highest TB-burden and 15th from 27 highest MDR-TB burden countries; and one of high HIV/AIDS prevalent in Sub-Saharan African countries ^[7]. TB is the leading cause of morbidity; the second leading cause of hospital death; and the fourth leading cause of hospital admission in Ethiopian hospitals ^[9]. MDR TB cases 90 (90%) were under anti-TB treatment twice or more compared with non-MDR TB patients 25 (8%); 54 (48%) of MDR TB and 85 (26%) of non-MDR TB patients had HIV-positive ^[10]. 12.3% (19/155) patients were died while on MDR TB treatment; and 30.3% (10/33) deaths were seen in MDR TB co-infected with HIV/AIDS patients while on treatment ^[11].

1.3 Significance of the study

The reason for the importance of such a research is to improve the overall achievements of MDR TB and co-infected with HIV/AIDS programs which have been running by different hospitals in the country by giving scientific evidence on survival rate and death associated factors.

Existing Studies regarding MDR TB in our country are; primary drug resistance to anti-TB drugs [12-14]; risk factors for MDR TB [9, 15]; determinant of MDR TB under first line anti-TB treatment [16]; pattern and trend of resistance to first line anti-TB drugs among culture positive retreatment cases [17, 18]; determine genotype of MDR TB isolate and assess the magnitude of their cluster [19]; role of technical assistance in the establishment and scale up of programmatic management of drug resistant TB [20]; prevalence and risk factor of adverse drug reaction associated with MDR TB treatment [21]; and survival and predictors of mortality among under MDR TB treatment [11].

Nevertheless, a little known about survival and its determinant of Multidrug-resistant Tuberculosis patients with HIV/AIDS co-infection in Ethiopia. Data on this is highly needed in order to evaluate the efficiencies/deficiencies of MDR-TB treatment program. Therefore it is essential to ascertain the role of HIV on MDR TB treatment outcome. Such findings would be used to guide policy change so as to improve MDR-TB treatment among HIV co-infected patients in Ethiopia.

2 Literature review

2.1 Burden of Multidrug-resistance Tuberculosis

According to 2015 World Health Organization (WHO) report, 3.3% (95% CI: 2.2–4.4%) of new TB cases and 20% (95%CI: 14–27%) of previously treated cases are estimated to have MDR-TB [1, 4]. This report is taken from 144 countries, contributing 95% of World population. Of them 72 countries have continuous surveillance system based on routine diagnostic drug susceptibility testing (DST) of all TB patients but the rest 72 depends on special surveillance system^[1]. Among 27 high burden countries (HBC) Eastern European and central Asian have the highest levels of MDR-TB, with 35% of new cases and 75% of previously treated cases ^[4]. Africa had 2.1% (0.5%–3.7%) new TB cases with MDR TB and 11% (6.7%–16%) retreatment TB cases with MDR TB; while Ethiopia is 15th from 27 HBC of MDR TB; had 1.6% (0.9%–2.8%) new TB cases with MDR TB and 12% (5.6%–21%) retreatment TB cases with MDR TB according to 2015 WHO report ^[1].

A retrospective study done from 1997 to 2009 in 309 hospitals, China Beijing; among 5523 patients 3752 (67.9%) were male; 3430 (62.1%) were history of previous treatment cases; 1999 (36.2%) were live in Beijing. The mean age was 45.8 + (-) 20.2 years (range 0.5–98.0 years) and majority of patients (n=3851, 69.7%) had age between 15-65 years and the rest; < 15 years (n=125, 2.3%), > 65 years (n=1547, 28%). In this study 47.1% (2604) had resistance to any anti-TB drug; resistance type by each ant-TB drug was: ethambutol (n=1455, 26.3%), streptomycin (1477, 26.6%), kanamycin (828, 15%), ofloxacin (536, 9.7%), levofloxacin (308, 5.6%) and para-amino salicylic acid (912, 16.5%). Patients with mono-resistant TB were 14.8%, poly-resistant TB were 19.8%, MDR TB were 19.4% and XDR TB were 1.3% ^[22].

Another retrospective study from 1989-1999, Hong Kong China; from 26,625 new cases 371 (1.4%) were develop primary MDR TB resistant and from 2432 retreated cases 232 (9.5%) develop acquired MDR TB. According to this study 60.4% (364) had age between 35-65 years of age of 603 total MDR TB cases; and overall prevalence of MDR TB in this age group highest (364, 2.6% of 13,842 cases) compared with age group 16-34 (132, 1.7% of 7750 cases) and age group > 65 (103, 1.4% of 7219 cases). This age group (35-65 years of age) had highest contributed (328, 2.7%) of MDR TB resistant cases of 11,931 smear-positive cases detected; it alone accounted for 208 (63.4%) of 328 smear positive MDR TB cases [23].

A retrospective cohort study on MDR TB patients treatment between 2000 and 2004 in Tomsk, Russian Federation; out of 614 MDR TB patients 83.2% were male, mean age was 35.9 years, 611 (99.55%) had history of previous anti-TB drug use; 31.8% had prior injectable and/or 15% fluoroquinolone exposure [24].

A retrospective review of prospective single cohort from 2002-2005, Orel, Russia; out of 200 patients enrolled in DOTS-Plus program, 165 (85%) were male, had mean age 42 years, 144 (72%) were previous TB treatment, 102 with second-line agents; 133 (67%) had isolated ethambutol (EMB), 69 (35%) had resistant to second-line injectable agent, 198 (99%) had initial resistance to both INH and RMP [25].

A retrospective cohort was done in Chennai and Madurai, India from June 2012 to May 2013, on multidrug-resistant tuberculosis based on positive follow-up smear results; among 520 smear and culture positive patients 389 (75%) male, 176 (34%) were HIV infected, mean age was 34.1 years (standard deviation 10.3), patients with culture negative during follow-up was 98% [26].

A cross-sectional survey in Mumbai, India from March 2013 to January 2014 on Alarming Levels of Drug-Resistant Tuberculosis in HIV-Infected Patients; of 1724 total patients 60% were male, median age 35 (Inter-quartile range, IQR: 24–44), 98% patients had pulmonary TB, 80% were on ART and 52% had CD4 cell counts less than 500 cell/ml at the last ART visit, 72 (4.2%)

had smear positive TB, 202 (11.7%) had culture positive TB, 11 TB patients were smear positive but culture negative and 141 patients were culture positive but smear negative ^[27].

A research done in Denmark from 1993-1995 on Multidrug-resistant tuberculosis based on retrospective evaluation of routine data; among 1354 TB cases 629 (46%) were Danish-born, the rest 725 (54%) were foreign born; 1188 (88%) culture positive and 374 (31%) were smear positive. Out of foreign born patients 10%-20% were INH mono-resistant, this was true 5-7% Danish born patients, and 1% foreign born and 1 Danish born patients had two or more anti-Tb drug resistance ^[28].

Population based retrospective study in Alberta and British Colombia from 1989 to 1998; out of 4606 TB patients 3553 (77.1%) were culture positive and among this culture positive cases 365 (10.3%) were drug resistant, and among drug resistant cases 24 (6.6%) were MDR. Of MDR TB patients 75% were male and average age was 52 ± 19 years ^[29].

Matched case-control study on Multidrug-resistant tuberculosis in Western Australia (WA) from 1 January to 31 December 2012; among 1352 TB patients 16 (1.2%) had NDR TB. Of 16 MDR TB cases 12 were female, had 26 years (8-58 years, range) median age, 15 out of 16 were born outside Australia and 11 of 16 had pulmonary disease^[30].

A retrospective survey on MDR and XDR TB among 27 (accounts 37%) hospitals in Gemen from 2004-2006; out of 4,557 culture confirmed Tb cases 184 (4%) had at least isoniazid and rifampicin resistant, 174 (95%) were isolated resistant to streptomycin, 119 (65%) were to ethambutol, 177 were MDR TB, and 7 were XDR TB. In this study female contributed 24% (45) with median age 28 years and male were 76 & (139) with median age of 39 years. 53% (94) MDR TB and 86% (6) XDR TB patients had history of taking anti-TB treatment for more than one month ^[31].

A retrospective cohort study on treatment outcome and follow up MDR TB patients West Coast/Wineland, South Africa from 1992 to 2002; out of 747 culture confirmed MDR TB patients 491 (66%) started at least two Second Line Drugs (SLD), 112 (15%) were treated with first line drugs and the remaining 144 (19%) didn't start treatment due to death or default by TB treatment before laboratory confirmation of MDR TB [32].

Institution based case-control study on determinants of MDR TB patients under first-line treatment in Addis Ababa, from November 2011 to February 30, 2012; among 134 cases 81 (60.5%) were male but out of 134 controls 70 (52.5%) were female; mean age in case group was 25.1 (SD=10.94) years and 30.72 (SD=11.4) years in control group. In this research 96 (71.6%) out of 134 cases had previous TB treatment more than two episodes, in control groups 14 (10.4%) had TB treatment two round [16].

A cross-sectional study on prevalence of MDR TB among presumptive MDR TB cases in Amhara National Regional state, Ethiopia from May 2012 to May 2013; out of 606 presumptive MDR TB cases 363 (59.9%) were male; mean age of participant was 35.6 years (range, 2-80 years); majority of participants (32.8%) had age 21-30 followed by 31-40 years of age which accounts 23.9%; 190 (31.4%) were smear positive and 416 (68.6%) were smear negative [12].

Another case-control study in the same region on risk factors for MDR TB patients from May 2013 to January 2014; 153 MDR TB patients and the same number of TB patients (non MDR TB) incorporate in the study, out of these 88 (57.5%) cases were male and 90 (58.8%) controls were male; 84 (54.9%) of cases and 81 (52.9%) of controls had mean age between 26-45 years. In this study 141 (92.2%) among cases and 137 (89.5%) among controls had pulmonary TB [14].

2.2 Multidrug-Resistant Tuberculosis and Human Immunodeficiency Virus

According 2015 WHO report among 9.6 million TB patients 1.2 million (12%) were HIV co-infection and Africa contribute 74% of estimated number of HIV-positive incident TB cases. Burden of TB/HIV ranges 6 % in Eritrea to 73 % in Swaziland ^[1].

A retrospective study on characteristics and treatment outcomes of MDR and XDR TB patients in 309 Hospitals in Beijing, China from 1996-2009; out of 5201 TB patients tested for HIV 3 were positive, but out of 3270 patients included in the final analysis tested for HIV no one was positive ^[33].

A prospective study on predictors for MDR TB among HIV infected patients in USA between April 1993 and June 1995; among 342 HIV infected patients 156 (45.61%) had pulmonary TB and out of 156 patients 16 (10%) had MDR TB^[34].

A retrospective case serious on HIV-positive patients treated with MDR TB in public health facility Lima, Peru from July 1996 to December 2005; at the time of MDR TB initiation 115 patients out of 4008 documented HIV positive but by different exclusion criteria 52 individuals included in the case series. Among 52 cases 45 (85%) treated with individualized regimen and the rest 15% treated with standardized regimen. 27 (51.95%) patients initiated HAART ^[35].

