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SCHOOL OF PHARMACY

DEPARTMENTOF PHARMACEUTICS AND SOCIAL PHARMACY

SURVIVAL TIME TO DEATH AND ITS PREDICTORS AMONG TUBERCULOSIS PATIENTS WHO HAVE STARTED ANTI-TB TREATMENT IN SELECTED HEALTH CENTERS OF ADDIS ABABA, ETHIOPIA: A RETROSPECTIVE COHORT STUDY

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Survival Time to Death and its Predictors among Tuberculosis Patients Who Have Started Anti-TB Treatment in Selected Health Centers of Addis Ababa, Ethiopia: A Retrospective Cohort Study

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This is to certify that the thesis prepared by Girma Teketelew, entitled: " Survival time to death and its predictors among tuberculosis patients who have started anti-TB treatment in selected health centers of Addis Ababa, Ethiopia: a Retrospective cohort study " and submitted in partial fulfillment of the requirements for the Degree of Master of Science in Pharmacoepidemiology and Social Pharmacy complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Background: Tuberculosis remains the leading cause of morbidity and mortality globally and in Ethiopia despite different strategies have been designed and implemented to combat it. Survival time and its predictors among tuberculosis patients who enrolled to care in selected health centers in Addis Ababa were assessed.

Method: A retrospective cohort study was conducted in 20 selected health centers of Addis Ababa city, Ethiopia. Data were collected from April 1 to August 30, 2018 by reviewing medical records of tuberculosis patients who were registered from May 2016 to May 2017. Statistical software STATA version 14 was used for analysis of the data. Kaplan–Meier curve and log-rank test was employed to investigate the statistical significance of the difference in survival experience among different categories of patients. Cox-proportional hazard and accelerated failure time model was used to assess the relationship between baseline variables and mortality. The strength of association was presented by hazard ratio with 95% CI and results were reported significant at $P \leq 0.05$.

Results: The medical records of 371 patients were included in the analysis of which 136 (36.7 %) died during the treatment period. Majority of TB deaths occurred within two months of the start of treatment and the overall estimated median survival time was 157 days. Based on akaikie information criterion, weibull accelerated failure time model manifested better results as compared with other models. In multivariable weibull model, age (HR=0.98, *P=0.04*), baseline weight (HR=0.96, *P=0.03*), tuberculosis treatment phase (continuation phase, HR=0.48, *P≤0.01*) and tuberculosis type (pulmonary negative TB, HR=19.92, *P≤0.01*) were found to be independent predictors of time to death of tuberculosis patients.

Conclusions: Most of the patients died at the end of study period. This warrants that, special attention and follow up with nutritional support for pulmonary negative patients and underweight patients to reduce deaths and for better clinical and treatment outcome.

Key words: Mortality, Predictors, Survival model, Survival time, Tuberculosis

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Table of Contents

List of Figures

List of Tables

Acronyms/Abbreviations

AIC	Akaikie information criterion
BRICS	Brazil, the Russian Federation, India, China and South Africa
CFR	Case fatality rate
DOTS	Directed observed therapy strategy
ETB	Extra pulmonary tuberculosis
FMOH	Federal ministry of health
HIV	Human immune virus
HIV/TB	HIV/TB coinfection
HR	Hazard ratio
MDR-TB	Multi-drug resistance tuberculosis
PMO	Person month observation
PTB	Pulmonary tuberculosis
PYO	Person year observation
Ref	Reference
SNTB	Smear negative tuberculosis
SPTB	Smear positive tuberculosis
Std.Err	Standard error
TB	Tuberculosis
USD	United states dollar
WHO	World health organization

1. Introduction

1.1. Background

Tuberculosis (TB) is an infectious disease which is caused by Mycobacterium tuberculosis and it is a major cause of death worldwide. The lungs is the major part of the body that can be affected by the bacillus (pulmonary TB) (WHO, 2018). Inhalation (breathing) is the major route for the bacilli to enter the body and blood stream, the lymphatic system, may spread the disease to other parts of the body from the lung (WHO, 2017).

Now a days tuberculosis is one of the major global problem and the second-highest cause of death though it is possible prevent and fix the illness (WHO, 2013). The situation is more grave in populations with high HIV prevalence; implying that HIV/AIDS might be major predictor to TB epidemic in different regions, especially in sub- Saharan Africa (Beyene *et al*., 2016)

It is possible to treat the infection using first line anti-TB drugs, including; isoniazid, rifampicin, ethambutol and pyrazinamide, for six months (two months of intensive phase and four months of continuation phase). However, irrational treatment may leads to poor treatment outcomes, namely; treatment failure, default, multidrug-resistant tuberculosis (MDR TB) and finally poor survival (WHO, 2015; Amante *et al*., 2015).

The major significant predictors that aggravate time to death of TB patients includes; poverty, homelessness, alcohol or drug addiction, irregular or inadequate treatment, late diagnosis of the disease, MDR-TB and advanced age (de Almeida *et al*., 2016). Additionally, comorbidities and baseline smear result were also significant predictors for time to death (Waitt and Squire, 2011). HIV infection is also the major driving cause for the progress of active TB infection where the risk is 20–30 times higher when compared to patients with negative HIV infection (CDC, 2011). The catastrophic collision of TB and HIV has yielded an extraordinary burden of suffering and death (WHO, 2017).

Survival analysis is a useful method for measuring time when a censoring mechanism prevents the observation of the precise time at what the event of interest occurs in some of the individuals. It is also the method used for modeling the incidence of events and timing of these events (Vetter and Schober, 2018). It is also useful to analyze survival probabilities of study participants at different follow-up time points (Kleinbaum, 2015). One of the advantages of survival models over other traditional modeling techniques is that it analyses the data with censored observations and time-varying covariates, meaning, linear regression ignores censoring observation and logistic regression ignores time. Hence, survival analysis is the best choice to appropriately analyze time to event data (Sastry, 1997).

Since data on Tuberculosis patients includes censored information, hence, it is not compatible with standard statistical models. For this type of data; proportional hazards model and parametric regression models are more appropriate to identify risk factors that have influence on the survival status of the patients. In developing countries including Ethiopia such information is very important since the burden is very high (WHO, 2017). Therefore, the current study is aimed to estimate the survival status of the patients and to investigate potential risk factors that influence their survival time during the course of treatment period in twenty public health centers of Addis Ababa, Ethiopia. The aim therefore, will be in generating evidence which could be utilized for betterment of the TB treatment service and improving the outcome.

1.2. Statements of the problem

In 2017, about 10 million TB incidence and 1.6 million deaths were reported worldwide, among these developing countries takes the highest percent, the South-East Asian accounts (44%) and the African Region accounts (25%). The above reported number should be falls to 10% by 2020 to reach the first milestones of the End TB Strategy (WHO, 2018).

Globally, Ethiopia is among the 30 high TB burden countries with a rank of 7th worldwide and 2nd in Africa (WHO, 2018). In 2015 Ethiopia has adopted new post-2015 Global TB Strategy called “END TB strategy” which launched to reduce TB incidence

and deaths by 90% and 95% between 2015 and 2035 respectively (FMOH, 2016, FMOH, 2018). Despite this plan, the annual estimated TB incidence accounted about 177/100,000 populations and death rate of 25 per 100,000 populations for 2016 (FMOH, 2018).

In previous study that was conducted in three selected health centers in Addis Ababa, Ethiopia, it was shown that 3.7% of patients died from tuberculosis (Getahun *et al*., 2011). The unpublished report of Addis Ababa Health Bureau showed that, among TB patients who were on treatment in one year, the percentage of deaths was 11.6% (AHB HMIS report, 2016/17), which is higher as compared to the previous study in same setting. Even though there are studies that investigated mortality among TB patients and its predictors associated with this mortality in different parts of Ethiopia (Senbeta *et al*., 2014; Birlie *et al*., 2015; Beyene *et al*., 2016), similar information is lacking in Addis Ababa.

Additionally, the current study had carried out in multicenter facilities that includes about 20 health centers and address the result of accelerated failure time (AFT) distribution. Furthermore, as per Hill's criteria to establish causation, the study should be reproduced by different researchers, in different settings, at different times using different study design to produce consistent finding. This study was therefore conducted to estimate survival time to death and identify its predictors among tuberculosis patients that influence their survival time.

1.3. Significance of the study

Evidence on time to death and associated factors is cornerstone for giving quality care for TB patients and contributes for ending both epidemics and alleviating subsequent mortalities.

The finding of this study will be useful in designing programs to improve clinical care of TB patients and in the prevention of TB at community level. Policy makers and health service managers at different levels may utilize the information generated from this study for decision making process. In addition, the current study will help clinicians to scale up

their knowledge regarding time at which death occurred in TB patients and associated predictors that influence their death and for best practices in the provision of quality care for their clients. The study will also contribute to researchers for further study that might be conducted on related topic and for organizations working with tuberculosis patients and may fill the research gap in the study area in this particular issue. It might be vital to stakeholders working in the study setting and area by showing proportion of death of tuberculosis patients and predictors associated with lower survival time.

2. Literature review

2.1. Burden of tuberculosis

Globally, tuberculosis is top 10 causes of time to death and millions of people infected with the disease each year. The 2018 report of WHO indicated that, about 10.0 million new cases of TB (range, 9.0–11.1 million): 5.8 million men, 3.2 million women and 1.0 million children with equivalent 133 cases (range, 120–148) per 100,000 population reported from different regions of the word. Among these, 1.3 million deaths (range, 1.2–1.4 million) were among patients without HIV and 300,000 deaths (range, 266 000–335 000) were of HIV infected people (WHO, 2018). Globally, the percentage of death was about 1.2 million per year and 5000 per day in 2014 (WHO, 2015).

Even though TB is a curable infectious disease, worldwide it is the second-highest cause of death from infectious diseases and remains a severe global public health concern which ranked second to Human Immunodeficiency virus (HIV) (WHO, 2013). The WHO South-East Asia Region (44%) and the WHO African Region (25%) were the most affected region. Of the estimated number about 90% were adults above 15 years, where 64% were male, 9% were people living with HIV (72% of them in Africa). However, the cases were in all countries and age groups (WHO, 2018). WHO reported that, the incident cases was decreased by 0.4 million people from that of 2016 incident cases, which was about 10.4 million new cases (WHO, 2017).

Fifty (50) percent of the world's TB cases was seen in Brazil, the Russian Federation, India, China and South Africa (BRICS) in 2015. In the year 2014, the burden of tuberculosis is estimated to cost about US$ 0.7 billion dollars globally both in direct and indirect costs per year. Hence, to prevent this infection BRICS uses domestic funding where as other 25 high TB burden countries outside BRICS uses international donors. The cost per patient treated is usually in the range of US$ 100–1000 for active TB (WHO, 2015).

In 1993 WHO announced as tuberculosis is a global health emergency and since then, global tuberculosis control have devised different mechanisms to combat it. Through this

effort, poor survival associated tuberculosis minimized and about 45 million patients have been saved from death. In spite of these advances, it was declared that about 9·6 million people TB incidence and 1·5 million deaths in 2014 all over the world. Now a days it is the most cause of mortality worldwide exceeding malaria and HIV *(*World TB day, 2016*)*. Globally, with this speed it resulted with two million deaths every year and majority of this cases is from developing countries (Silva *et al*., 2010).

India is the highly affected country with TB infection. The incidence of TB in the country accounts about two million cases each year where about 280,000 patients died of the disease. Both new Smear-positive and smear-negative pulmonary TB patients had CFR of 11% where it is higher at 24 % in patients having previous TB history (Patel *et al*., 2016).

Cohort study conducted in USA revealed that, 3451 cases diagnosed as active TB, and among these 417 cases were deaths (Horne *et al*., 2010). Another retrospective study carried on in Portugal showed that, 17.5% of inpatient cases and 5.7% outpatient cases mortality reported which was higher than the national estimate which was (6.4%) (Bastos *et al*., 2016). Another cohort study conducted in Canada showed that, 8.9% CFR of TB (Gao *et al*., 2015). Similarly, death of 700,000 women reported in study conducted in Ireland (Ajagbe *et al*., 2014). In Taiwan TB related death is estimated to be 81·8% where patients older than 65 years dies at the rate (82·1%). Nationwide Survey of TB indicated that, China had CFR of 5.1%, specifically a CFR of 5.5% in Shanghai between 2000 and 2004 (Wang *et al*., 2012).

Globally, Africa is the first in total TB incidence which was about 237(211-263) with the estimated mortality of 39 and 24 in patients with HIV and without HIV infection respectively, whereas South East Asia ranked as second 226 with the mortality about 32 and 1.4 with HIV infected and non HIV patients respectively per 100,000 population (WHO, 2018).

Cameroon had prevalence of 69,000 and about 14100 deaths (Djouma *et al*., 2015). In Zimbabwe the estimated TB death was 50 cases per 100,000 populations, despite the fact that, different strategies are ongoing on to halve the TB death rate by 2015. The burden of

poor survival due to HIV/TB coinfection accounts about 69% of the cases (Takarinda *et al*., 2017). Another cohort study conducted in Nigeria reported that the case fatality rate of 16.6% as a whole and the crude mortality rate of 3.68 per 100 PMO (Adamu *et al*., 2017).

Currently, Ethiopia is one of the 22 high burden countries and the country in which poor survival is seen due to TB infection; in 2013 TB mortality was estimated to be 32 per 100,000 of the population (Beyene *et al*., 2016). The annual mortality rate due to TB infection in Addis Ababa, Hawassa and Yirgalem is 6.3 and 1.02 per 100 PYO respectively (Getahun *et al*., 2011; Senbeta *et al*., 2014). But, in 2017, Ethiopia had about 164 new TB cases per 100,000 population (WHO, 2018) which was 341 per 100,000 in 2015. As per report of Ethiopian federal ministry of health, about 129,743 cases of TB founded and Ethiopia stands 7th in the list of high Burden Countries for TB infection (FMOH, 2016).

2.2. Risk factors for death due to tuberculosis

Though Tuberculosis is a killing disease by itself, there are several independent factors that may precipitate death of the patients. Identifying these determinant factors is very important to make and modify intervention to control the disease and improve treatment outcomes.

In published evidences of recent systematic review; poverty, homelessness, alcohol or drug addiction, irregular or inadequate treatment, late diagnosis of the disease, multidrug-resistant TB (MDR-TB), advanced age and HIV infection were identified as significant risk factors for poor survival of TB patients *(*de Almeida *et al., 2016)*. Additionally, comorbidities and smear results were identified as significant risk factors of death in regions of low TB incidence and low HIV prevalence (Waitt and Squire, 2011).

Study from Spain identified that being >50 years (HR = 36.9), being retired (HR = 2.4), HIV infection (HR = 3.4) and smear-positive sputum (HR = 2.3) as statistically independent risk factors of death among patients with TB during the intensive phase (Rodrigo *et al*., 2016). Similar study reported that Older (P< 0.001), malignancy (P<

0.001), renal insufficiency (P< 0.001), presence of fever (P< 0.020) and anorexia (P< 0.031) were significant covariates of death among patients with TB (Feng *et al*., 2011; Feng *et al*., 2012). On the other hand malnutrition, lower BMI, lower baseline weight identified as significant factors (Waitt and Squire, 2011).

Similarly, several studies from different parts of Ethiopia identified that advanced age, baseline weight, HIV infection, SPPTB, ETB, sex, health service coverage and socioeconomic status as statistically significant factors associated with patients infected with TB (Birlie *et al*., 2015; Senbeta *et al*., 2014; Beyene *et al*., 2016; Getahun *et al*., 2011; Biruk *et al*., 2016).

The HIV infection is an important predictor related to the increased morbidity and mortality of TB in different regions of the world and has resulted in an increased number of hospital admissions and it is known to be the cause of the increased mortality in adults (Mane, *et al*., 2013; Senbeta *et al*., 2014). Being HIV positive increases mortality of the patient on treatment in HIV prevalent regions. Patients having lower CD4 count at the start of the treatment and immune-deficient patients tends to die at the highest rate (Waitt and Squire, 2011; Takarinda *et al*., 2014).

Advancing age significantly associated with decreased survival of the patient during anti-tuberculosis treatment due to lowered immunity and comorbidities as well partly due to confection and general physiological deterioration with age (Shen *et al*., 2009; Yen *et al*., 2017; Beyene *et al*., 2016).

Different level of potential health service coverage and socioeconomic status was considered as major contributory causes of TB death. TB patients who are on good economic status were less likely to die than poor patients, meaning poor survival is related with low socioeconomic status (Senbeta *et al*., 2014).

2.3. Outcome of tuberculosis patients who have initiated treatment

In Cohort Study conducted in Cameroon: 134 (39.8%) had completed treatment, 71 (21.1%) were cured, 99 (29.4) died, 18 (5.3%) were not evaluated, 14 (4.2%) were lost to

follow-up and 1 (0.3%) failed during the study period with overall treatment success rate of 60.8% (Agbor *et al*., 2014).

In a cohort of 1584 patients, 952 (60.1%) had successful treatment outcome and 632 (39.9%) had unsuccessful treatment outcome, among these 281 (17.7%) died. Majority of the patient (55.7%) were males with mean age was 28.3 (SD ± 1.47) years (Biruk *et al*., 2016). Similar study from north of Ethiopia shows that, 103 (12.7%) cured case and 582 (71.9%) completed case with the treatment success rate of 84.6% (Birlie *et al*., 2015).

2.4. Survival status of tuberculosis patients

Study conducted in Canada found that from the start of the treatment, the survival time of TB death was less than 15.5 months. Among the overall 217 death reported, 48(22.1%) deaths occurred before treatment initiation and 96(44.2%) observed during intensive phase of the treatment (Gao *et al*., 2015).

In cohort study in Shanghai, a total of 440 (5.5%), where 49.5% of the deaths directly caused by TB, during the treatment course (Zhang *et al*., 2012). In the same manner a total of 708 deaths reported and 120 cases had direct association with TB infection during the treatment course (Wang *et al*., 2015). Study conducted in Ireland explained that, of 647 on treatment, 62 patients died with the overall median survival time of 51 days. The study identified that the cumulative survival function of men was lower than that of women (Ajagbe *et al*., 2014). Study from India reported that, from the patients on treatment about 11% were died during treatment course. The finding of this depicted that, patients having previous TB history had higher CFR. Majority of the patients died during intensive phase of treatment course (Patel *et al*., 2016).

A retrospective cohort study from Nigeria found that, mortality of 237 (22% mortality was from HIV infected patients not initiate ART at treatment) patients with case fatality of 16.6% (Adamu *et al*., 2017). Democratic Republic of Congo reported, death of 390 patients with mortality rate of 0.01 per person-month, in which 52% of mortality occurred during the first 2 months of treatment initiation. The median survival time of the patients in the study was 59 days (IQR = 27–108) (Henegar *et al*., 2012). Study

conducted by Birlie *et al.,* also explained that 7.4% (12.8/1000 PMO) death with the median survival time to death of 60 days and the study depicts that intensive phase of the treatment course is stage in which most of the patients (56.7%) died (Birlie *et al*., 2015).

Study conducted in different parts of Ethiopia also reported different outcomes with different median survival time. Finding from southern part of Ethiopia shows that, 5.9% death with mortality rate of 1.02 per 100 PMO. In Northeast Ethiopia, about 18.6 % patients died with mortality rate of 18.4 per 100 PYO and the median survival time was 210 days during the entire study period. The studies also reported that majority of death during intensive phase of treatment phase (Beyene *et al*., 2016; Senbeta *et al*., 2014). One cohort study done on study setting seven years back found that mortality of 6.3%. The study also shows proportion of death in different TB type: where PPTB accounts 2.7%, PNTB accounts 3.6% and ETB accounts about 4.3% (Getahun *et al*., 2011).

2.5. Over view of survival analysis and survival model

Survival analysis is statistical model which is used for data analysis when the data is time to event data, where the time variable is called survival time. The time gives the time that an individual has survived over some follow-up period. The concept was emerged when life tables were originated. The model have the advantage of analyzing censored data over normal regression analysis (Kleinbaum, 2015).

Survival analysis is used in several fields. At the time of invention survival models were used only in the field of biostatistics to analyze life table data and to study death as an event (Baghestani *et al*., 2015), now a days, its application is expanded; it can be used in modeling human lifetimes *(*Cox, 1972; Oakes, 1984), in economics and sociology (Allison, 1984; Mayer *et al*., 1989), engineering (Akpan and Bassey, 2017), in social interaction (Allison and Liker, 1982), for organizational behavior (Fichman, 1988), for clinical trials (Greenhouse et al., 1989) and the life course (Johnson, 1988).

Survival models have unique properties that make them fit to the survival data than classical regression models such as linear and logistic regression. The model can be used

with censored observations and time-varying covariates which is impossible with normal regression approaches (Sastry, 1997).

In survival analysis, patients/participants followed over a specified time period and the time at which the event happened is the focus of the analysis. Any observation is said to be censored while survival time shows incomplete information. In survival analysis left censoring and right censoring are types of censoring. Right censoring is the most commonly encountered form. Left censoring of data can occur when a person's true survival time is less than or equal to that person's observed survival time (Ajagbe *et al*., 2014; Kleinbaum, 2015).

Survival includes nonparametric, semi-parametric and parametric regression analysis. Among these, Cox proportional hazard model is majorly used type of the survival analysis by most researchers since it has less assumptions than the others (T. Ibrahim, 2009; Dress, 1986). However, there is a time in which parametric model have an advantage over it; the distribution of parametric model are the most favorable for survival analysis of the data (Datwyler *et al*., 2011). In case of parametric regression model, interpretation of data is based on its distribution (exponential, lognormal, loglogistic and weibull) of the time to event rather than proportional hazard assumptions and in some case the assumptions of cox proportional hazard model fails to hold and will result in unreliable outcomes (Pourhoseingholi *et al*., 2011). Proportional hazard model is used by Pamela to estimate predictors for the survival of tuberculosis patients and he used kaplan-meier curves and logrank tests to explore differences in their survival (Pamela, 2011).

Semi-parametric Cox model make the researcher to focus on the regression distribution and lacks to consider the underlying distribution. But, parametric accelerated time regression model gives precise estimations of survival probabilities and provides a better understanding of the event and it allows for explicit modelling of the underlying death risk (Nakhaee and Law, 2011; Yiannoutsos,

3. Conceptual framework

Patient factor (socio-demographic, economic factor, non-adherence, substance use), health care provider factor (counselling, health education), disease and drug related factors (severity, co-morbidity, drug side effects, ART use) and clinical factors (initial weight, baseline BMI, TB category) were identified predictors of survival time to death of TB patients who have started anti-TB treatment (Waitt and Squire, 2011; Senbeta *et al*., 2014; Beyene *et al*., 2016; De Almeida *et al*., 2016).