A retrospective cohort study on prevalence and risk factors for MDR-TB in HIV-infected patients from January 2005 to May 2011 at the National Medical Center of Korea; out of 814 HIV patients registered 119 had anti-TB treatment and among 119 patients 55 had Drug Sensitivity Test (DST), 8 had previous anti-TB treatment and the rest 47 were primary TB cases ^[36].

A retrospective cohort on risk of death among HIV co-infected MDR TB patients compared with general population in South Africa from 2000 to 2004; HIV positive patients were 554 (39.2%) out of 1413 tested for it. Around 63% of patients were age group between 25-34 and 35-44 years old [37].

A retrospective study on HIV infection and MDR TB in Durban, South Africa from January 1991 to April 1995; among 295 patients 42 (14.2%) were HIV positive, female patients (21/110, 19.1%) with median age 20-29 years contribute more than male patients (21/185, 11.4%) had median age 30-39 years. Among 295 patients 273 (92.5%) were Blacks and the rest had Indian, Wight and mixed race [38].

A prospective study in South Africa on outcomes of MDR TB with high HIV prevalence from 2000 to 2004; out of 1023 TB patients tested for HIV 287 (38%) had positive and the rest 470 (62%) were negative result for HIV test. Ninety two percent (92%) of patients had previous anti-TB treatment and 98% had pulmonary TB [39].

A facility based cross-sectional on assessment of MDR TB burden in Khayelitsha, South Africa between May and November 2008; among 1842 suspected pulmonary TB patients 732 were primary TB and 843 cases were history of anti-TB treatment for more than one month. Eighty eight percent (88%) of new cases were tested for HIV and 55% of them had positive; 90% of previously treated patients were tested for HIV and 71% of them had positive [40].

A retrospective observational study on HIV co-infection MDR and XDR TB results in high mortality in Tugela Ferry, South Africa from January 2005 to December 2007; out of 272 MDR TB patients tested for HIV 90% of them had positive, and among 382 XDR TB patients tested for HIV 98% of them had positive. But only 15% MDR TB and 22% XDR TB patients on Antiretroviral Therapy (ART) before their drug-resistant TB diagnosis. Out of MDR TB patients

75% of them and among XDR TB patients 69% patients were history of previous anti-TB treatment ^[41].

A cross-sectional study on primary DR anti-TB drugs in major towns of Amhara region, Ethiopia from January 2008 to October 2008; come across the following findings, of 93 patients 25 (26.9%) had HIV positive and the rest 68 (73.1%) were negative for HIV test. HIV positive patients were likely to develop resistance to any one of anti-TB drugs compared with HIV-negative cases (OR 2.76: p=0.09) ^[13].

A hospital based retrospective study on pattern of anti-TB drug resistance among previously treated TB patients, St. Peter Ethiopia, from January 2004-December 2008; out of 376 culture positive M-tuberculosis 274 (72.9%) were resistance to at least one anti-TB drug; resistance to STM (67.3%), resistance to INH (56.1%), resistance to RIF (46.1%) and resistance to ETM (43.5%). Poly resistance was 29 (7.7%), prevalence of MDR-TB was 174 (46.3%) and among MDR-TB cases 140 (80.5%) were resistance to all first line anti-TB drugs ^[15].

A cross-sectional study on prevalence of anti-TB drug resistance in HIV/AIDS referral hospital in Rio de Janeiro, Brazil, from 2001 to 2005; had come with out of 344 TB patients 31.2% had HIV co-infection, but 15.7% was unknown status due to unavailable HIV test result ^[42].

2.3 Treatment outcome and survival of MDR TB co-infected with HIV

According to retrospective observational study conducted in KwaZulu-Natal, South Africa from 2000-2003 on high treatment failure and default rates for patients with MDR TB; among 1209 patients on MDR TB treatment outcomes, 491 (41%) were cured, 252 (21%) defaulted on treatment, 223 (18%) passed away on treatment, 208 (17%) failed on treatment, 35 (3%) treatment completed, in general 526 (44%) had favorable outcome (cured or completed) but 683 (56.5%) had unfavorable outcome (defaulted, died, failed) ^[43].

A retrospective observational study on culture conversion among HIV co-infected MDR TB patients in Tugela Ferry, South Africa from February 1, 2008 to February 28, 2009; out of 33 patients who had culture positive at the starting of MDR TB therapy, 29 (88%) converted their culture result with the first 6 months of treatment. These were 23/27 (85%) MDR-TB with HIV co-infected and 6/6 (100%) HIV-negative patients. The median time for culture conversion was 54 days (IQR 41-90) for HIV co-infected patients and 103.5 days (IQR 86-116) for HIV non-infected MDR TB patients on treatment. In general in this study out of 45 study subjects, 5 (11%) were transferred out to another health facility, 1 (2%) refuse further treatment, 4 (9%) passed away while on therapy ^[44].

A randomized clinical trial on improved survival in MDR-TB patients receiving integrated TB and ART treatment conducted an outpatient clinic in Durban, South Africa from 2008 to 2012; among 23 MDR-TB patients, 7 (30%) died in combined integrated treatment arm and 5 in sequential treatment arm but death rate were similar until 6 months of treatment on both groups. In the combined integrated treatment arm group mortality rate was 11.9/100 person-years (py; 95% CI 1.4-42.8) while 56/100 py (95% CI 18.2-13.8) in the sequential treatment arm ^[45].

A retrospective cohort study on impact of MDR-TB on the Survival of HIV-infected patients in South Africa from January 1999 and December 2004; out of 225 TB patients, 194 (86.2%) were cure or treatment completed, 9 (4%) were died, 9 (4%) were transfer out, 7 (3.1%) were treatment failure, and 6 (2.67%) were defaulter. Median survival time in patients with MDR-TB with HIV co-infection was 13.9 month and those without MDR-TB was 67.7 months. And mortality among MDR-TB patients taking ART drug was 1.9% but for those MDR-TB co-infected with HIV not receiving ART drug had 5.95 of mortality; overall mortality was 4% ^[46].

A retrospective study in Brazil, from 2003-2008, on outcomes of TB treatment by HIV status in National recording systems; out of 109,820 TB patients tested for HIV 20,881 (19%) had

positive and 88,939 (81%) were HIV-negative. In this study treatment outcome of TB patients by HIV status was, out of 20426 TB with HIV co-infected patients 11369 (55.7%) were cured, 4705 (23%) were passed away, 2,792 (13.7%) were defaulted, 1536 (7.5%) were transferred out and 24 (0.12%) were develop MDR-TB; while out of 87,693 HIV-negative TB patients, 75185 (85.7%) were cured, 6185 (7%) were defaulted, 3652 (4.2%) were died, 2608 (3%) were transferred out and 63 (0.075%) develop MDR-TB ^[47].

A retrospective national cohort conducted in Lithuania from 2002 to 2008, on survival of drug-resistant TB; total followed time was 4089.3 person-years out of 1807 followed patients. Median survival for MDR TB patients was 4 (95% CI 3.7 to 4.4) years and for XDR TB patients 2.9 (95% CI 2.2 to 4.3) years; for HIV positive patients 1.9 (95% CI 0.4 to 3.5) years and HIV negative 4.9 (95% CI 4.3 to 6.8) years of median survival; primary MDR TB patients had 4.2 (95% CI 3.7 to 5.1) years median survival and acquired MDR TB patients had 3.7 (95% CI 3.4 to 4.3) years of median survival; primary XDR TB patients had 2.7 (95% CI 1.8 to no upper limit) years median survival and acquired XDR TB patients had 2.9 (95% CI 1.4 to 4.9) years of median survival^[48].

A retrospective medical record review on treatment outcome and survival based on drug resistant patterns of MDR TB in Korea, from January 2000 to December 2002; comes out 45.3% treatment successes (cure 30.2%, treatment complete 6.6%) out of 1407 MDR TB participants ^[49].

A retrospective medical record review in, Seoul, Korea, from January 1 to December 31, 2004 on treatment outcome and mortality among MDR TB patients in 3 public TB hospitals; had the following findings, out of 202 patients 75 (37.1%) treatment successes (n=46, 22.8% cured and n=17, 8.4% treatment completed); and 127 (62.9%) had poor outcome; (75 (37.1%) defaulted, 9 (4.5%) died on treatment, 3 (1.5%) treatment failed ^[50].

A retrospective cohort study on treatment outcome and long-term survival in patients with XDR TB in, Korea from 2000 to 2002; come with findings, successfully treated patients (cured; 425, 30.2% and treatment completed; 93, 6.6%) was 637 (45.3%) out of 1407, died while on treatment was 26.7% XDR TB and 9.3% MDR TB patients; treatment failure was 16 % in XDR TB and 4% in MDR TB patients; total defaulter rate was 32.2% (453/1407) among these 16% defaulter was XDR TB and 4% was MDR TB defaulters ^[51].

A retrospective cohort study in, Nigeria from July 2010 to October 2012, on intensive phase treatment outcome among hospitalized MDR TB patients had come findings; out of 162 MDR TB patients on treatment 138 (85%) were alive and the remaining 24 (15%) were passed away at the end of intensive phase treatment. All patients alive at the end of intensive phase had culture and sputum smear negative ^[52].

2.4 Determinants for survival of MDR TB/HIV patients

There are several factors that may predict death of MDR-TB in general and more so among HIV co-infected patients. These are important because intervention can be modified based on these factors to improve treatment outcomes.

A retrospectively study on drug-resistance patterns after 5–8 years of follow-up; on Treatment Outcomes and Survival Based on Drug Resistance Patterns in Multidrug-resistant Tuberculosis in USA: predictors of long term survival in multivariate analysis was XDR-TBre 3.15 (95% confidence interval [CI], 2.06–4.83; P , 0.001) compared with non-XDR MDR-TB; 2.15 (95% CI, 1.49–3.09; P , 0.001) in those with XDR-TBor; and 1.38 (95% CI, 0.80–2.39; P 5 0.252) in patients with XDR-TB(or-re). Other indicters of poor long term survival was XDR-TBre 3.76 (95% CI, 2.43–5.83; P, 0.001), pre- XDR-TBo 1.62 (95% CI, 1.09–2.40; P 5 0.018), or pre-

XDR-TBs 1.57 (95% CI, 1.01–2.44; P 5 0.048) Compared with the survival of patients with the other form of MDR-TB ^[51].

Another retrospective study on Outcome of hospitalized MDR-TB patients; Israel 2000–2005 in Israel; factors independently associated with death were age (OR=1.036, 95% CI 1.0–1.1, p=0.014), hypoalbuminemia (OR=2.95, 95% CI 1.1–7.6, p=0.025), sputum smear positive for acid-fast bacilli at diagnosis (OR=3.7, 95% CI 1.2–11.4, p=0.023), alcohol abuse (OR=4.8, 95% CI 1.7–13.7, p=0.004) and the presence of XDR-TB (OR 8.3, 95% CI 1.5–44.6, p=0.014) ^[53].