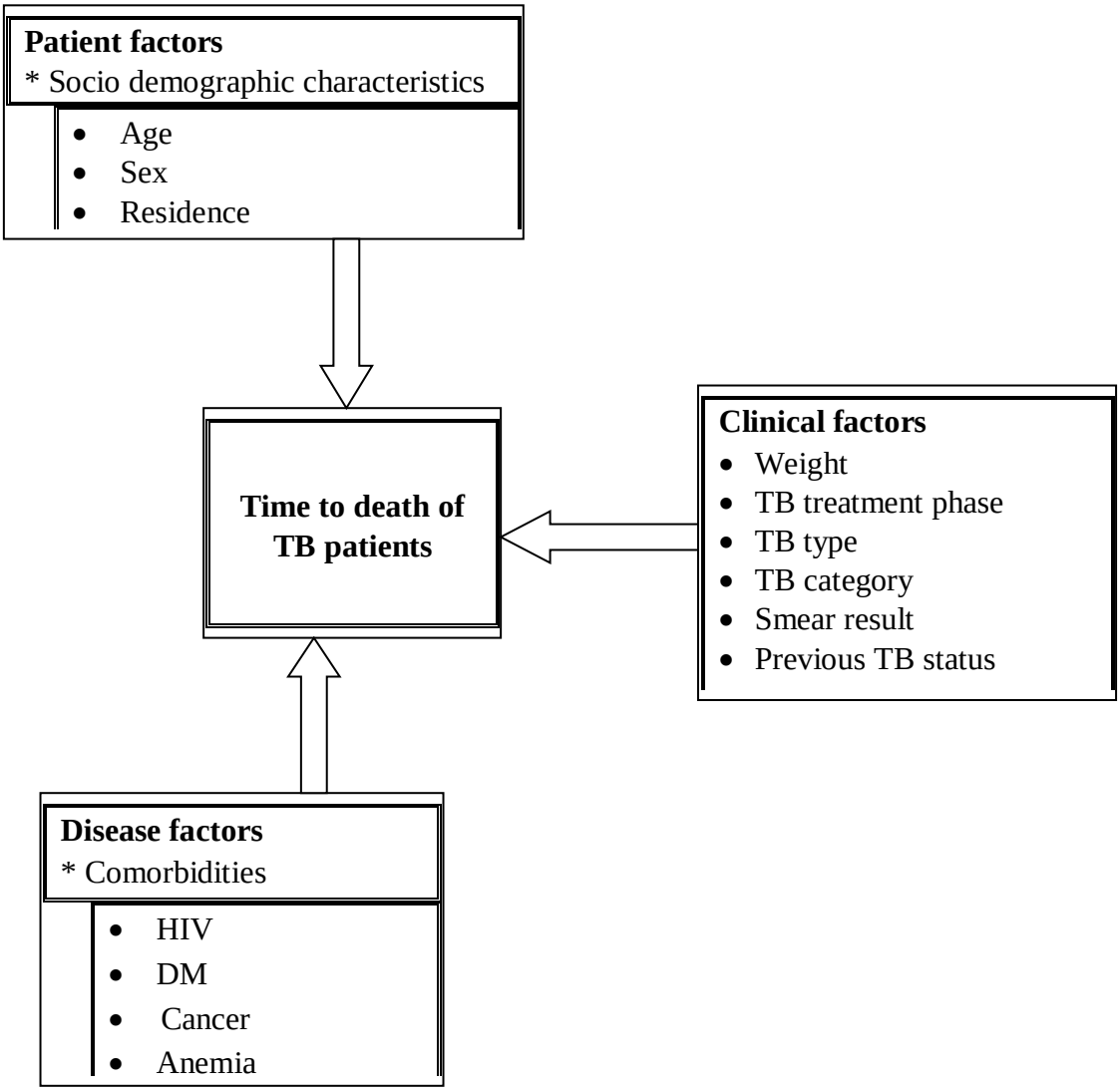


Figure 1: Conceptual framework for factors associated with survival of tb patients who have started anti-tb treatment

4. Objectives of the study

4.1. General objective

- ✓ To estimate survival time to death and identify its predictors among patients who have started anti-TB treatment from May 2016 to May 2017 in 20 selected health centers in Addis Ababa, Ethiopia.

4.2. Specific objectives

- ✓ To estimate median survival time to death of TB patients
- ✓ To estimate and compare the risks towards time to death of TB patients
- ✓ To identify predictors associated with time to death of TB patients
- ✓ To propose the appropriate model to analyze mortality of TB patients

5. Method

5.1. Study area and setting

The study was conducted in Addis Ababa, the political capital city of Ethiopia which has an area of 540 sq. km (World Population Review, 2018). The administration of the city is organized into ten sub-cities and 116 woredas (an administrative division of Ethiopia, managed by a local government). The projected population of the city in 2017 was 3,433,999, of which 52.7% were females (CSA, 2017). During the study period, Addis Ababa had 12 public hospitals, 25 private hospitals and 96 health centers which are managed by the health bureau of the Addis Ababa City Administration (HRI, 2017/18). During the study period, all the health centers (96 of them) were providing TB diagnosis and treatment services. In the year 2016/17 there were a total of 2779 patients enrolled in treatment; high patient load and high death was observed in Yeka (patient load = 508; number died =39) and Kolfe-Keraniyo, (patient load = 405; number died = 21) sub-cities (AHB HMIS report, 2016/17). TB clinic of selected facilities were being run by trained nurses, all of them provide the service based on revised TB guideline (FMOH, 2016) and generally, almost all facilities record the patient information as per logbook found at each health center.

5.2. Study design and period

A retrospective cohort study was conducted by reviewing treatment cards of TB patient and TB log book in the study health centers. Data were collected from April 1 to August 30, 2018.

5.3. Source and study population

The reference population was all TB Patients who had been enrolled for anti-TB treatment from May 2016 to May 2017 in 96 health centers in Addis Ababa. All TB patients who were enrolled for anti-TB treatment in 20 selected Health Centers of Addis Ababa in the same period and who fulfilled the eligibility criteria were the study population.

5.4. Eligibility criteria

5.4.1. Inclusion criteria

Patients diagnosed for TB and who were on anti-TB in 20 study health centers from May 2016 to May 2017.

5.4.2. Exclusion criteria

Incomplete registries, transfer out and MDR-TB patients who were on anti-TB in 20 study health centers from May 2016 to May 2017.

5.5. Sample size and sampling technique

5.5.1. Sample size

The sample size was calculated using a single population proportion formula (Daniel, 2009). The 3.7% of patients died from tuberculosis in previous study (Getahun *et al.*, 2011) was taken as the best available estimate for sample size estimation:

$$n=\frac{n0}{1+\frac{no}{N}}$$ Where,

n = the desirable sample size(total sample size required)

$n_0 = PQ\ [(Z\alpha/2)/d]^2$

N = total number of patients illegible in the study.

$Z_{\alpha/2}$ = the standard normal value at α level of significance ($Z_{\alpha/2}=Z_{0.05}=1.96$)

P= proportion of death from Tuberculosis

d=margin of error (2 %)

$n_0 = 0.037*0.963*(1.96)^2/ (0.02)^2 = 384$

The sample size was calculated to be 384.

The expected number of source population in the study setting (N) during the study was about 2779, which is <10,000. Hence, the corrected sample size, using the correction

formula below was 337. Finally, considering a 10% contingency, final sample size was calculated to be 371.

$$nf = \frac{ni * N}{ni + N}$$

5.5.2. Sampling technique

The selection of the health center was done by using simple random sampling technique. The technique is preferred for it provides equal chance for all patients. Accordingly, 20 health centers were selected from a total of 96 health centers in the city. A total of 2779 TB patients were enrolled during the study period (2016/17) in these 20 health centers. The total sample size determined for the study was then proportionally allocated to these health centers. Among the total of 2779 cases registered, registers of 371 TB patients who were enrolled to care from May 2016 to May 2017 were included in the study. The sample allocated to each health center is indicated in (Table 1).

$$n_h = \frac{Nh}{N} * n \qquad h=1, 2 \ldots 20$$

Where: n_h = sample size required from each health center

N_h = total number of patients in the h health centers

N = total number of patients in selected health centers included in the study

n = over all sample size

Table 1: Sample size allocation to each health center of Addis Ababa, Ethiopia, May 2016 to May 2017

Health Centers	Total number of patients enrolled in each health centers in 2016/2017	Total sample size in each health centers
Addis Ketema Health Center	127	17
Felege Meles Health Center	75	10
Akaki Health Center	173	23

Kality Health Center	172	23
Woreda 8 Health Center	45	6
Woreda 1 Health Center	68	9
Kotebe Health Center	187	25
Yeka Health center	285	38
Kazanchis Health Center	105	14
Meshwalkiya Health Center	120	16
Hiwot Amba Health Center	127	17
Alem Bank Health Center	180	24
Mikyliland Health Center	97	13
Woreda 3 Health Center	180	24
Tekelehaymanot Health Center	210	28
Woreda 1 Health Center	60	8
Beletshachew Health Center	97	13
Nifas Silk No2 Health Center	142	19
Woreda 2 Health Center	232	31
Woreda 8 Amoraw Metasebia HC	97	13
Total	**2779**	**371**

5.6. Study Variables

5.6.1. Dependent variables (response variables)

- ✓ Time to death from TB treatment initiation until the occurrence of an event (death) or end of the treatment.
- ✓ Treatment outcome status (died/censored)

5.6.2. Independent variables (covariates)

Demographic variables

- ✓ Age at the beginning of treatment
- ✓ Sex

- ✓ Residence (sub-cities)

Clinical variables

- ✓ Initial Weight (kg)
- ✓ TB type
- ✓ TB Category (new, relapse, failure defaulter)
- ✓ Base line smear result
- ✓ TB treatment phase
- ✓ Previous TB status
- ✓ Presence of co-morbidity (diabetes mellitus, cancer, anemia)
- ✓ HIV infection

5.7. Data collection process and instrument

A structured data abstraction format was used to collect information from medical records of patients which were adopted from TB log book and patients' follow up charts (patient card). Pre-test was done by the principal investigator at health centers on clinician follow up card and logbook of the patients. Five health centers were considered in the pretest and 20 (5%) TB patients from each facility were included in the pretest. The clinician follow up card was reviewed to collect information on presence of comorbidities, date of diagnosis and previous TB status. Accordingly, necessary modification was made (DM, cancer and anemia added to the data extraction format after pretest was done). These health centers (which included in the pretest) didn't included in the main study. The pretested structured data collection tool consisted of three parts. Part I was aimed at collecting information on basic socio-demographic variables of the patients. Part II consisted of questions required to gather information on baseline clinical characteristics of the patients. Part III includes questions to assess previous clinical information of TB treatment. Data was collected by nurses (one nurse from each health center) who were working at TB clinic in each health center.

5.8. Data quality assurance

After getting approval to conduct the research, a two day training was given for all data collectors (one nurse from each TB clinic) in four cycles. The first cycle consists of five

trainees from five health centers, the second cycle consists of five trainees from another five health centers, the third cycle consists of five trainees from other five health centers and the last cycle also includes five trainees from the last five health centers. Continuous and supportive supervision was given throughout the data collection process. The principal investigator checked the completeness and consistency of collected data on daily basis.

5.9. Data analysis and interpretation

Data were entered into SPSS version 25, after coding and checking for completeness and consistency; were exported to STATA version 14 statistical software for analysis. Data exploration technique was employed. Survival time was determined from date of treatment initiation to the date of event occurs. Days were used as time scale to calculate survival time. Kaplan-Meier and Log-rank test survival estimates were employed to investigate the significance of the difference in survival experience among different categories of study subjects after initiation of the treatment (i.e. to conclude whether there was significant difference between different survival curves).

The association between the independent variables and outcome variable (time to death) was assessed by Cox-proportional hazard model. It attempts to evaluate survival curves taking into account of other variables that may affect the survival of the patient (confounders). This is used to investigate the association of a single covariate with survival status of TB patients to screen out potentially important variables before directly included in the multivariable model. All the potential risk factors that had a P-value of less than or equal 0.25 in single covariate Cox proportional hazard analysis were candidate for multivariable Cox proportional hazard analysis. By using backward stepwise selection process and after checking for their interaction, the final significant predictors were identified ($P < 0.05$).

Model checking was done by checking Cox proportional assumption: Proportional hazard assumption test was checked based on Schoenfeld residuals using significant covariates from multivariable cox proportional, i.e. overall goodness fit (Rho) is a relation between time and residuals, in this case, if the p-value is greater than 0.05, it indicates that the Cox

proportional hazard assumptions are fulfilled. Additionally, graphical assessment also done for each covariate, i.e. if $ln(-lnS(t))$ *vs.* $ln(time)$ cross each other and slightly parallel, the assumption fails (violated) to fit the data. Linearity of covariates in the model assessed for continuous variables using plot of martingale residual, to check whether the correct functional form of a continuous covariate holds in the model proposed to describe the data.

Finally, the model was diagnosed using cox Snell residual plots (cumulative hazard function), i.e. the model fits the data well if the hazard function follows the 45-degree line and if it has an exponential distribution with a hazard rate of one. After all the above steps, cox proportional hazard model failed (violated) to fit the data and further steps were followed.

AFT parametric regression model was used to fit the data. With AFT parametric regression model, comparison of each distribution (exponential, lognormal, weibull and loglogistic) was made based on AIC and BIC, i.e. the distribution which has the least AIC or BIC considered as best model. Based on this principle, among the AFT parametric regression model assessed, weibull model was selected to fit the data set. All variables with p-value ≤0.25 were candidate for the final multivariable weibull model analysis. By using backward stepwise technique and after checking for interaction, the final significant predictors were identified ($p < 0.05$). Finally, diagnosis of weibull model was assessed to measure the overall goodness of fit. Likelihood Ratio, coefficient of determination (R^2) and Cox-Snell residuals were used in this model diagnosis. The model is adequate when, likelihood ratio test significant ($p \leq 0.05$), when coefficient of determination shows least result and the weibull baseline distribution cumulative hazard function of residuals against Cox-Snell residuals is a straight line. Hazard ratio was used as measure of association.

5.10. Ethical consideration

Ethical approval was obtained from both the Research and Ethics Review Committees of the School of Pharmacy, Addis Ababa University and Addis Ababa Regional Health Bureau (ERB/SOP/08/10/018). Support letter was obtained from Addis Ababa Regional

Health Bureau and given to each health center administrator office. Permission consent was assured from concerning administrative body of the health centers. Confidentiality was assured by using of data collector nurses from TB program clinic of the selected health facilities. Additionally, daily collected data were kept in locked cabinets until its final safe removal and the data entered to password protected computer. Moreover, patient identifiers (medical registration number) were not included in the data collection forms and replaced by new identification number during data collection and entry.

5.11. Operational definitions

According to the standard definitions of the Ethiopian National Tuberculosis and Leprosy control Program guideline (NLCP) [FMOH, 2016], the following are operationally defined as follows:

Pulmonary TB, smear-positive- when two or more sputum result become positive or when the result of one positive sputum result and that of chest radiographic abnormalities result show consistent finding with active TB).

Pulmonary TB, smear negative – when a result of two or more sputum result of the patient become negative and the chest radiography shows consistent result with active TB and clinically, when the patient has symptom which suggest TB.

Extra pulmonary TB (EPTB) – when TB infects other organs out of lung which includes lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges, etc.

New cases – patients who have no previous TB history.

Transfer in - a patient who started treatment in one health facility and transferred to another health facility to continue treatment.

Cured- finished treatment with negative bacteriology result at the end of treatment).

Treatment completed- when patients completing their treatment course and no bacteriology test done at the end of the treatment

Incomplete registries – if one of the independent variables missed from the logbook of the patient.

Transferred out - patients whose treatment results are unknown due to transfer to another health facility.

Successfully treated – when patients completed their treatment and confirmation test suggesting cure is done.

Died - patients who died from any cause during the course of treatment.

Other -a patient who does not fit in any of the above-mentioned categories.

Survival time - the time in days from the beginning of treatment to death from tuberculosis as the main or associated cause.

Censoring occurred either at the end of the study or due to death from other causes and include defaulters and transfer outs.

6. Results

6.1. Demographic characteristics and descriptive statistics

Data from a total of 371 TB patients who were treated in 20 public health centers in Addis Ababa during the study period were analyzed in this study. Among the total study participants 189(50.9%) were females, 74(19.9%) had previous history of TB treatment, 220(59.3%) had positive baseline smear results, 215(58%) had no TB/HIV coinfection and 137(36.9%) were pulmonary positives TB patients. Majority of the study participants (80.1%) were new TB cases.

Of the 371 registered patients, 235(63.3%) survived the entire follow-up period and the remaining 136(36.7%) died in the course of TB treatment. Out of the total deaths, 63(58.3%) occurred in pulmonary negative patients, 82(40%) in continuation phase of treatment phase, 59(37.8%) in HIV positive patients, 82(38.1%) in patients who had no comorbidity and 32(43.2%) occurred in patients who had no previous TB treatment history.

Cancer, anemia and diabetes mellitus were found to be the most common comorbid diseases. Out of the study participants with these comorbidities, 7(38.9%) of comorbid with cancer, 17(48.6%) of comorbid with anemia and 19(45.2%) of comorbid with diabetes were died during the entire study period (Table 2).

Table 2: Demographic and health factors of categorical covariate by TB in Addis Ababa, Ethiopia, May 2016 to May 2017

Covariate	Covariate Categories	Death	Censored	Total (%)	Median survival days
Sex	Male	63(34.6)	119(65.4)	182(49.1)	155(140, 161)
	Female	73(38.6)	116(61.4)	189(50.9)	159(143, 161)
TB treatment phase	Intensive phase	54(32.5)	112(67.5)	166(44.7)	70(56, 139)
	Continuation phase	82(40)	123(60)	205(55.3)	162(159, 166)
TB type	Pulmonary positive	6(4.4)	131(95.6)	137(36.9)	161(157 ,163)
	Pulmonary negative	63(58.3)	45(41.7)	108(29.1)	147(131 ,161)
	Extra pulmonary	67(53.2)	59(46.8)	126(34)	148(130 ,160)
TB category	New	109(36.7)	188(63.3)	297(80.1)	157(150, 161)
	Relapse	22(38.6)	35(61.4)	57(15.4)	167(125, 185)
	Failure	3(33.3)	6(66.7)	9(2.4)	121(49, 169)
	Defaulter	2(25)	6(75)	8(2.2)	158(1, 169)
Previous TB status	Yes	32(43.2)	42(56.8)	74(19.9)	169(148,180)

	No	104(35.0)	193(65)	297(80.1)	155(143,160)
Baseline smear results	Positive	48(21.8)	172(78.2)	220 (59.3)	159(154 ,161)
	Negative	88(58.3)	63(41.7)	151(40.7)	153(132 ,162)
HIV infection	Positive	59(37.8)	97(62.2)	156(42)	154(137 ,161)
	Negative	77(35.8)	138(64.2)	215(58)	159(153, 161)
Presence of co-morbidity	Yes	54(34.6)	102(65.4)	156(42)	140(132, 155)
	No	82(38.1)	133(61.9)	215(58)	160(156, 162)
Presence DM	Yes	19(45.2)	23(54.8)	42(11.3)	161(136, 180)
	No	117(35.6)	212(64.4)	329(88.7)	156(146, 160)
Presence cancer	Yes	7(38.9)	11(61.1)	18(4.9)	167(75, 180)
	No	129(36.5)	224(63.5)	353(95.1)	156(146, 160)
Presence anemia	Yes	17(48.6)	18(51.4)	35(9.4)	180(139, 180)
	No	119(35.4)	217(64.6)	336(90.6)	155(144, 160)
Total		**136(36.7)**	**235(63.3)**	**371(100)**	**157(148, 160)**

6.2. The Kaplan- Meier survival curve estimates of TB patients

The Kaplan- Meier survival curve estimates: the overall estimated median survival time was 157 days and the median survival time for those who died was 168 days and for those that censored was 112 days respectively. Most of the deaths occurred in the first 60 days (during intensive phase) of treatment initiation, i.e. relatively, a large number of patients died at the earlier days of TB treatment initiation (Figure 2). Accordingly there was a significant survival difference between patients TB treatment phase, previous TB status, TB category and presence of anemia with respect to survival time.

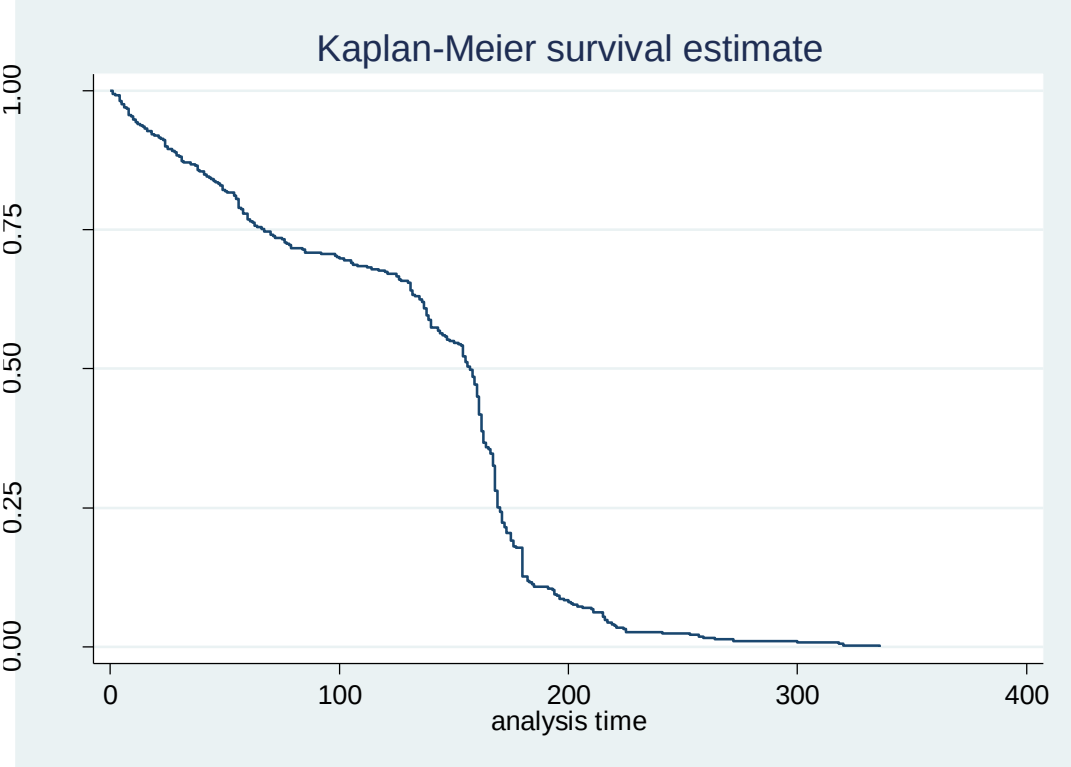


Figure 2: The Kaplan-Meier survival curve of the overall TB patients, in Addis Ababa, Ethiopia, May 2016 to May 2017

Kaplan-Meier survival curves below; shows the survival functions of TB patients stratified by TB treatment phase (Figure 3) and previous TB status (Figure 4).

Examination of the plot shows that higher death at the early stage of treatment initiation and with TB patients who had previous TB history respectively.

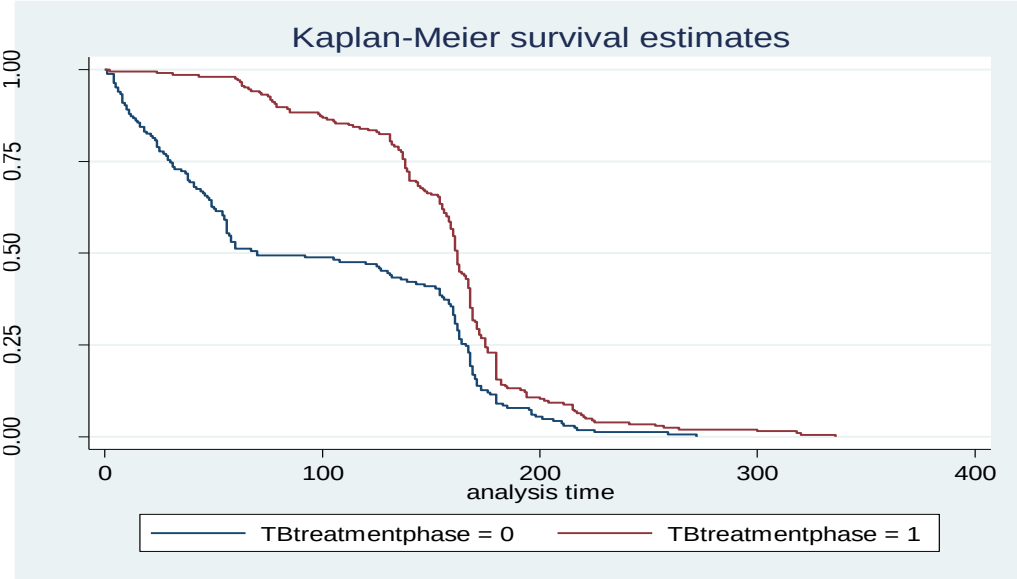


Figure 3: The Kaplan-Meier survival curve of the TB patients in relation to treatment category in Addis Ababa, Ethiopia, May 2016 to May 2017

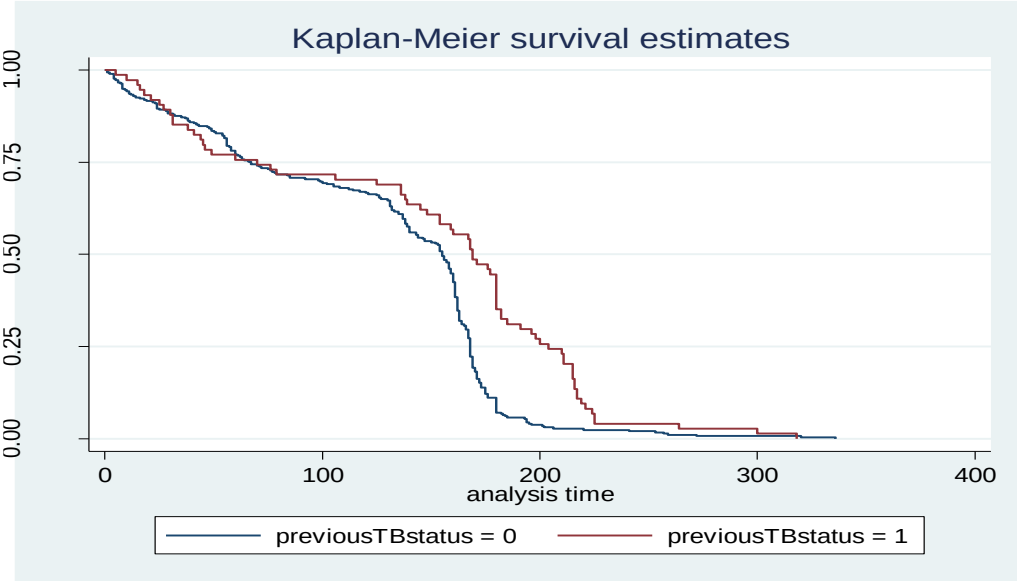


Figure 4: The Kaplan-Meier survival curve of the TB patients in relation to previous TB status in Addis Ababa, Ethiopia, May 2016 to May 2017

Plots of the Kaplan-Meier curves of different covariates to the survival and hazard experience of time- to- death is shown in figure in appendix I. The survival plot decreases at increasing rate at the beginning and decreases at decreasing rate later. This indicated the existence of significant differences between survival probabilities of the patients.