A Case-control study on Risk Factors for Mortality among MDR- and XDR-TB Patients in a High HIV-Prevalence Setting; in South Africa; associated factors for high mortality in MDR TB patients was CD4 count less than 50 cells/mm³ (HR 4.08, p=0.02) and CD4 count of 51-200 cells/mm³ (HR 3.87, p=0.01); in addition factors for higher mortality in XDR TB patients were CD4 cell count less than 50 cells/mm³ (HR 4.46, p=0.01), and resistance to all six drugs tested (HRESCxKm; HR 2.54, p=0.04), but taking ART (HR 0.34, p=0.009) was protective ^[54].

A retrospective study on Risk Factors for Poor Treatment Outcomes in Patients with MDR-TB and XDR-TB in China; the independent risk factor associated with death was the presence of tumor (OR, 23.584; 95% CI, 5.361-103.737, P<0.0001) ^[55].

A retrospective study on Minimal Diversity of Drug-Resistant Mycobacterium tuberculosis Strains in South Africa; independently associated factors of mortality were Low CD4 count, presence of extra-pulmonary TB, and recent hospitalization ^[56].

Another retrospective study on risk factor and outcome of human immunodeficiency virus-infected patients with sporadic multi-drug resistance tuberculosis in New York City, IN USA; CD4-lyphosight count less than 200 (5.56, 95% CI, 1.09-28.56) was factor for short term survival in MDR TB with HIV co-infection patients ^[57].

Other retrospective study Outcome of pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study in Taipei, Taiwan: age greater than 45 years of age is significantly associated with death for pulmonary multidrug-resistant tuberculosis patients ^[58].

A retrospective study done on Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB in Estonia; independently associated factors for the death of MDR TB patients was having HIV co-infection (OR 10.16, 95% CI, 1.17–88.84; p50.04), previous TB treatment (OR 2.88, 95% CI, 1.50–5.52; p50.001), Resistance to ofloxacin (OR 2.30, 95% CI, 1.17–4.51; p50.02) and positive AFB smear (OR 2.09, 95% CI, 1.04–4.20; p50.04) at the start of anti-TB treatment ^[59].

3 Objectives

3.1 General objective

The main objective of this study was to determine the Survival and their determinants in Multi-Drug Resistance Tuberculosis patients co-infected with Human Immune Virus; Addis Ababa, Ethiopia.

3.2 Specific objectives

The specific objectives of this study are the following:

1. To determine clinical characteristics of MDR_TB patients Co-infected with HIV/AIDS.
2. To determine and compare the survival time of patients under certain predictor variables.
3. To identify predictive factors (determinants) associated with survival.

4. Methods

4.1 Study design

A retrospective cohort study was done reviewing by MDR TB log book at St. Peter TB specialized hospital.

4.2 Study area and period

St. Peter TB specialized hospital is established in 1961 G.C in Addis Ababa for the purpose of TB diagnosis, treatment, care and support. First cohort of Ethiopian MDR patients started on Global Health Committee (GHC) drugs at St. Peter's Hospital of 9 first cohort patients one is dead but the remaining 8 are treated successfully. St. Peter hospital serves 922 MDR-TB patients from the starting till June 2015.

In addition to TB and MDR TB treatment and care services St. Peter hospital gives several services to the community. Among them; ART treatment and care service, 24 hrs Emergency service, 24 hours pharmacy service, Anti-natal care service, 24 hrs delivery service, physiotherapy service, psychiatry service..... are some of the services the hospital gives to the community. The study was conducted from February to March 2016.

4.3 Populations

4.3.1 Source population

Source population were all MDR TB record who had been initiated for MDR TB treatment at St. Peter hospital; since the Hospital starting to give MDR TB treatment (Feb 2009) to December 2015.

4.3.2 Study population

Study populations were Patients (MDR TB) who had been enrolled for MDR TB treatment from January first 2014 to last December 2015 at St. Peter hospital.

4.4 Inclusion and exclusion criteria

4.4.1 Inclusion criteria

- MDR TB patients age greater than and equal to 15 years who had been enrolled to MDR TB treatment from January 1/2014 to December 31/2015.

4.4.2 Exclusion criteria

Patient under follow up and with incomplete information such as date of entry and exit, HIV test result, age, sex were excluded.

4.5 Sample size and Sampling procedure

4.5.1 Sample size Calculation

Sample size was calculated using Epi-info 7 for each variable to get maximum sample size based on the following assumptions ; 95% CI, 80% Power, 1:2 proportion.

1. When we calculate sample size using mortality of MDR TB co-infected with HIV; HR=5.6 (95% CI, 3.2-9.7) (37), death among unexposed 12.3% (11) come out with 27 exposed and 53 unexposed.
2. When we calculate sample size using primary MDR TB; HR=2.33 (P=0.0001) (39), prevalence of primary MDR TB 16.9% (12) come out with 100 exposed and 200 unexposed.
3. When we calculate sample size using MDR TB with low BMI at the starting of treatment; HR=2.26 (51), Prevalence of low BMI at the baseline of treatment 42.9% (24) come out with 80 exposed and 159 unexposed.

Finally take the sample size with large number of exposed 100 and non-exposed 200.

Table 1: Sample size determination of study subjects; St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia Dec. 2016

Variable	Power (%)	CI (%)	HR	Proportion	Prevalence among non-exposed (%)	Sample exposed	Sample non-exposed
Mortality by MDR TB	80	95	5.6	1:2	12.3%	27	53
Primary MDR TB	80	95	2.33	1:2	16.9%	100	200
MDR TB with low BIM	80	95	2.26	1:2	42.9%	80	159

4.6.2 Sampling procedures

St. Peter hospital was selected by convenient sampling because it is the first hospital to give service for MDR TB patients. Then stratify them with exposed groups (MDR TB with HIV/AIDS co-infection) and non-exposed group (patients with MDR TB without HIV/AIDS co-infection). In each stratum select all patients on the registry which are 93 exposed and 213 non-exposed study subjects. **(Figure 1)**

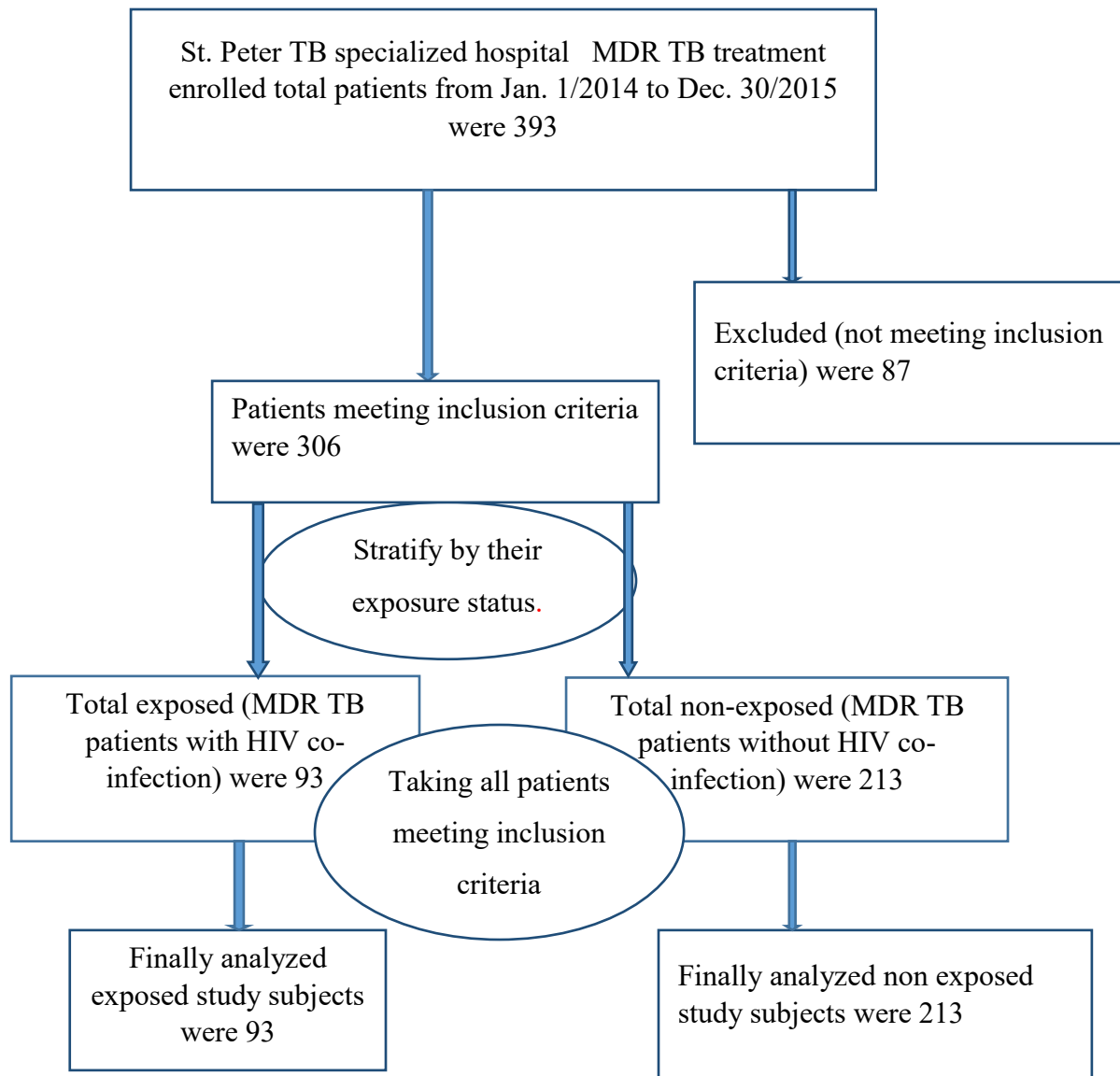


Figure 1: Schematic presentation of the sampling procedure, Addis Ababa Ethiopia, Dec. 2016

4.7 Variables

4.7.1 Dependent variable

The dependent variable is death and its time of occurrence in any of the treatment follow up period.

4.7.2 Independent variables

4.7.2.1 Demographic variables

- Age at the beginning of treatment
- Sex
- Region (Address they came from)
- Educational status

4.7.2.2 Behavioral variables

- Use of alcohol
- Use of cigarette smoking
- Use of kchat abuse

4.7.2.3 Clinical variables

- Presence of co-morbidity
- Number of prior TB treatment
- Started treatment as ambulatory or hospitalized
- Presence of therapeutic delay
- Registration group (New, Relapse, After lost to follow up, Failure of regimen, After failure of retreatment, Transfer in from another MDR TB initiating center, Other)
- Type of MDR TB

- Type of resistance
- Types of drug used in intensive phase
- Types of drug used in continuous phase
- Base line BMI
- Base line smear result
- Base line culture result
- Presence of HIV/AIDS
- Taking ART drug
- Smear result conversion
- Culture result conversion
- Prior use of SLD (second line drugs)

4.8 Data collection procedures and technique (Instrument, personnel, data quality control)

Data extraction formats was adapted from similar literature and patients' registration and follow up charts. All relevant variables were extracted from patient registration book (log book) and follow up charts and patient cards. Data was extracted by trained data collectors. The data collection processes was supervised by principal investigator.

4.9 Operational definition

Exposed: In this study exposed mean MDR TB patient **with** HIV/AIDS co-infection during the study period (January first 2014 to last December 2015).

Non-exposed: In this study non-exposed mean MDR TB patient **with-out** HIV/AIDS co-infection during the study period (January first 2014 to last December 2015).

Event: A patient who dies for any reason during the course MDR TB treatment.

Censored: A patient does not develop event (defaulters, transferred out, treatment completed and cured, treatment failed, lost follow up)

4.10 Data Entry, Cleaning and Analysis

Data was entered in to SPSS version 20 and export to STATA version 12 for analysis. Descriptive statistical analysis such as median, percentage was used to describe demographic and clinical characteristics of the study population. Survival time was determined from date of treatment initiation to date of date of event occurs. Days were used as time scale to calculate survival time. Kaplan-Meier was employed to determine cumulative survival probability of study subjects after initiation of the treatment. Survival of exposed and non-exposed group was compared by Kaplan-Meier survival functions using log-rank test. Base line factors that would be associated with outcome variables at 20 % ($p < 0.20$) significant level in the bivariate analysis were included in the final Multivariable analysis. Hazard Ratios (HR) with 95% confidence intervals was computed and statistical significance was declared when the significant at the 5% level ($p < 0.05$). Cox proportional hazards regression model was used to determine factors associated with risk of death by controlling confounding and effect modifier. Model was fitted (selected) using back ward selection among variables and significance was check, if p value < 0.05 .

4.11 Data quality management

To ensure the quality of data, pre-test was done on 10% of subjects in St. Peter TB specialized hospital MDR TB clinic. The pre-test was used to determine the clarity of the questions, terms, and time required to complete the checklist. Following the pre-test, checklist formats evaluated and improved (remove variables presence of adverse effect, action taken for adverse effect because they were not registered and added variables use of alcohol, use of cigarette smoking, use of kchat abuse, started treatment as hospitalized or ambulatory, base line height, baseline

BMI, number of prior TB treatment, use of SLD prior to this treatment). Give training to data collectors on data encoding and closely supervised by principal investigator at the time of data collection. Training help to got common understanding (familiar to the check list) and to avoid confusion on the check list between the data collectors and principal investigator. Data completeness and consistency were checked by running frequencies of each variable.

4.12 Ethical consideration

Ethical clearance of this study was obtained from the research ethics committee of the School of Public Health, College of Health Sciences in Addis Ababa University. As well as St. Peter TB specialized hospital research ethics committee. Since it is secondary data taken retrospectively I was not gotten any informed consent for individuals (study subjects) instead of them I was gotten informed written consent from St. Peter hospital. To ensure confidentiality, patient records coded and accessed only by personnel working in the hospital.

5. Result

5.1 Demographic characteristics of MDR_TB patients Co-infected with HIV/AIDS

Out of 93 exposed groups 48 (51.61%) were female and the rest 45 (48.39%) were male; out of 213 non-exposed groups 112 (52.58%) were female and the rest 101 (47.42%) were male. Regarding age group 6 (6.45%) belongs age category 15-24 years of age, 28 (30.11%) had age 25-34 years of age, 42 (45.16%) had age 35-44 years of age, 13 (13.98%) had age 45-54 years of age, 3 (3.23%) had age 55-64 years of age, and the rest 1 (1.08%) had age greater than or equal to 65 years of age among exposed group and age distribution among non-exposed group was 78 (36.62%) had between 15-24 years of age, 74 (34.74%) had between 25-34 years of age, 36 (16.90%) had age 35-44 years of age, 15 (7.04%) had age 45-54 years of age, 6 (2.82%) had age 55-64 years of age, and the rest 4 (1.88%) had greater than or equal to 65 years of age. The median age was 30 (± 11.09 SD) years old. Address of study subjects among exposed group was 75 (80.65%) come from Addis Ababa, 12 (12.9%) from Oromiya, and 6 (6.45%) from others; and address of non-exposed groups was 161 (75.59%) from A.A, 24 (11.27%) from Oromiya, and 28 (13.15%) from others.

Regarding educational status 14 (15.05%) illiterate, 31 (33.33%) had primary school, 35 (37.63%) had secondary school, 13 (13.98%) had above secondary school among exposed; and educational status among non-exposed groups was 42 (19.72%) illiterate, 72 (33.8%) had primary school, 59 (27.7%) had secondary school, and 40 (18.78%) had above secondary school. Abusers (unhealthy behavior) (smoker or alcoholic or kchat chewing) condition of exposed group 16 (17.2%) were abusers and the rest 77 (82.8%) were non-abusers; for non-exposed group 24 (12.27%) were abusers and 189 (88.73%) were non-abusers.

Table 2: Socio-demographic distribution of study subjects; St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia Dec, 2016

Characteristics	Exposed	Percent (%)	Non-exposed	Percent (%)
Sex				
Female	48	51.61	112	52.58
Male	45	48.39	101	47.42
Age group				
15-24	6	6.45	78	36.62
25-34	28	30.11	74	34.74
35-44	42	45.16	36	16.90
45-54	13	13.98	15	7.04
55-64	3	3.23	6	2.82
>=65	1	1.08	4	1.88
Address (Region)				
Addis Ababa	75	80.65	161	75.59
Oromiya	12	12.90	24	11.27
Others	6	6.45	28	13.15
Educational status				
Illiterate	14	15.05	42	19.72
Primary school	31	33.33	72	33.8
Secondary school	35	37.63	59	27.7
Above secondary school	13	13.98	40	18.78

5.2 Clinical characteristics of MDR-TB patients Co-infected with HIV/AIDS

Among 93 exposed study subjects 11 (11.83%) never treated tuberculosis before, 51 (54.84%) treated once before for TB, 31 (33.33%) treated twice and above for TB; among 213 non-exposed group 28 (13.15%) never treated tuberculosis before, 109 (52.29%) treated once before for TB, 76 (35.68%) treated twice and above for TB previously.

Treatment started condition of exposed group 78 (83.87%) was hospitalized, 15 (16.13%) was ambulatory (non-hospitalized); and among non-exposed group 150 (70.42%) was hospitalized, 63 (28.58%) was ambulatory (non-hospitalized) at the beginning of treatment initiation.

Out of 93 exposed study subjects 35 (37.63%) had no co-morbidity, 58 (62.37%) had one or more co-morbidity; and among 213 non-exposed study subjects 79 (37.09%) had no co-morbidity and 134 (62.91%) had one or more co-morbidity.

Drug regimen on exposed group 90 (96.77%) take Z,Cm,Lfx,Eto,Cs , 3 (3.23%) take other drug regimens; and among non-exposed group 204 (95.77%) take Z,Cm,Lfx,Eto,Cs , 9 (4.23%) take other drug regimens.

Smear result at the beginning of treatment on exposed group was 33 (35.48%) had smear positive, 52 (55.91%) had smear negative, 8 (8.61%) had no smear result (unknown smear result); non-exposed group smear result 101 (47.42%) had smear positive, 91 (42.72%) had smear negative, 21 (9.86%) had no smear result (unknown smear result).

Culture result at the beginning of treatment on exposed group was 29 (31.18%) had culture positive, 37 (39.79%) had culture negative, 27 (29.03%) had no culture result (unknown culture result); non-exposed group culture result 80 (37.56%) had culture positive, 57 (26.76%) had culture negative, 76 (35.68%) had no culture result (unknown culture result).

There was no study subject got therapeutic delay on both exposed and non-exposed group.

Out of 93 exposed study subjects 44 (47.31%) start continuation phase treatment; and 100 (46.95%) of non-exposed study subjects start continuation phase treatment.

Eighty seven (93.55%) take Anti-retro viral therapy (ART) and the rest did not take it. Among 93 exposed study subjects 91 (97.24%) had no history of taking second line drugs (SLD), 2 (2.15%) had history of taking SLD; out of 213 non-exposed study subjects 205 (96.25%) had no history of taking SLD, 8 (3.76%) of them had history of taking SLD before this treatment.

Among 93 exposed study subjects 19 (20.43%) had develop event (death) and the rest 74 (79.57%) had failure to develop event (censored); among 213 non-exposed study subjects 20 (9.39%) develop event (death) but the rest 193 (90.61%) had failure to develop event (censored).

Table 3: Clinical characteristics study subjects St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia Dec, 2016

Characteristics	Exposed	Percent (%)	Non-exposed	Percent (%)
Prior TB treatment				
Never treated before	11	11.83	28	13.15
Treated once before	51	54.84	109	52.29
Treated twice before	31	33.33	76	35.68
Stared treatment as at				
Hospitalized	78	83.87	150	70.42
Ambulatory (non-hospitalized)	15	16.13	63	28.58
Presence of co-morbidity				
No	35	37.63	79	37.09
Yes	58	62.37	134	62.91
Base-line BMI category				
<18.5Kg/m ²	42	45.16	107	50.23
>=18.5-25Kg/m ²	23	24.73	71	33.33
>=25 Kg/m ²	28	30.11	35	16.43
Site of TB				
Pulmonary	83	89.25	187	87.79

Extra-pulmonary	10	10.75	26	12.21
Prior use SLD				
No	91	97.85	205	96.24
Yes	2	2.15	8	3.76

5.3 Survival time of patients under certain predictor variables

Ninety three exposed study subjects survived for a total of 26,581 person days, and 213 non-exposed study subjects survived for a total of 63,782 person days. **Median** survival time of MDR TB with HIV co-infected groups was 269 person days and those MDR TB without HIV co-infection had 254 person days medial survival time.