6.3. Comparison of survival experience on TB patients using Log Rank tests across different covariates

Kaplan-Meier survivor estimates for the different covariates' groups are plotted to check whether there is significant difference between the survivals of a patient by covariates, in Figure 2, 3 and 4 in the above plot and statistical test is made by using log-rank test in Table 3. Accordingly, there was a significant survival difference between patients TB treatment phase, previous TB status, TB category and presence of anemia with respect to survival time. However, there was not a significant survival difference between covariates sex, residence, TB type, baseline smear results, HIV infection, presence of co-morbidity, presence of DM and presence of cancer of study participants (Table 3).

Table 3: Comparison of survival experience of TB patients using log-rank test in Addis Ababa, Ethiopia, May 2016 to May 2017

Covariates	Degree of freedom	Log –rank test	
		Chi-square	P –value
Sex	1	0.02	0.89
Residence	7	11.71	0.11
TB treatment phase	1	28.65	≤0.01
TB type	2	0.65	0.72
TB category	3	15.17	0.02
Previous TB status	1	20.36	≤0.01
Baseline smear results	1	0.02	0.88
HIV infection	1	0.34	0.56
Co-morbidity	1	1.44	0.23

Diabetic mellitus	1	0.80	0.37
Cancer	1	1.14	0.29
Anemia	1	7.07	0.01

*** Significant association p<0.05**

6.4. Summary results from modeling time to death of TB patients under anti-TB treatment

In bivariate analysis of time to death, the following variables (*P<0.25*) were identified as candidates for multivariable analysis: age, residence, TB treatment phase, TB type, TB category, previous TB status, presence comorbidity and presence of anemia at enrollment. Because of their clinical importance baseline weight, baseline smear result and HIV infection were included in multivariable analysis regardless of their level of significance in bivariable analysis.

In multivariable cox regression analysis patient age, TB treatment phase, presence of comorbidity and HIV infection were significantly associated with increased mortality of TB patients during their treatment course (Table 4).

Table 4: Results from Cox-proportional model of time to death in patients with tuberculosis under treatment in Addis Ababa, Ethiopia, May 2016 to May 2017

Covariates	P- value	HR (95% CI)	P- value	AHR (95% CI)
Sex				
Male		**Ref**		
Female	0.92	0.92 (0.81, 1.21)		
Age	0.01	1.01 (1.01, 1.02)	**0.01***	1.01 (1.01,1.02)
Residence				
Yeka		**Ref**		
Nefas silk	0.21	1.26 (0.88, 1.79)	0.15	1.34(0.89, 1.98)
Kolfe	0.67	1.08 (0.77, 1.51)	0.56	1.12 (0.77, 1.63)
Kirkos	0.14	1.32 (0.92, 1.90)	0.17	1.34 (0.88, 2.02)
Bole	0.28	1.38 (0.77, 2.48)	0.34	1.35 (0.73, 2.51)
Akaki	0.22	1.26 (0.87, 1.81)	0.24	1.27 (0.86, 1.88)
Lideta	0.64	1.09 (0.76, 1.55)	0.44	1.18 (0.77, 1.79)

Addis Ketema	0.18	1.36 (0.87, 2.12)	0.10	1.53 (0.92, 2.55)
Baseline weight	0.35	0.99 (0.99, 1.01)	0.29	0.99 (0.98, 1.01)
Baseline smear result				
Positive		**Ref**		
Negative	0.572	1.06 (0.86, 1.31)	0.12	0.74 (0.51, 1.08)
TB treatment phase				
Intensive		**Ref**		
Continuation	≤0.01	0.57 (0.46, 0.69)	**≤0.01 ***	0.59 (0.48, 0.73)
TB type				
SPPTB		**Ref**		
SNPTB	0.20	1.18 (0.92, 1.52)	0.08	1.53 (0.96, 2.45)
EPTB	0.51	1.09 (0.85, 1.38)	0.11	1.28 (0.95, 1.72)
TB category				
New		**Ref**		
Relapse	0.09	0.79 (0.59, 1.04)	0.77	0.92 (0.51, 1.62)
Failure	0.55	1.23 (0.63, 2.38)	0.87	1.06 (0.51, 2.23)
Default	0.71	1.14 (0.57, 2.31)	0.71	0.87 (0.41, 1.83)

Previous TB status				
No		**Ref**		
Yes	0.03	0.76 (0.58, 0.98)	0.29	0.76 (0.45, 1.28)
Presence of Comorbidity				
No		**Ref**		
Yes	0.20	1.14 (0.93, 1.41)	**0.02 ***	1.60 (1.07, 2.39)
HIV infection				
No		**Ref**		
Yes	0.91	1.01 (0.82, 1.24)	**0.03 ***	0.62 (0.40, 0.96)
Presence of DM				
No		**Ref**		
Yes	0.90	0.98 (0.71, 1.35)		
Presence of Cancer				
No		**Ref**		
Yes	0.80	0.94 (0.60, 1.48)		
Presence of anemia				
No		**Ref**		
Yes	0.23	1.08 (0.59, 1.19)	0.19	1.39 (0.84, 2.27)

6.5. Model checking

6.5.1. Test of the assumption of proportional hazards

Age, baseline weight, TB treatment phase, TB type, HIV infection and overall global test were significant, hence they did not fulfill the proportional hazards assumption. This result occurs when regression coefficients are dependent on time or time interact with covariates. Therefore, hazard ratio for covariates is not constant over time. Additionally, the tendency for the effect of age and TB treatment phase rises with time while for the effect of residence, baseline smear result, TB category, previous TB status, presence of comorbidities and presence of anemia remains constant over time. In other words, there is enough evidence to reject the null hypothesis that baseline weight, TB treatment phase, TB type, HIV infection did not satisfy the assumption of proportional hazard (Table 5).

Table 5: Test of proportional-hazards assumption in Addis Ababa, Ethiopia, May 2016 to May 2017

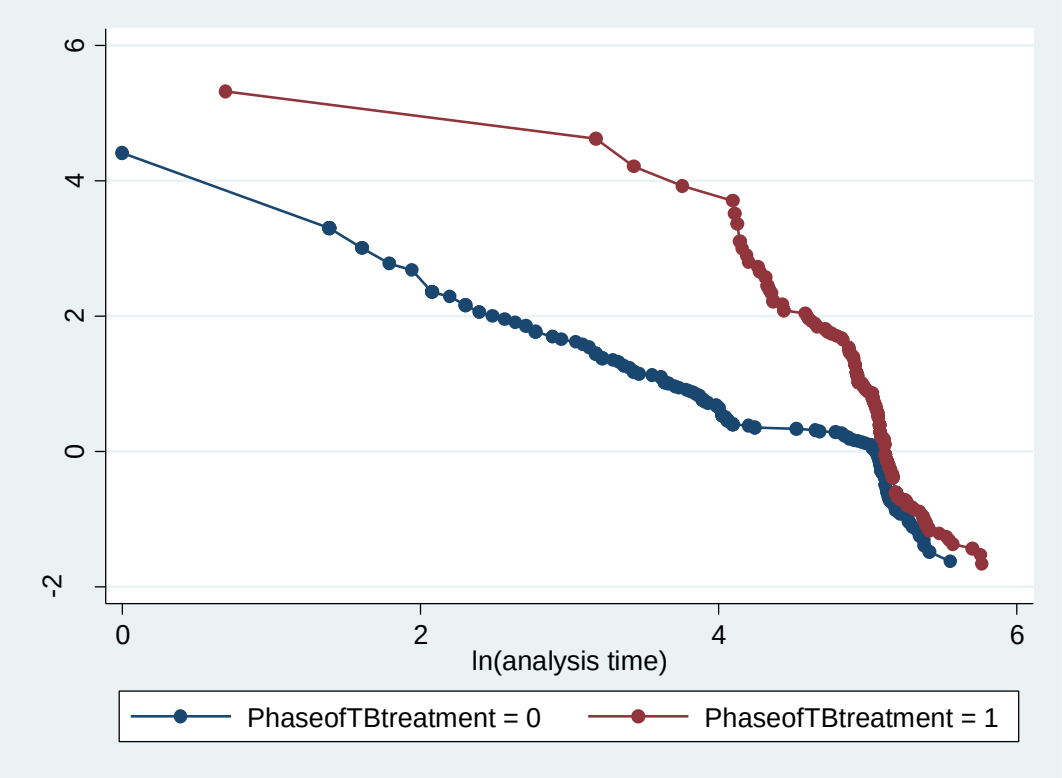
Covariates	Chi-square	Rho	Df	P-Value
Age	13.00	-0.18	1	**≤0.01***
Residence	0.35	-0.03	1	0.55
Baseline weight	8.41	0.14	1	**≤0.01***
Baseline smear result	0.05	0.01	1	0.83
TB treatment phase	34.30	0.31	1	**≤0.01***
TB type	7.03	-0.13	1	**0.01***
TB category	0.00	-0.001	1	0.99
Previous TB status	0.39	-0.03	1	0.53
Presence of comorbidity	2.03	-0.07	1	0.15

HIV infection	5.34	0.12	1	**0.02***
Presence of Anemia	2.85	-0.08	1	0.09
Global test	73.67		11	**≤0.01***

*** Significant association P<0.05**

6.5.2. Graphically test proportional hazard assumption

The variables included in the final model age, TB treatment category, previous TB status, presence of comorbidity and HIV infection did not fulfill the proportional hazard assumption because $ln(-lnS(t))$ *vs.* $ln(time)$ cross each other and slightly parallel.



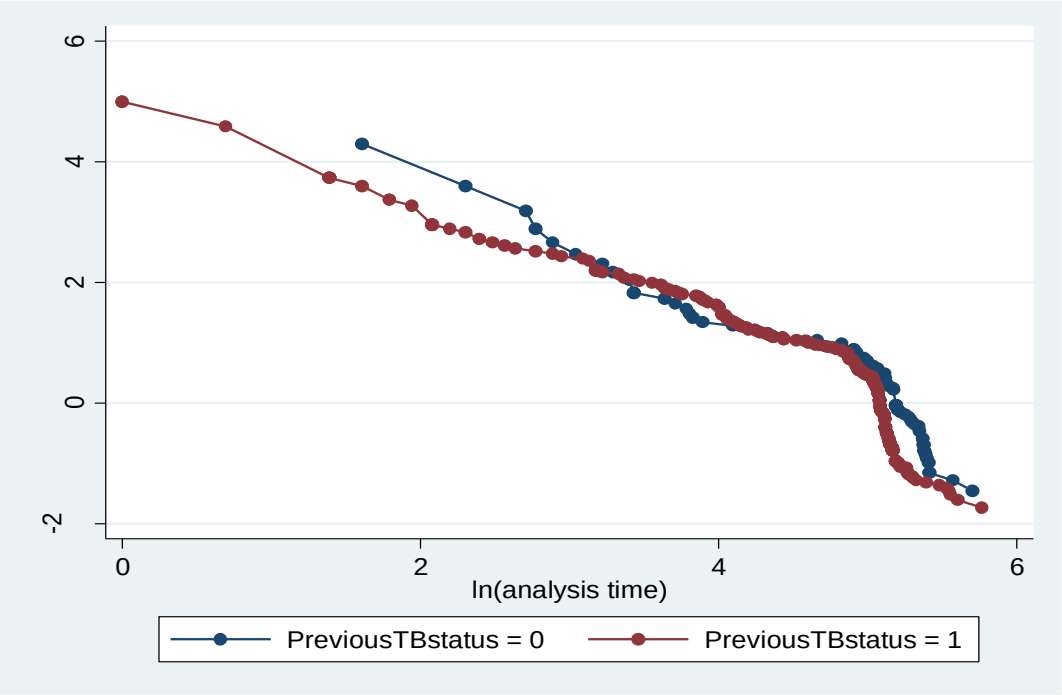
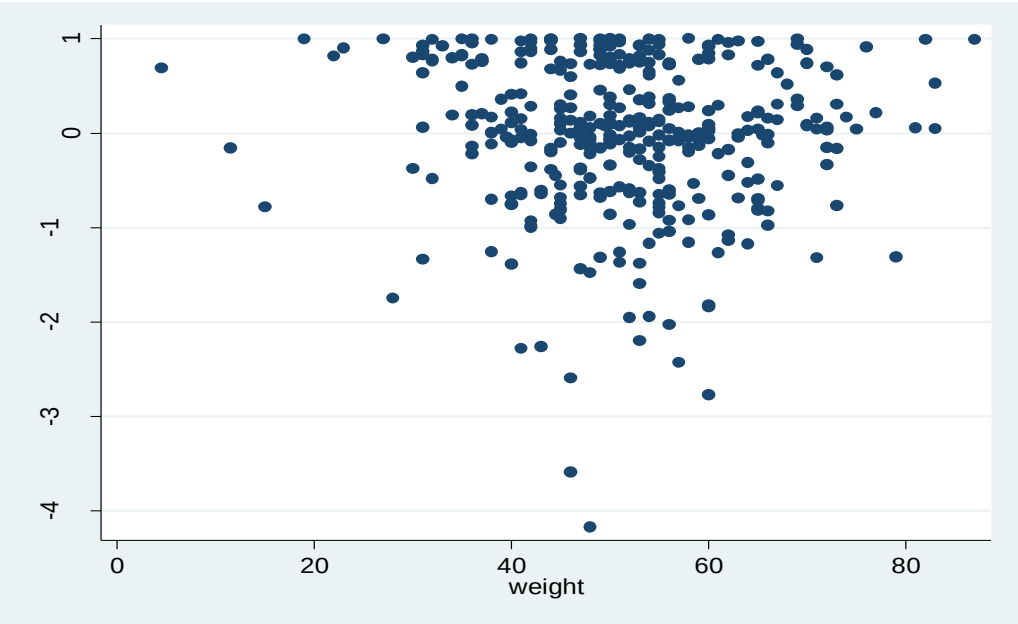


Figure 5: Graphical assessments of covariates for Cox PH assumptions in Addis Ababa, Ethiopia, May 2016 to May 2017

6.5.3 Assessment of linearity of covariates in the model



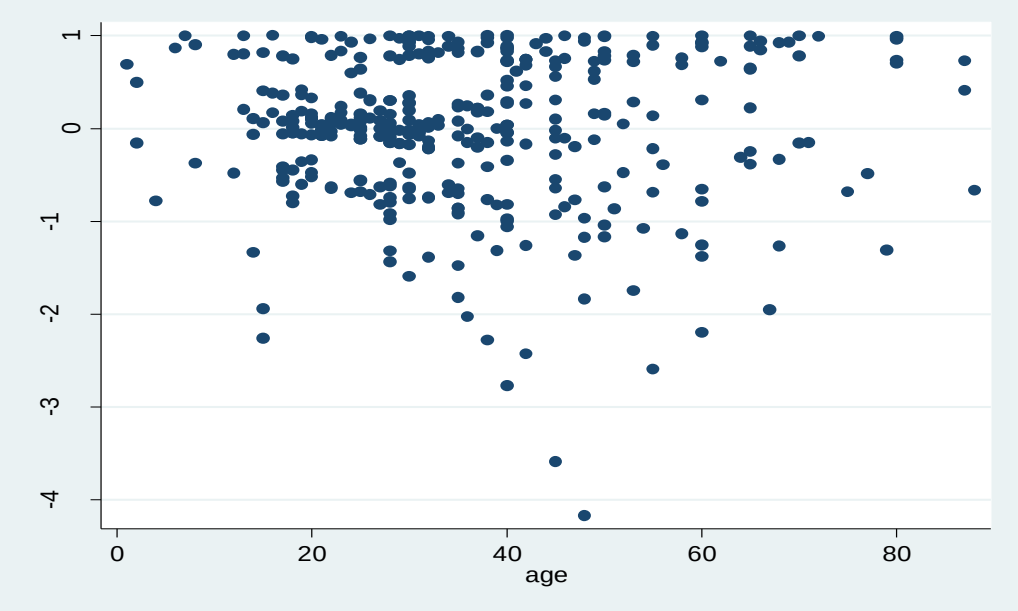


Figure 6: Plot of martingale residual versus linearity of covariates in Addis Ababa, Ethiopia, May 2016 to May 2017

The covariates age and weight showed systematic patterns or trends and the resulting smoothed plots are straight line. Therefore, the plots of martingale residual confirm that age and weight of a patient have a linear relationship with the survival time of TB patients (Figure 6).

6.6. Diagnosis of the Model

The Cox Snell residual plots (together with their cumulative hazard function) showed that the line related to the Cox-Snell residuals of the models were not on the line through the origin (the overall hazard function did not follow 45 degree), implying that the model did not describe the TB data set well. Overall, the final model did not fit to the data very well (Figure 7).

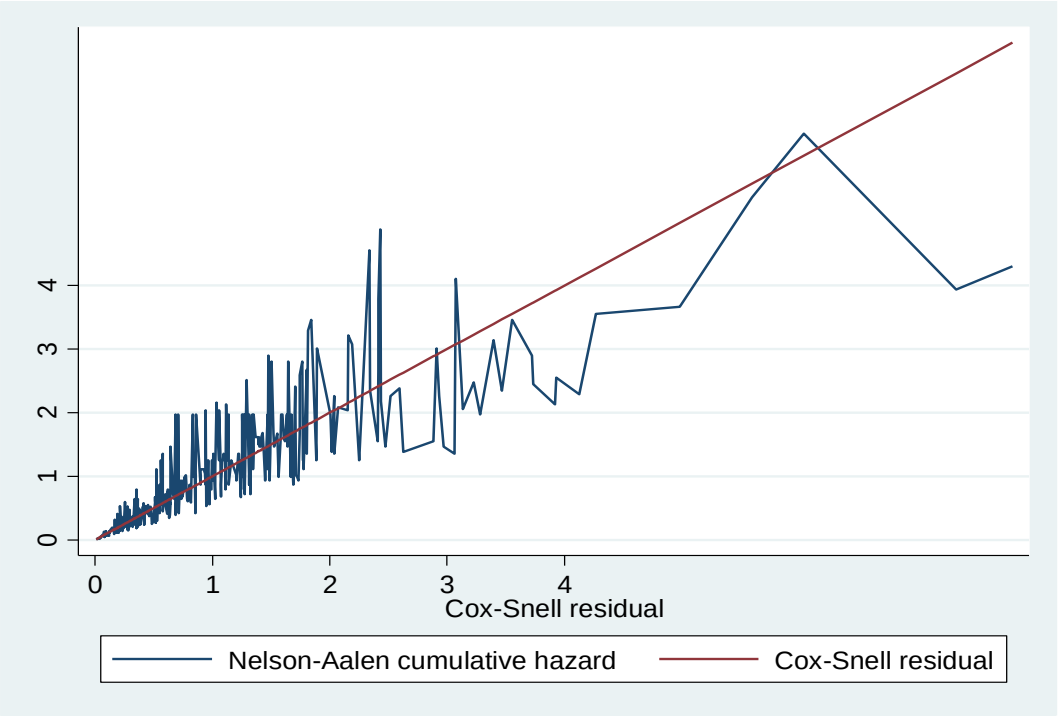


Figure 7: The Cox Snell residual plots for model diagnosis in Addis Ababa, Ethiopia, May 2016 to May 2017

6.7. Accelerated Failure Time Models

The assumption of Cox proportional hazard model was violated for age and TB treatment phase (Table 5). In this case AFT model is appropriate.

6.7.1. Comparison of accelerated failure time models

For the data of TB patients of this study, the parametric AFT models were fitted. The criterion used to select the best model is the akaikie information criterion (AIC) and BIC (bayesian information criterion) proposed by Akaikie in 1974. The weibull model had the least AIC value; hence the weibull AFT model was the better to fit TB patients' data in this study (Table 6).

Table 6: Comparison of AFT model based on AIC and BIC in Addis Ababa, Ethiopia, May 2016 to May 2017

Baseline Distribution	AIC	BIC
Exponential Model	941.38	972.71
Weibull Model	785.69	820.93
Lognormal Model	957.87	993.12
Log-Logistic Model	894.98	930.22

For every combination of the covariates fitted, the weibull model yield a minimum value of akaike's information criteria (AIC). Hence, we used the AFT weibull model with a combination of covariates to further analyze the effect of covariates on time to death. Therefore, interpretation of the covariate is based on the AFT weibull model.

6.8. Summary result of univariable and multivariable Weibull AFT Regression model

In univariable AFT weibull regression model analysis, eight variables namely: age, baseline weight, baseline smear result, TB treatment phase, TB type, TB category, previous TB status and presence of DM were identified as candidates *(P<0.25*) for multivariable AFT Weibull regression model analysis. Thus, these data were further analyzed by multivariable weibull AFT regression analysis. Because of their clinical importance, two variables: presence of HIV infection and presence of comorbidities were included in multivariable weibull AFT regression analysis regardless of their significance in bivariable analysis (Table 7).

In the multivariable AFT weibull regression model, the age of the patient, baseline body weight, TB treatment phase, and TB type, were significantly associated with the time to TB-related mortality ($P \leq 0.05$). Baseline smear result, TB category, previous TB status, presence of comorbidity, HIV infection, presence of DM, presence of cancer and presence of anemia, were not significant predictors associated with the time to death (Table 8).

Table 7: Univariable estimate of Weibull AFT model in Addis Ababa, Ethiopia, may 2016/2017

Covariates	Category	β	P-value	HR	95% CI of HR
Sex		0.08	0.64	1.08	[0.77, 1.52]
Age		-0.01	**≤0.01***	1.01	[1.01, 1.02]
Residence	Yeka	**Ref**			
	Nefas silk	0.49	0.09	1.63	[0.91, 0.90]
	Kolfe	-0.26	0.33	0.77	[0.45, 1.31]
	Kirkos	0.01	0.98	1.01	[0.51, 1.99]
	Bole	0.28	0.60	1.32	[0.47, 3.71]
	Akaki	0.20	0.49	1.23	[0.69, 2.17]
	Lideta	-0.50	0.09	0.61	[0.34, 1.07]
	Addis Ketema	0.24	0.52	1.27	[0.61, 2.64]
Baseline weight		0.01	**0.08***	1.02	[1.01, 1.03]

Baseline smear result	Positive	**Ref**			
	Negative	1.05	**≤0.01***	2.85	[2.01, 4.06]
TB treatment phase	Intensive phase	**Ref**			
	Continuation phase	-0.63	**≤0.01***	2.85	[2.01, 4.06]
TB type	Pulmonary positive	**Ref**			
	Pulmonary negative	2.79	**≤0.01***	16.32	[7.06, 37.70]
	Extra pulmonary	2.07	**≤0.01***	7.92	[3.39, 18.46]
TB category	New	**Ref**			
	Relapse	-0.76	**≤0.01***	0.47	[0.30, 0.75]
	Failure	0.30	0.61	1.35	[0.43, 4.26]
	Defaulter	0.09	0.89	1.10	[0.27, 4.47]