The hazard rate among exposed group was higher compared to non-exposed group. Hazard rate of exposed was 7.15 with 95% CI (4.56, 11.21) and hazard rate of non-exposed was 4.32 with 95% CI (2.02, 4.86) deaths per 10000 person days. **(Table 4)**

In addition, the Kaplan Meier survival curve shows lower survival (long-rank test, $P < 0.010$) was seen in exposed groups relative to non-exposed group throughout the follow up time with parallel survival estimate curve. The graph shows there was a better survival among non-exposed groups than exposed groups. **(Figure 2)**

Table 4: Survival time and hazard rate of different variables; St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia Dec. 2016

Variable	Exposed (MDR TB with HIV co-infection)		Non-exposed (MDR TB without HIV co-infection)		Long-rank test (P-value)
	Person days	Hazard rate	Person days	Hazard rate	
HIV reactive	26581	7.15 (4.56, 11.21)	-----	-----	0.010
HIV negative	-----	-----	63782	4.32 (2.02, 4.86)	
Sex					0.054
Female	13382	5.98 (2.99, 11.95)	34210	2.92 (1.57, 5.43)	
Male	13199	8.33 (4.62, 15.05)	29572	3.38 (1.82, 6.28)	
Had co-morbidity					0.013
No	10800	5.56 (2.50, 12.37)	25604	1.17 (0.38, 3.63)	
Yes	15781	8.24 (4.78, 14.19)	38178	4.45 (2.77, 7.16)	
Site of TB					0.008
Pulmonary	22809	8.33 (5.31, 13.06)	56209	3.38 (2.16, 5.30)	
Extra-Pulmonary	3772	0 (-----, -----)	7573	1.32 (0.19, 9.37)	
Intensive phase drug regimen					0.040
Z,Cm,Lfx,Eto,Cs	26108	6.89 (4.34, 10.94)	60614	2.97 (1.87, 4.71)	
Others	473	21.14 (2.98, 150.08)	3168	6.31 (1.58, 25.24)	
Intensive Smear result					0.019
Positive	10164	7.87 (3.94, 15.74)	31363	2.23 (1.06, 4.68)	
Negative	14734	5.43 (2.72, 10.86)	26639	3.75 (2.02, 6.98)	
Unknown	1683	17.83 (5.75, 55.27)	5780	5.19 (1.67, 16.09)	
Prior SLD used					0.000
No	26492	6.42 (3.99, 10.32)	60689	3.13 (2.00, 4.91)	
Yes	89	224.72 (56.20, 898.53)	3093	3.23 (0.46, 22.95)	
Age category					0.000
15-24	1750	5.71 (0.80, 40.57)	24335	1.64 (0.62, 4.38)	
25-34	7507	6.66 (2.77, 16.00)	19652	3.56 (1.70, 7.47)	
35-44	12422	6.44 (3.22, 12.88)	13902	1.44 (0.36, 5.75)	
45-54	4300	6.98 (2.25, 21.63)	3433	8.74 (2.82, 27.09)	
55-64	597	16.75 (2.36, 118.91)	1822	10.98 (2.75, 43.89)	
>=65	5	2000 (281.73, 14298.14)	638	31.35 (7.84, 125.34)	
Address					0.018
Addis Ababa	22860	7.00 (4.29, 11.42)	48174	2.28 (1.26, 4.12)	
Oromiya	2676	7.47 (1.87, 29.88)	6007	9.99 (4.49, 22.23)	
Others	1047	9.57 (1.35, 67.33)	9601	3.12 (1.01, 9.69)	

History of prior TB treatment					
No TB treatment	1436	27.86 (10.45, 74.21)	8622	5.80 (2.41, 13.93)	0.020
Once	13929	6.46 (3.36, 12.42)	30317	2.31 (1.00, 4.84)	
Twice or more	11216	5.35 (2.40, 11.91)	24843	3.22 (1.61, 6.44)	
Starting condition					
Hospitalized	21696	8.30 (5.22, 13.17)	42417	4.72 (3.04, 7.31)	0.000
Non-hospitalized	4889	2.04 (0.29, 14.52)	21365	0 (-----, -----)	
BMI category**					
<18.5	12597	5.56 (2.65, 11.66)	31852	2.83 (1.47, 5.43)	0.003
>=18.5<25	7221	5.54 (2.08, 14.76)	21226	1.41 (0.46, 4.38)	
>=25	6763	11.83 (5.92, 23.65)	10704	7.47 (3.74, 14.945)	
Abusers***					
Yes	4825	4.15 (1.04, 16.58)	7345	2.84 (1.74, 4.63)	0.034
No	21758	7.81 (4.86, 12.57)	56437	5.45 (2.04, 14.51)	

**Source: World Health Organization(2006)“BMI classifications” http://www.who.int/bmi/index.jsp?introPage=intro_3.html

***Abusers (unhealthy behavior) (smoker or alcoholic or kchat chewing)

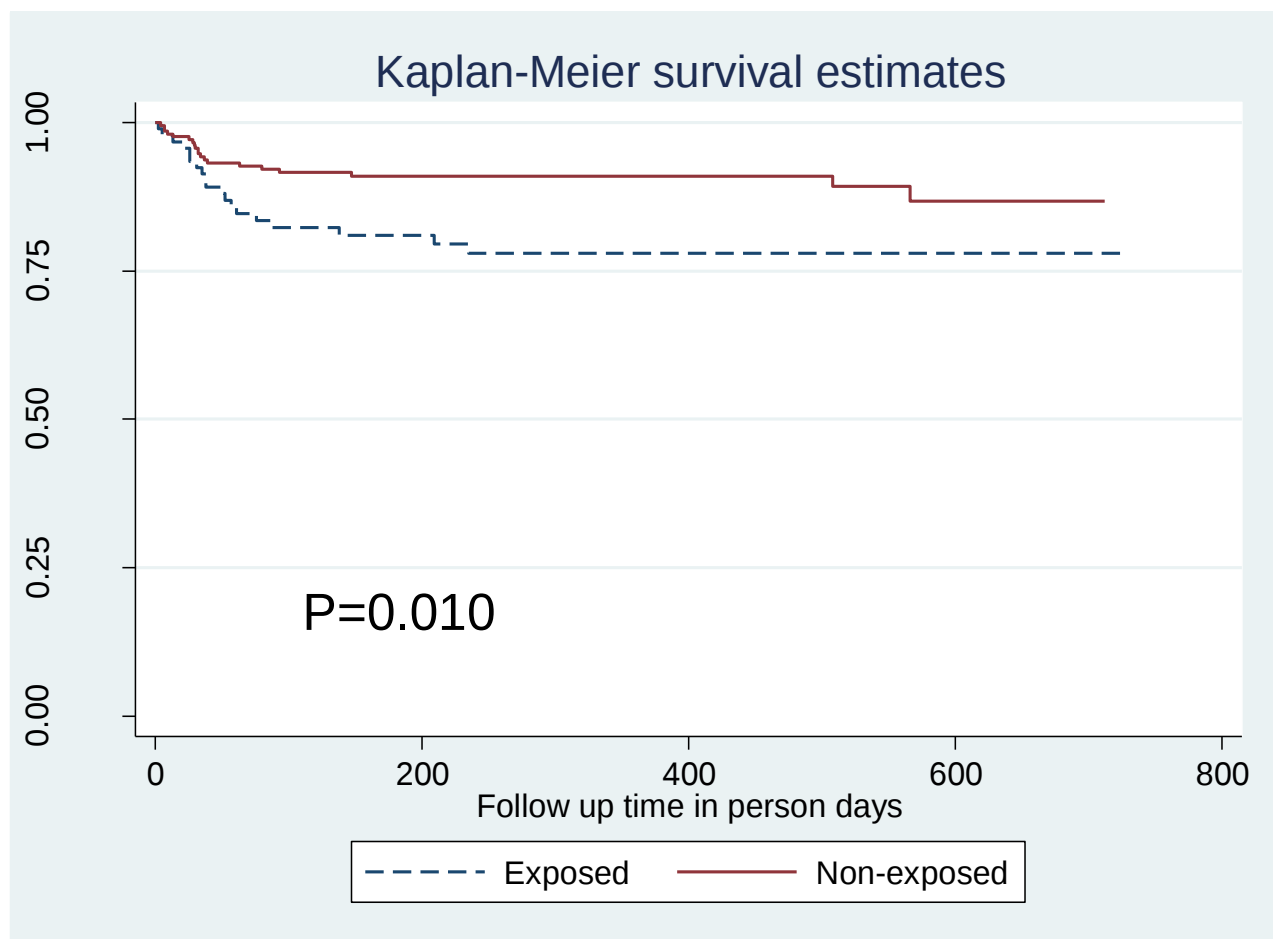


Figure 2: Kaplan-Meier survival curve based on their exposure status; St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia Dec. 2016

Mortality rate of study subjects who had exposed with pulmonary MDR TB were higher than those who had exposed with extra-pulmonary MDR TB. Risk of death among exposed pulmonary MDR TB study subjects were 8.33 with 95% CI (5.31, 6.13.06) deaths per 10000 person days follow up time and had 22809 person days cumulative survival time. But there was no death among exposed extra-pulmonary study subjects which means hazard rate of exposed with extra-pulmonary MDR TB study subjects were 0 (zero) with a total of 3772 person days cumulative survival time. (Table 3)

Mortality rate of study subjects who had non-exposed with pulmonary MDR TB were higher than those who had non-exposed with extra-pulmonary MDR TB. Risk of death among non-exposed pulmonary MDR TB study subjects were 3.38 with 95% CI (2.16, 5.30) deaths per 10000 person days follow up time and had 56209 person days cumulative survival time. Whereas hazard rate of non-exposed with extra-pulmonary MDR TB study subjects were 1.32 with 95% CI (0.19, 9.37) deaths per 10000 person days follow up time and had a total of 7573 person days survival time. **(Table 3)**

Mortality rate of study subjects who had exposed with pulmonary MDR TB were higher than those who had non-exposed with pulmonary MDR TB. Risk of death among exposed pulmonary MDR TB study subjects were 8.33 with 95% CI (5.31, 6.13.06) deaths per 10000 person days follow up time and had 22809 person days cumulative survival time. Whereas hazard rate of non-exposed pulmonary MDR TB study subjects were 3.38 with 95% CI (2.16, 5.30) deaths per 10000 person days follow up time and had a total of 56209 person days survival time. **(Table 3)**

Mortality rate of study subjects who had non-exposed with extra-pulmonary MDR TB were higher than those who had exposed with extra-pulmonary MDR TB. Risk of death among non-exposed with extra-pulmonary MDR TB study subjects were 1.32 with 95% CI (0.19, 9.37) deaths per 10000 person days follow up time and had 7573 person days cumulative survival

time. But there was no death among exposed with extra-pulmonary MDR TB study subjects. That means the hazard rate of exposed with extra-pulmonary MDR TB study subjects was 0 with a total of 3772 person days cumulative survival time. **(Table 3)**

Mortality rate among exposed pulmonary MDR TB were highest with hazard rate 8.33 (5.31, 13.06), then followed by non-exposed pulmonary MDR TB with hazard rate 3.38 (2.16, 5.30), then followed by non-exposed extra-pulmonary MDR TB with hazard rate 1.32 (0.19, 9.37) then finally there was 0 hazard among exposed with extra-pulmonary MDR TB. (Table 3)

In the Kaplan Meier survival estimate among four lines non-exposed with extra-pulmonary MDR TB crossed once the two lines (exposed with pulmonary MDR TB and non-exposed pulmonary MDR TB lines) at few days of initiation of treatment but did not crossed exposed with extra-pulmonary line then keep parallel with street line. The rest three lines (exposed with extra-pulmonary MDR TB, non-exposed with pulmonary MDR TB, and non-exposed with extra-pulmonary MDR TB lines) had parallel with no crossings. And also the graph shows best survival (long rank test, $p=0.008$) among exposed with extra-pulmonary MDR TB study subjects, then followed by non-exposed with extra-pulmonary study subjects, then followed by non-exposed with pulmonary MDR TB study subjects and the worst survival was seen among exposed with pulmonary MDR TB study subjects. **(Figure 3)**

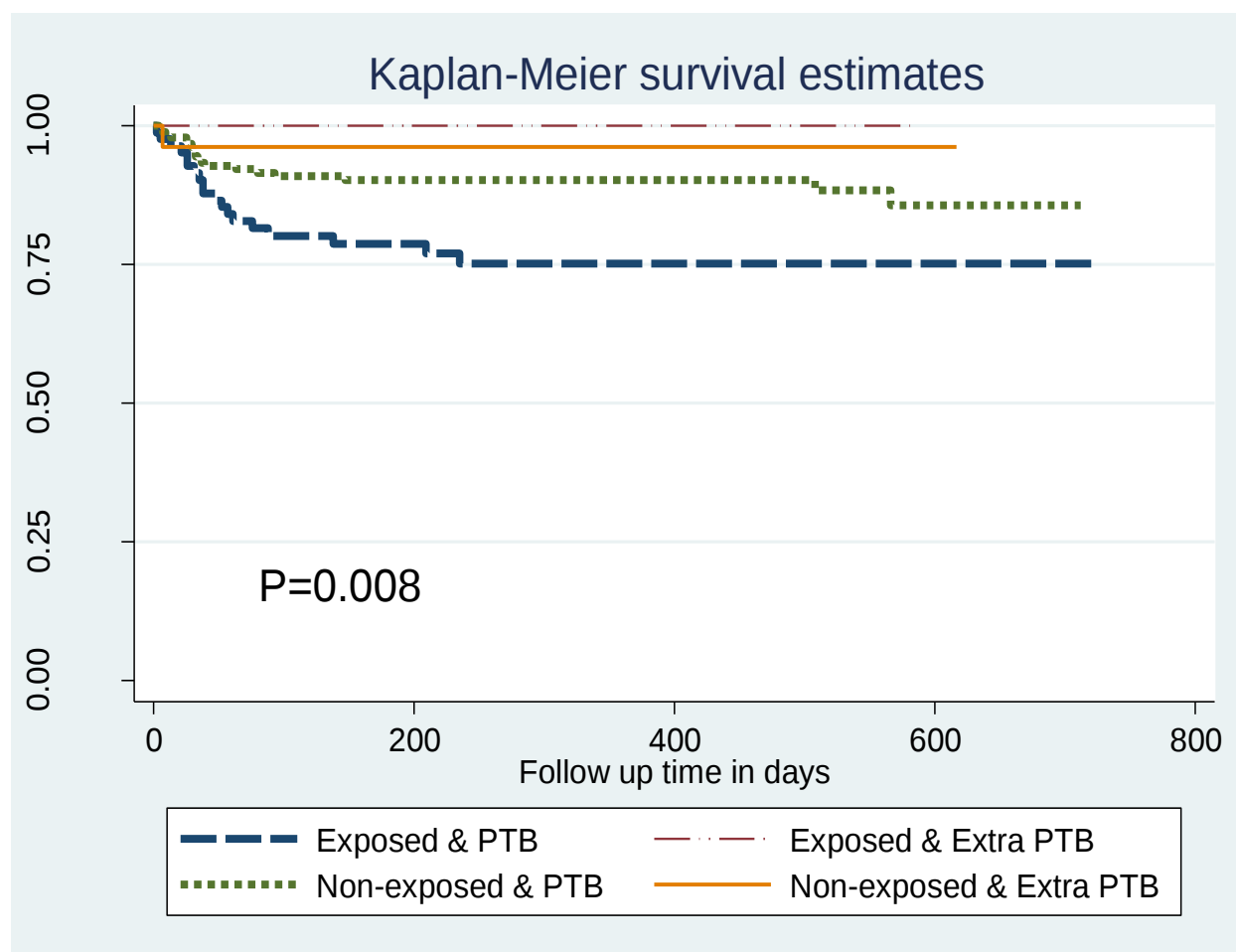


Figure 3: Kaplan-Meier survival estimate by exposure status and site of MDR TB; St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia Dec. 2016

Distribution of mortality among exposed study subjects who had co-morbidity were higher than those exposed study subjects who had no co-morbidity. Risk of death among exposed study subjects with co-morbidity were 8.24 with 95% CI (4.78, 14.19) deaths per 10000 person days follow up time and had 15781 person days cumulative survival time. Whereas the risk of death among exposed study subjects who had no co-morbidity were 5.56 with 95% CI (2.50, 12.37) deaths per 10000 person days follow up time and had 10800 person days cumulative survival time. (Table 3)

Distribution of mortality among non-exposed study subjects who had co-morbidity were higher than those non-exposed study subjects who had no co-morbidity. Risk of death among non-exposed study subjects with co-morbidity were 4.45 with 95% CI (2.77, 7.16) deaths per 10000 person days follow up time and had 38178 person days cumulative survival time. Whereas the risk of death among non-exposed study subjects who had no co-morbidity were 1.17 with 95% CI (0.38, 3.63) deaths per 10000 person days follow up time and had 25604 person days cumulative survival time. (Table 3)

Distribution of mortality among exposed study subjects who had co-morbidity were higher than those non-exposed study subjects who had co-morbidity. Risk of death among exposed study subjects who had co-morbidity were 8.24 with 95% CI (4.78, 14.19) deaths per 10000 person days follow up time and had 15781 person days cumulative survival time. Whereas the risk of death among non-exposed study subjects who had co-morbidity were 4.45 with 95% CI (2.77, 7.16) deaths per 10000 person days follow up time and had 38178 person days cumulative survival time. (Table 3)

Distribution of mortality among exposed study subjects who had no co-morbidity were higher than those non-exposed study subjects who had no co-morbidity. Risk of death among exposed study subjects who had no co-morbidity were 5.56 with 95% CI (2.50, 12.37) deaths per 10000 person days follow up time and had 10800 person days cumulative survival time. Whereas the risk of death among non-exposed study subjects who had no co-morbidity were 1.17 with 95% CI (0.38, 3.63) deaths per 10000 person days follow up time and had 25604 person days cumulative survival time. (Table 3)

Distribution of mortality among exposed study subjects who had co-morbidity were highest with hazard rate 8.24 (4.78, 14.19), then followed by exposed study who had no co-morbidity with hazard rate 5.56 (2.50, 12.37), then followed by non-exposed study subjects who had co-

morbidity with hazard rate 4.45 (2.77, 7.16) then finally the list risk of death were seen among non-exposed study subjects who had no co-morbidity with hazard rate 1.17 (0.38, 3.63).(Table 3)

In the Kaplan Meier survival estimate among four lines exposed and had no co-morbidity crossed the two lines (exposed with had co-morbidity and non-exposed with had no co-morbidity) at few days of initiation of treatment but did not crossed or touch the line of non-exposed with had no co-morbidity. And also the graph shows best survival (long rank test, $p=0.013$) seen among non-exposed study subjects with had no co-morbidity, then followed by non-exposed study subjects with had co-morbidity, then followed by exposed study subjects with had no co-morbidity and finally the worst survival was seen among exposed study subjects with had co-morbidity. (Figure 4)

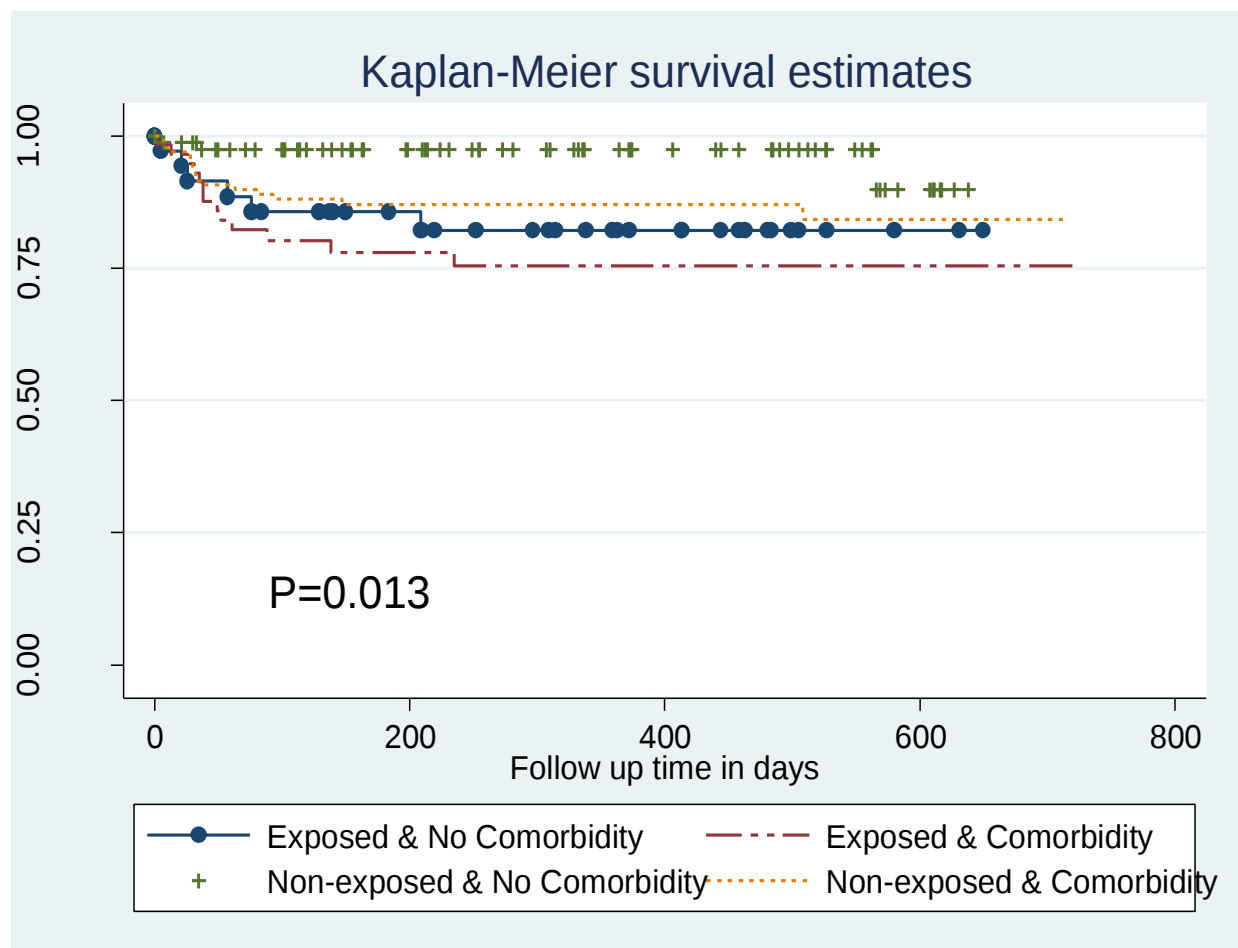


Figure 4: Kaplan-Meier survival estimate by exposure status and presence of co-morbidity; St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia Dec. 2016