Previous TB status	No	**Ref**			
	Yes	-0.53	**≤0.01***	0.59	[0.40, 0.88]
Presence of Comorbidity	No	**Ref**			
	Yes	0.19	0.26	1.22	[0.86, 1.72]
HIV infection	No	**Ref**			
	Yes	0.18	0.31	1.19	[0.85, 1.68]
Presence of DM	No	**Ref**			
	Yes	0.54	**0.03***	1.71	[1.04, 2.81]
Presence of cancer	No	**Ref**			
	Yes	0.20	0.58	1.23	[0.60, 2.51]
Presence of Anemia	No	**Ref**			
	Yes	-0.11	0.67	0.90	[0.54, 1.49]

***Significant association P<0.05**

Table 8: Summary result multivariable parameter estimate of Weibull AFT model in Addis Ababa, Ethiopia, May 2016 to May 2017

Covariates	Category	β	P-value	HR	95% CI of HR
Age		-0.02	**0.04***	0.98	[0.97, 0.99]
Baseline weight		-0.04	**0.03***	0.96	[0.91, 0.98]
Baseline smear result	Positive	**Ref**			
	Negative	-0.19	0.45	0.82	[0.50, 1.36]
TB treatment phase	Intensive phase	**Ref**			
	Continuation phase	-0.74	**≤0.01***	0.48	[0.33, 0.69]
TB type	Pulmonary positive	**Ref**			
	Pulmonary negative	2.99	**≤0.01***	19.92	[7.49, 52.96]
	Extra pulmonary	2.25	**≤0.01***	9.49	[3.99, 22.62]
TB category	New	**Ref**			
	Relapse	-0.52	0.28	0.59	[0.23, 1.51]

	Failure	0.10	0.89	1.11	[0.24, 5.15]
	Defaulter	-0.25	0.73	0.78	[0.19, 3.23]
Previous TB status	No	**Ref**			
	Yes	-0.38	0.37	0.68	[0.29, 1.56]
Presence of Comorbidity	No	**Ref**			
	Yes	0.48	0.09	1.62	[0.93, 2.83]
HIV infection	No	**Ref**			
	Yes	-0.15	0.59	0.86	[0.49, 1.49]
Presence of DM	No	**Ref**			
	Yes	-0.05	0.87	0.95	[0.55, 1.65]

***Significant association P<0.05**

6.9. Interpretation and presentation of weibull AFT regression model

The model that fit to the TB patient's data in Table 8 has two continuous linear covariate (Age and weight) and eight categorical covariates.

There was 2% decrease in rate of death for every year increase in age of TB patients; (HR = 0.98, 95%CI = [0.97, 0.99], P = 0.04). For every one unit decrease in weight of TB patients, there was 4% increase exposure to death; (HR = 0.96, 95% CI [0.91, 0.98], P= 0.03). Patients in continuation phase at any time point during the study period were 52% less likely to die than patients in intensive phase (there was higher death at early stage of treatment initiation, meaning during intensive phase); (HR = 0.48, 95% CI [0.33, 0.69], P ≤ 0.001). Similarly, the hazard rate of patients who had ETB and SNTB TB was respectively 9.49 and 19.92 times greater than those patients with SPTB TB type, which means, patients with smear negative TB patients died at a rate 19.92 times higher compared to smear positive TB and Extra TB patients; (HR = 19.92, 95% CI [7.49, 52.96], P ≤ 0.001). The 95% CI of independent predictors for weibull AFT model did not include one, this shows that statistical significance of association of the covariates with the death of TB patients (Table 8).

6.10. Model diagnostics

It is recommended to determine whether a fitted AFT regression model describes the data after fitting a given model.

The Cox-Snell residuals, R^2 and Likelihood Ratio were used in this model diagnosis. The final step in the model assessment is to measure the overall goodness of fit.

From the respective plots of AFT model distributions, the Weibull regression model was the best model for fitting the data among the parametric models, since it has the lowest AIC value (820.93).

A best model has low R^2 due to the presence of censored data. Thus, the model fitted in this study has a value of R^2 statistic of 0.061. This implies that Weibull AFT regression model fits the data set.

$$R^2=1-\left\{\exp\frac{2}{371}[L_O - L_P]\right\}$$

L_P=log likelihood for fitted model with six covariates

L_o = log likelihood for fitted model with no covariate

$$R^2=1-\left\{\exp\frac{2}{371}[-605.9443-(-594.2574)]\right\}= 0.061$$

Additionally, it was the model with the best adherence to the model assumptions (cumulative hazard closer to the reference line; the plot for weibull baseline distribution make straight line better than exponential, lognormal and Log-logistic baseline distribution) as illustrated in the Cox-Snell residuals plots (Figure 10).

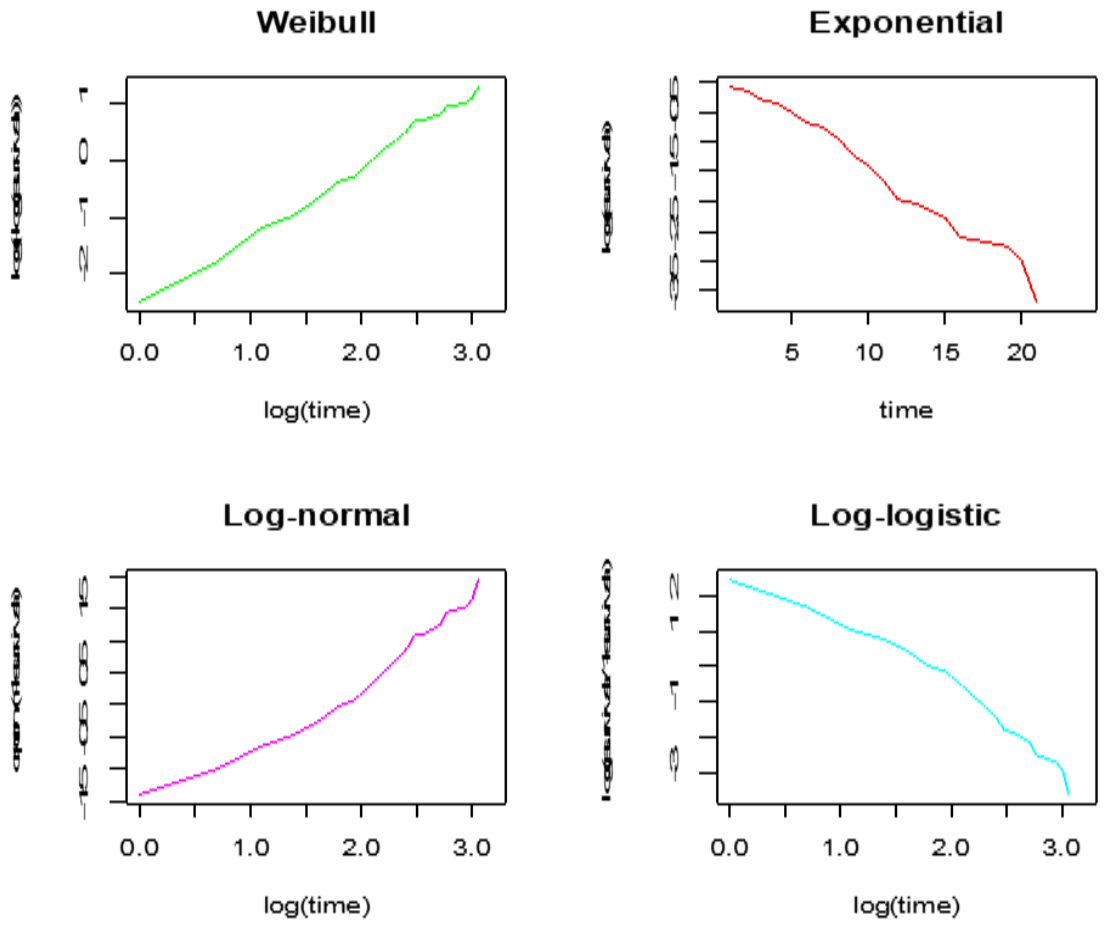


Figure 8: The graph of weibull, exponential, log logistic and lognormal base line distribution of survival analysis of TB patients.

Furthermore, the likelihood ratio test revealed that weibull AFT regression model is significant ($p \leq 0.001$) and using the log likelihood values of the null model and the full model it can be seen that the model has a significant improvement after the covariates are added in the model (Table 9).

Table 9: The likelihood ratio and significance of the Weibull AFT in Addis Ababa, Ethiopia, May 2016 to May 2017

Loglik (Intercept only)	Loglik (Full model)	Degree of freedom	Chi sq.(X^2)	P-value
-605.9443	-594.257	7	41.78	≤0.001

6.10.1. Assessment of adequacy of the weibull AFT model

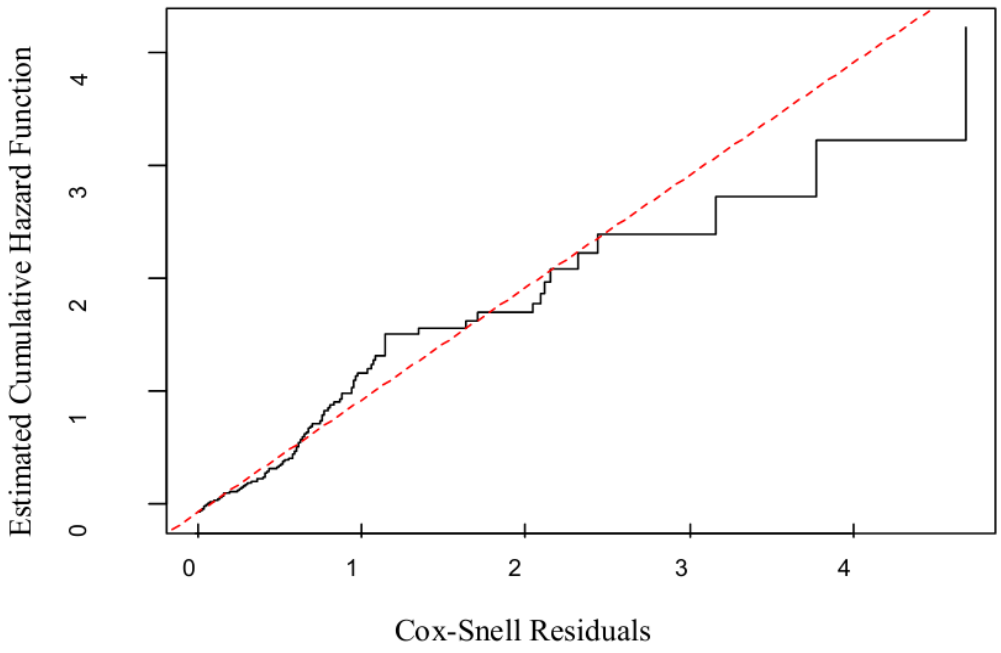


Figure 9: Cox- Snell residuals plots of Weibull baseline distribution for survival time of TB patient in Addis Ababa, Ethiopia, May 2016 to May 2017

Adequacy of a final fitted model was assessed with Cox –Snell residual after a model had constructed to determine whether a fitted weibull AFT regression model adequately describes the data set or not. The plot of the cumulative hazard function of the Cox-Snell residuals against maximum likelihood estimation with cumulative hazard functions is presented in Figure 9. From the plot it was shown that the cumulative hazard function of

residuals against Cox-Snell residuals was approximately a straight line, hence, the model fits the data.

7. Discussions

This study was conducted to estimate survival time to death and identify its predictors among tuberculosis patients on treatment in 20 selected health centers in Addis Ababa, Ethiopia. In this study, a higher proportion of TB death was documented. Predictors significantly associated with survival time were age, baseline weight, TB treatment phase and TB type. The overall estimated median survival time was also found to be 157 days.

Among the total of 371 registered patients in this study, proportion who died during the study period was 36.7%. This is much higher than what were documented by previous studies in Ethiopia which ranged from 3.7 to 12.7% (Datiko and Lindtjørn, 2010; Getahun *et al*., 2011; Tolosie and Sharma, 2014; Birlie *et al*., 2015; Damtew *et al*., 2015; Ejeta *et al*., 2016*).* This discrepancy might be due to difference in study setting and study subjects, difference in number of facilities included in the study (this study encompasses about twenty health centers which is prominent comparable to the previous studies) and crowded settlement and poorly ventilated transportation system. The proportion was also higher than previous findings out of Ethiopia, which ranged from 6.5% to 25% (Babatunde *et al*., 2015; Djouma *et al*., 2015; Adamu *et al*., 2017; Abedi *et al*., 2017). On the other hand, the current finding is in agreement with the studies done in Cameroon (29.4%), China (30.7%) and Philippines (37.5%) (Shimazaki *et al*., 2013; Agbor *et al*., 2014; Wang *et al*., 2015).