Mortality rate of exposed study subjects who had hospitalized were higher than those exposed study subjects who had no hospitalization at the initiation of treatment. Risk of death among exposed study subjects who had hospitalized were 8.30 with 95% CI (5.22, 13.17) deaths per 10000 person days follow up time and had 21696 person days cumulative survival time. Whereas the risk of death among exposed study subjects who had no hospitalization were 2.04 with 95% CI (0.29, 14.52) deaths per 10000 person days follow up time and had 4889 person days cumulative survival time. (Table 3)

Mortality rate of non-exposed study subjects who had hospitalized were higher than those non-exposed study subjects who had no hospitalization at the initiation of treatment. Risk of death among non-exposed study subjects who had hospitalized were 4.72 with 95% CI (3.04, 7.31) deaths per 10000 person days follow up time and had 42417 person days cumulative survival time. But no death seen among non-exposed study subjects who had no hospitalization at the initiation of treatment which means hazard rate was 0 (zero) with a total of 21365 person days cumulative survival time. (Table 3)

Mortality rate of exposed study subjects who had hospitalized were higher than those non-exposed study subjects who had hospitalization at the initiation of treatment. Risk of death among exposed study subjects who had hospitalized were 8.30 with 95% CI (5.22, 13.17) deaths per 10000 person days follow up time and had 21696 person days cumulative survival time. Whereas the risk of death among non-exposed study subjects who had hospitalized were 4.72 with 95% CI (3.04, 7.31) deaths per 10000 person days follow up time and had 42417 person days cumulative survival time. (Table 3)

Mortality rate of exposed study subjects who had no hospitalized were higher than those non-exposed study subjects who had no hospitalization at the initiation of treatment. The risk of death among exposed study subjects who had no hospitalization were 2.04 with 95% CI (0.29, 14.52)

deaths per 10000 person days follow up time and had 4889 person days cumulative survival time. But no death seen among non-exposed study subjects who had no hospitalization at the initiation of treatment which means hazard rate was 0 (zero) with a total of 21365 person days cumulative survival time. (Table 3)

Mortality rate among exposed study subjects who had hospitalized were highest with hazard rate 8.30 (5.22, 13.17), then followed by non-exposed study subjects who had hospitalized were with hazard rate 4.72 (3.04, 7.31), then followed by exposed study subjects who had no hospitalized with hazard rate 2.04 (0.29, 14.52) then finally there was 0 (zero) hazard among non-exposed study subjects who had no hospitalized at the initiation of treatment. (Table 3)

In the Kaplan Meier survival estimate four lines not crossed or touch each other after the initiation of treatment. They were parallel till the end of each line. And also the graph shows best survival (long rank test, $P=0.000$) among non-exposed study subjects who had no hospitalized, then followed by exposed study subjects who had no hospitalized, then followed by non-exposed study subjects who had hospitalized and the worst survival was seen among exposed study subjects who had hospitalized at the initiation of treatment. **(Figure 5)**

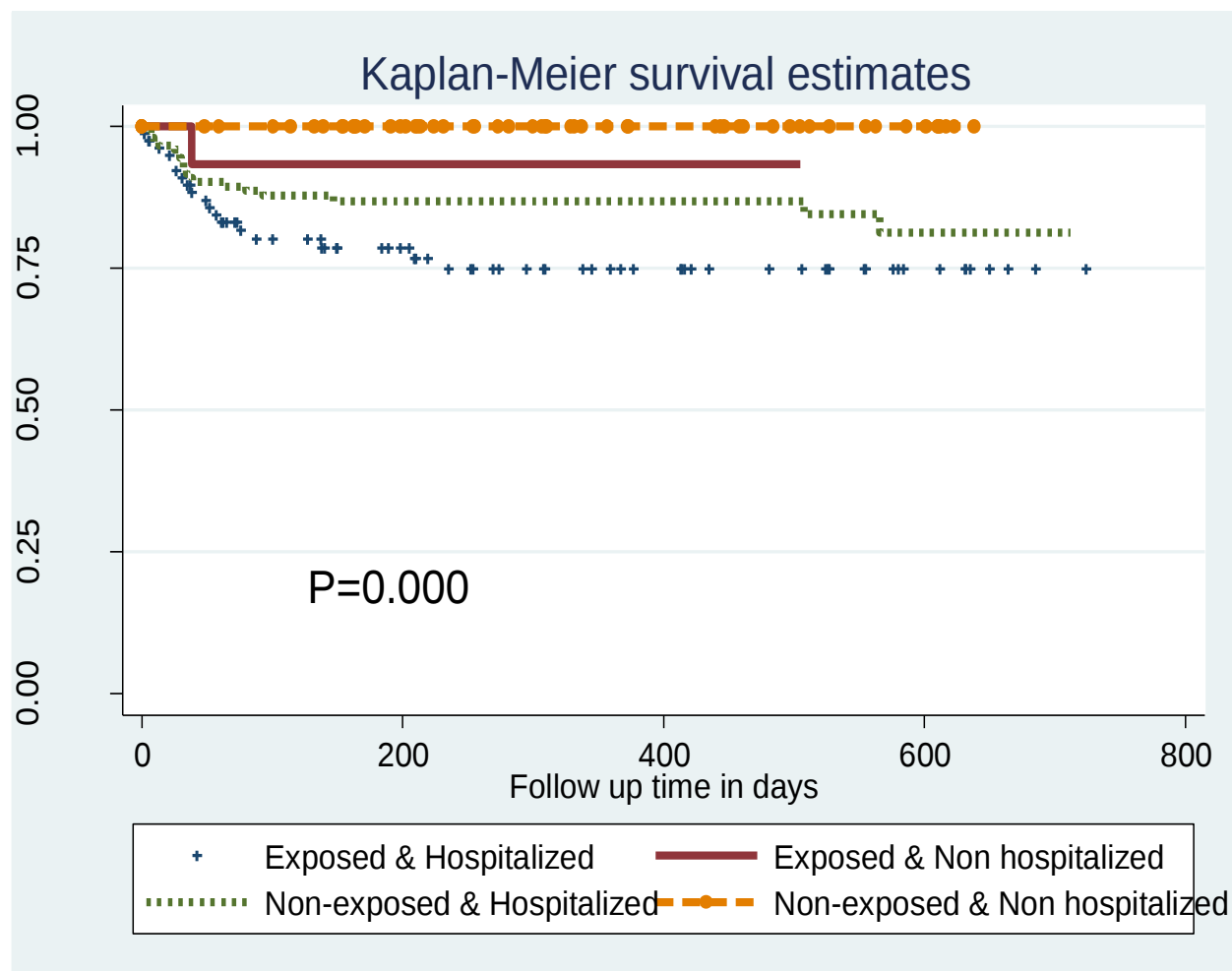


Figure 5: Kaplan-Meier survival estimate by exposure status and treatment starting condition; St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia Dec. 2016

5.4 Predictive factors (determinants) associated with survival

Predictor variables on the bivariate analysis was address of study subjects, had history of TB treatment before the present treatment, starting condition of patient at as ambulatory or hospitalized, level of education, presence of one or more co-morbidity, site of MDR TB, age, had use of SLD previously, presence of HIV co-infection (exposed); this variables had predictors of poor survival time on bivariate analysis.

On the multivariable analysis hospitalization at the starting of treatment, presence of HIV co-infection and age greater than or equal to 65 were independently predict the poor survival time. (Table 5)

Table 5: Multivariable analysis of covariate associated with risk of death St. Peter tuberculosis specialized hospital, Addis Ababa, Ethiopia Dec. 2016.

Variable	Number of subjects	Multivariable analysis	
		Hazard Ratio (95%CI)	P-value
Starting condition			
Hospitalized	228	8.64 (1.11, 67)	0.03
Non-hospitalized	78	R.	
HIV result			
Positive	93	2.15 (1.04, 4.46)	0.039
Negative	213	R.	
Age category			
15-24	84	R.	0.410 0.982 0.191 0.102 0.009
25-34	102	1.58 (0.53, 4.71)	
35-44	78	1.01 (0.32, 3.18)	
45-54	28	2.35(0.65, 8.49)	
55-64	9	3.50 (0.78, 15.73)	
>=65	5	10.07 (1.80, 56.29)	

Risk of mortality among MDR TB with HIV co-infected study subjects were significantly higher than those MDR TB without HIV co-infection with AHR 2.15 95% CI (1.04, 4.46); MDR TB patients who had HIV co-infection were about 2.15 times more likely to die than those MDR TB patients who had no HIV co-infection.

Age greater or equal to 65 years are significantly higher risk of poor survival time compared with age between 15-24 years with AHR 10.07 95% CI (1.80, 56.29). Age greater or equal to 65 years study subjects were 10.07 times more likely to die than those study subjects who had age 15-24 years.

Hospitalization at the time of initiation of treatment has independently association with risk of death compared with non-hospitalized (ambulatory) patients with AHR 8.64 95% CI (1.11, 67). Hospitalized study subjects were 8.64 times risk of death compared to non-hospitalized study subjects at the initiation of treatment of MDR TB. (Table 5)

6. Discussion

This study was conducted to determine and compare survival time among MDR TB patients with HIV co-infection (total of 93 exposed study subjects) and MDR TB patients without HIV co-infection (total of 213 non-exposed study subjects); and the study also explain predictors of mortality.

The study showed there was significant difference of survival time between MDR TB patients with HIV co-infection (exposed) and MDR TB patients without HIV co-infection (non-exposed) study groups. MDR TB patients without HIV co-infection had a better survival and lower risk of death compared with exposed MDR TB patients with HIV co-infection. Hospitalized study subjects at the time of MDR TB initiation had poor (short) survival time compared with un-hospitalized (ambulatory) patients during MDR TB initiation. And also study subjects whose age greater than or equal to 65 were short survival time compared with study subjects whose age were 15-24 years old.

This study emphasize screening all HIV positive patients for MDR TB and give accesses to all population by prioritizing elders for early diagnosis and treatment of MDR TB.

In this study risk of mortality was higher in MDR TB with HIV positive study subjects than MDR TB with HIV negatives study subjects with hazard ratio of 2.15. This finding is consistent with studies done in South Africa, Lithuania and Nigerian ^[37, 39, 43, 48, 52].

But in this study finding regarding to HIV was had not consistent with study done in Russia and Israel which showed HIV co-infection was not independent predictor of risk of death ^[24, 53]; This inconsistency may due to decrease immunity by HIV and also due to pill burden of medication for HIV, MDR TB and other medications for opportunistic infections in this study. But in Russia and Israel studies study subjects may had better immunity status compared to this study because

the number of study subjects who had MDR TB with HIV co-infection was very few [in Russian 0.8% and in Israel 6.1%].

Regarding the association of death and hospitalization our study understand non-hospitalized patients were lower hazard than hospitalized. Most of the time hospitalized patients are critically sick or indications of hospitalization are seriousness of the disease and when the patient cannot takes per mouth medications. This finding was consistent with study done in South Africa hospitalization in the past one year increase risk of death compared to non-hospitalized ^[54].

Regarding the age of the patients our study find out as age increase the risk of death also increased specially age greater than or equal to 65 had higher risk of death compared to age 15-24. This finding was in line with other studies done in Lithuania, Korea, Israel, South Africa ^[48, 50, 51, 53, 56].

But our finding regarding to association between increase age and increased risk of death was inconsistent with study done in South Africa showed excesses mortality decreased with increasing age ^[37]. This inconsistency may be due to socio-economic difference of the two countries or may due to difference on risk behavior of the young population among the two countries or may due to accessing difference to the service between the youngest and the old population in South African study.

In this study presence of XDR TB was not associated with risk of death. This finding was not in line with studies done in Korea, South Africa, Israel ^[50, 51, 53, 56, 57]. This may be due to availability and capacity difference in identifying (investigating) resistance of second line drugs.

Base line smear positive had no association with risk of death in this study. But study done in Israel showed sputum smear positive for acid fast bacilli was independently predictor of risk of death^[53]. This inconsistency may be due to geographical difference and the quality as well as availability of laboratory to detect samples correctly.

7. Strengths and Limitations of Study

7.1 Strength of the Study

The strength of the study was incorporating (availability) of different co-morbidities such as DM, HTN, Hepatitis, Anemia and Malnutrition.

7.2 Limitation of the study

This study had its own limitations this were: -

- 1) Since it was secondary data some important variables such as marital status, family size, presence of adverse effect, action taken for adverse effect because had not available totally (not registered).
- 2) Out of available variable there were missing (unavailable) study subjects for example smear result conversion, culture result conversion, CPT use, time of ART started these variables had some missing.

8. Conclusion

This study find out better survival was seen in multidrug-resistant patient without human immune deficiency virus co-infection (non-exposed group) than those multidrug-resistant patient with HIV co-infection (exposed group).

Presence of human immune deficiency virus co-infection increased the risk of death. Better survival was seen among non-exposed groups.

Hospitalization at the beginning of treatment starting increased the risk of death. Non-hospitalized study subjects had better survival.

As the age of the patient increased the risk of death increased. Younger study subjects had better survival time.

9. Recommendations

- ❖ Early detection and treatment of MDR TB for HIV positive patients.
- ❖ Early diagnosis and treatment of MDR TB patients decrease hospitalization by decreasing complication (severity) of illness (disease).
- ❖ Regular medical check-up for MDR TB is very necessary especially for aged people which helps to detect the problem before it become complicated and disseminated.
- ❖ Further studies on survival of older people and MDR TB.

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11. Annexes

Annex 11.1. Check list

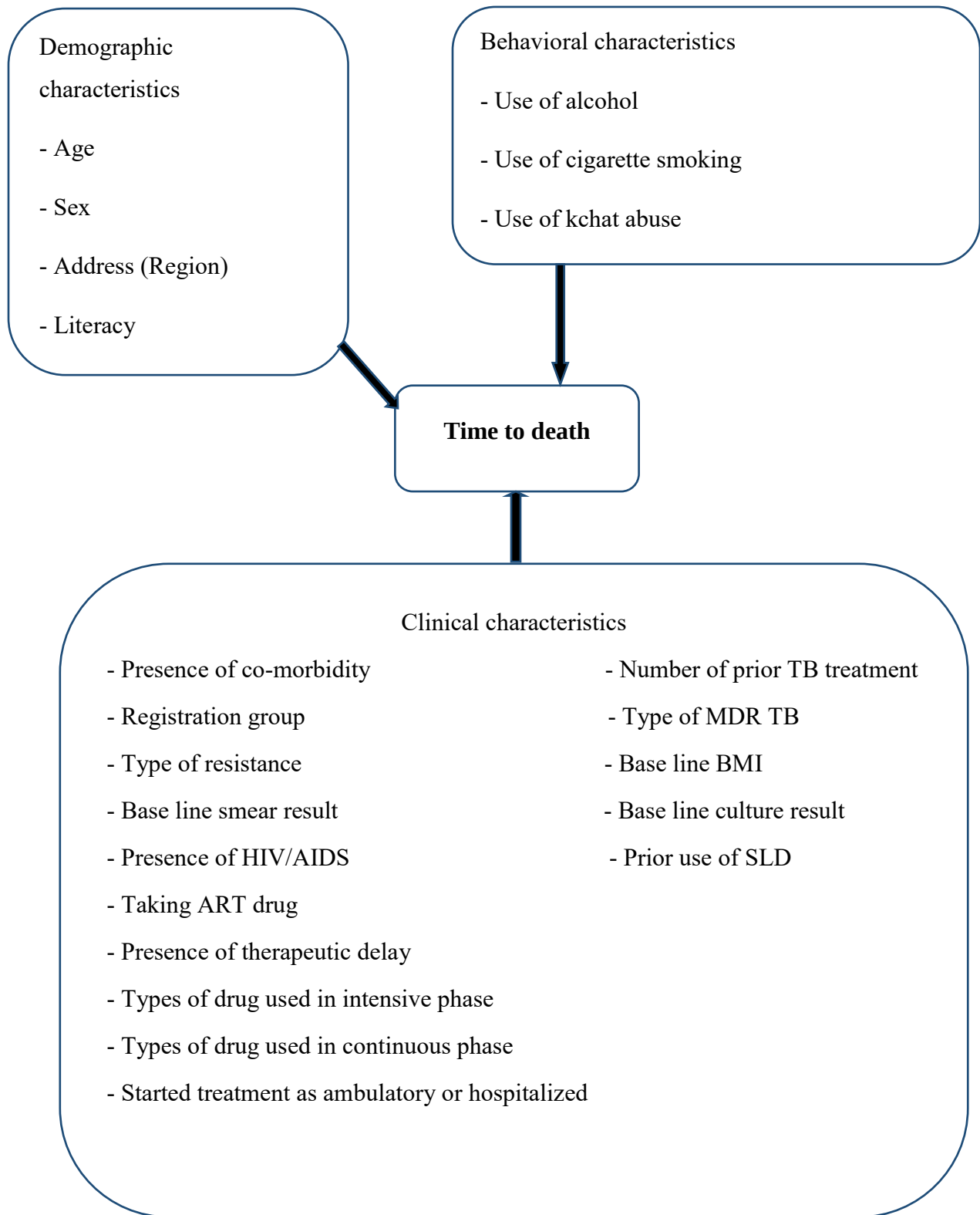
Data extraction check list on MDR TB with HIV co-infection

S. No	Question (description)	Response (Category)	Skip
01	Serial number		
02	Address (region) of patient	1) Tigray 2) Afare 3) Amhara 4) Oromiya 5) Somali 6) Benshangule Gumez 7) SNNPR 8) Gambela 9) Hararie 10) Addis Ababa 11) Dire Dawa 12) Non Ethiopian	
03	Sex	1) Female 2) Male	
04	Age	 Years	
05	Literacy	1) Yes 0) No	Skip to Q7, if Ans. Is 0
06	Grade (years of education)	 Years	
07	Had history of smoking	1) Yes 2) No	
08	Had history of alcohol drinking	1) Yes 2) No	
09	Had history of drug abuse	1) Yes 2) No	
10	Had history of prior TB treatment	1) Yes 2) No	Skip to Q12, if Ans. Is 2
11	How many times	Times	
12	Had history of close contact to MDR TB patient	1) Yes 2) No	
13	Started treatment at	1) Hospitalized 2) Ambulatory (non-hospitalized)	
14	Had you other co-morbidities	1) Yes 2) No	Skip to Q16, if Ans. Is 2

15	Specify		
16	Registration group	1) New 2) Relapse 3) After lost to follow up 4) Failure of new regimen 5) After failure of retreatment 6) Transfer in from another MDR TB initiating center 7) Other	
17	Site of MDR TB	1) Pulmonary 2) Extra-pulmonary	Skip to Q19, if Ans. Is 1
18	Specific site of extra-pulmonary TB		
19	Resistance type	1) RR 2)MDR 3)XDR 4)Poly 5) clinical	
20	Had base line Wight	1) Yes 2) No	Skip to Q22, if Ans. Is 2
21	Wight at base line	Kg	
22	Had base line height	1) Yes 2) No	Skip to Q24, if Ans. Is 2
23	Height at base line	Mt.	
24	Had base line BMI	1) Yes 2) No	Skip to Q26, if Ans. Is 2
25	BMI at base line	Kg/M ²	
26	Intensive phase drug regimen (specify)		
27	Treatment started date	DD.....MM.....YY	
28	Smear result at intensive phase	1) Positive 2) Negative 3) Unknown	
29	Culture result at intensive phase	1) Positive 2) Negative 3) Unknown	
30	Presence of therapeutic delay	1) Yes 2) No	Skip to Q32, if Ans. Is 2

31	How long	1) > 30 days 2) < 30 days	
32	Had started continuation phase	1) Yes 2) No	Skip to Q36, if Ans. Is 2
33	Smear result at continuation phase	1) Positive 2) Negative 3) Unknown	
34	Culture result at continuation phase	1) Positive 2) Negative 3) Unknown	
35	Continuation phase drug regimen (specify)		
36	Treatment out come	1) Cured 2) Treatment completed 3) Died 4) Failure 5) Lost to follow up 6) Transfer out 7) On treatment	
37	Date of treatment out come	DD.....MM.....YY	
38	HIV test result	1) Reactive 2) Non-reactive	Skip to Q44, if Ans. Is 2
39	Time since HIV positive	DD.....MM.....YY	
40	CPT used	1) Yes 2) No	Skip to Q42, if Ans. Is 2
41	Time since on CPT	DD.....MM.....YY	
42	ART used	1) Yes 2) No	Skip to Q44, if Ans. Is 2
43	Time since on ART	DD.....MM.....YY	
44	Prior used for SLD	1) Yes 2) No	

Annex11.2 Conceptual frame work



Annex 11.3: Letters for declaration

I, the under signed, declared that this is my original work, has never been presented in this or any other University, and that all the resources and materials used for the thesis, have been fully acknowledged.

Name: YEMARWUHA ABEBE

Signature: _____

Date: _____

Place: Addis Ababa University, Ethiopia

Date of submission: December, 2016

This thesis has been submitted for examination with my approval as University advisor.

Name: WONDIMU AYELE (M.SC, PhD candidate)

Signature: _____

Date: _____