Our study indicated that, for every additional year of patients on treatment, the risk of death falls by 2%; meaning, the occurrence of death is increased in younger age (HR = 0.98 CI at 95% (0.97, 0.99), P = 0.04) of the study participants. Inconsistent to this finding, the result of previous studies in Ethiopia and elsewhere in the world showed that, the risk of death increases as the patient get older (Sterling *et al*., 2006; Albuquerque *et al*., 2009; Getahun *et al*., 2011; Shimazaki *et al*., 2013; Tolosie and Sharma, 2014; Wang *et al*., 2015; Beyene *et al*., 2016; Teklu *et al*., 2016; Rodrigo *et al*., 2016). This variation might be explained by, lower number of geriatric participants compared to the other age category (6.2%) in this study. On the other hand, in other studies it was indicated that, difference in age had no risk with survival time to death of TB patients *(*Lin *et al*., 2014; Djouma *et al*., 2015; Amante

and Ahemed, 2015; Moosazadeh *et al*., 2015; Ejeta *et al*., 2016; Sinshaw *et al*., 2017; Adamu *et al*., 2017; Fløe *et al*., 2017; Abedi *et al*., 2017).

Results of this study showed that, patients attending their treatment in continuation phase were 52% less likely to die than patients in intensive phase i.e. exposure to death (developing risk of death) was higher within two months of anti-TB treatment initiation (HR = 0.48, 95% CI [0.33, 0.69], P≤0.001). This probably be due to the fact that, decreased immunity and late diagnosis due to advanced disease during early stage (Waitt and Squire, 2011), decreased patient knowledge about their treatment (they may miss daily drug collection from health facilities), difficulty of making daily visit to health facilities for DOT due to distance of facilities from their residence. Furthermore, it may have implication on their work and social life. Additionally, in some health facilities unavailability of facilities in support of TB care (lack of water) (Obri-Danso *et al*., 2009). This finding is comparable with the study done in Ethiopia and elsewhere in the world where, majority of death recorded within the two months of anti-TB treatment initiation (Shaweno and Worku, 2012; Shimazaki *et al*., 2013; Tolosie and Sharma, 2014; Senbeta *et al*. 2014; Djouma *et al*., 2015; Rodrigo *et al*., 2016; Nagu *et al*, 2017). In contrast to the current finding, the previous studies in Addis Ababa (75%) and Spain (51.7%), revealed that continuation phase was a TB treatment stage in which higher death was observed (Getahun *et al*., 2011; Rodrigo *et al*., 2016). On the other hand, studies in United States and Canada (Sterling *et al*., 2006) indicated similar occurrence of mortality throughout the study period i.e. during both TB treatment phase.

The current study demonstrated that, as the weight decreases by one unit, the occurrence of death increases by 4% [AHR=0.96 CI at 95% (0.91, 0.98)] which is relatively concordant with previous studies conducted in Dangila and Addis Ababa (Birlie *et al*., 2015) (Getahun *et al*., 2011). This may be assumed that, underweight is due to malnutrition and this might result in deterioration of immunity and increased severity of the disease (Kim *et al*., 2010; Lai *et al., 2017*; Yen *et al*., 2016; Yen *et al*., 2017).

In this study, it is found that pulmonary negative TB patients had 19.92 times [AHR = 19.92 CI at 95% (7.49, 52.96)] higher rate of death and extra pulmonary TB patients had 9.49 times [AHR = 9.49 CI at 95% (3.99, 22.62)] higher rate of death than pulmonary positive patients, implicating the effect of pulmonary negative result on the survival time to death during TB treatment. The reasons might possibly be due to delays in the diagnosis and treatment since it requires assessing the response to antibiotic therapy as well reviewing radiological investigations and the disease being active and in progress due to longer interval of clinical and health care system (Whitehorn *et al*, 2010; *Ekinci et al*., 2014; Pourostadi *et al*., 2018). On top of this, the possibility that persons diagnosed with culture-negative TB may not have had TB and died of other causes (Sterling *et al*., 2013). Eastern Ethiopian researcher and of Gondar University found consistent finding where patients with pulmonary negative had 3.2 times [AHR = 3.204 CI at 95% (2.277–4.509) and extra pulmonary 3.18 ([AHR = 3.175 CI at 95% (2.201–4.581)] higher rate of death (Amante *et al*., 2015; Biruk *et al*., 2016). However, a study in northern Ethiopia identified that pulmonary positive patients were 58.3% most likely die compared to patients with pulmonary negative (Beyene *et al*., 2016), which may be due to difference in study setting, study population and survival model used in the studies. On the other hand, study in China revealed similar survival among all TB type cases (Wang *et al*. 2015) and other studies in Ethiopia identified that TB type had no association with survival of the patients (Datiko and Lindtjørn, 2010; Getahun *et al*., 2011; Senbeta *et al*., 2014; Toleshi and Sharma, 2014; Birlie *et al*., 2015).

In this study, it was ascertained that the overall median survival time to death was 157 days, which is shorter as compared to study done in Northeast Ethiopia (210days) (Beyene *et al*., 2016), Northwest Ethiopia (231 days) (Birlie *et al., 2015*), Vietnam (240days) (Vree *et al*., 2007). The contributing factors might be due to difference in study setting, health facilities, study population and study time gap. On the other hand, the finding is higher than study done in Taiwan (20 days) (Lin *et al*., 2014), Ireland (51 days) (Ajagbe *et al*., 2014), Democratic Republic of Congo (59 days) (Henegar *et al*., 2012) as well as study in

Ethiopia (60 days) (Birlie et al., 2015) and relatively similar to the study in Iran (168 days) (Abedi *et al*., 2017).

8. Strength and limitations of the study

8.1. Strength

This study was conducted in multi-center facilities. Both Cox- proportional hazard model and weibull accelerated failure time model applied for the analysis of the data and test and diagnosis of these models done using different assumptions. Additionally, different co-morbidities such as DM, cancer and Anemia were incorporated as covariates.

8.2. Limitations

Our study has some limitations. It was conducted retrospectively and relied on a medical record of the patients in each health facility. Hence, data on some demographic characteristics (religion, height, economic status) and behavioral characteristics (drinking alcohol, smoking cigarettes, chewing khat) could not be available in the record of the patient and these variables were not integrated in the study. Mortality might be overestimated, since any death occurred during TB treatment was considered as TB related.

9. Conclusions

The finding of this study indicated that, higher proportion of the patients (36.7%) were died. Most of the death occurred within the first two months of anti-TB initiation and the overall median survival time of the patients was found to be 157 days. Pulmonary negative TB type, intensive phase of TB treatment, being underweight and younger age of the patients were found to be probable predictors for the survival time to death of the patients. The study also demonstrated that, weibull model best fits to the current data to predict the survival time of TB patients.

10. Recommendations

Based on the findings of this study, the following recommendations are forwarded to respective bodies:

For respective health facilities

- ✓ Should give attention for early diagnosis of pulmonary negative TB patients.
- ✓ Should follow the treatment plan including nutritional support hence, patients should be critically followed during intensive phase.

For Ministry of health

- ✓ Should assess the death report from each health facilities and rule out whether the death is really due to TB case. Additionally, should revise the current TB registration log-book to include variables missed from this study (height, history of alcohol consumption and cigarette smoking, educational status, religion and marital status.

For research community

- ✓ By taking this study as an input, research communities are encouraged to conduct further prospective studies to have strong evidences on survival time to death
- ✓ The effect of some predictors such as DM survival time to death of TB patients should be assessed on.
- ✓ Important variables such as economic factor, behavioral characteristics (use of alcohol, cigarette and kchat abuse) and demographic characteristics (educational status, religion and marital status) should be studied.

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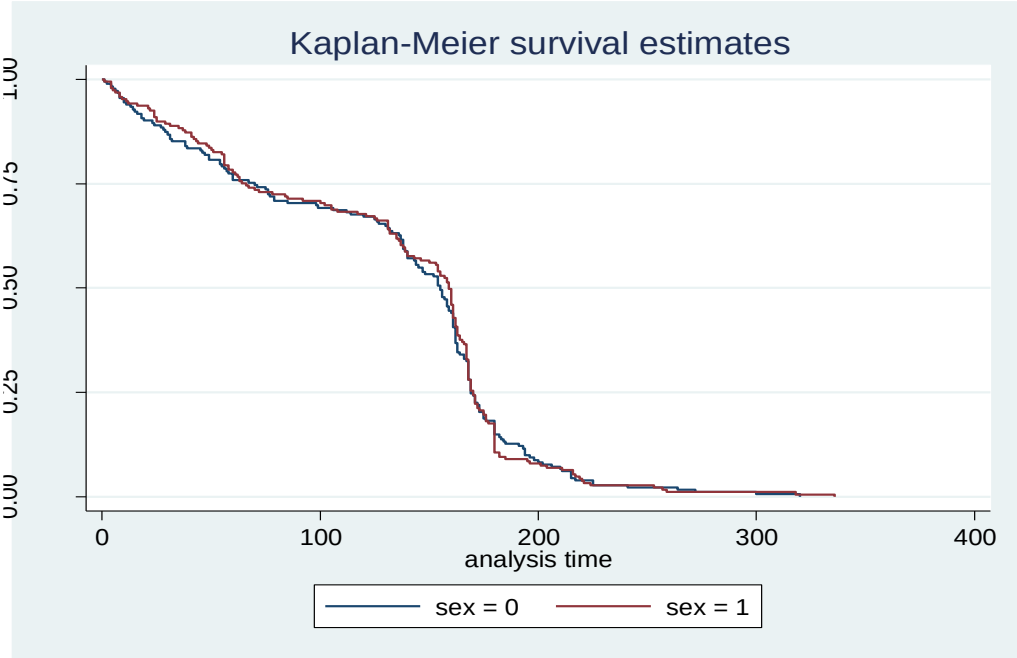
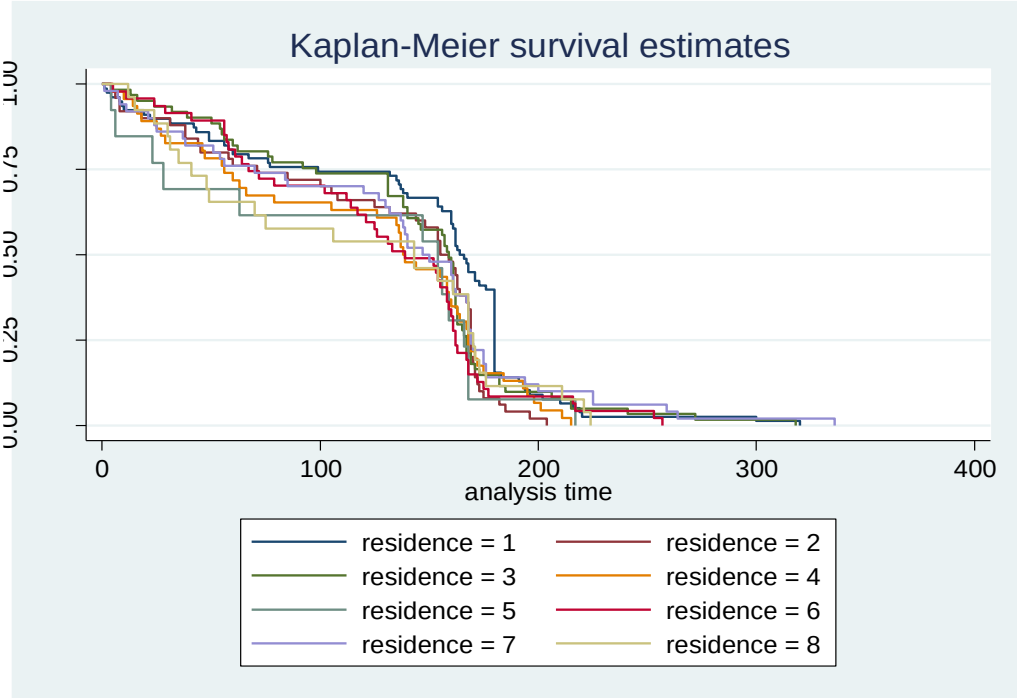
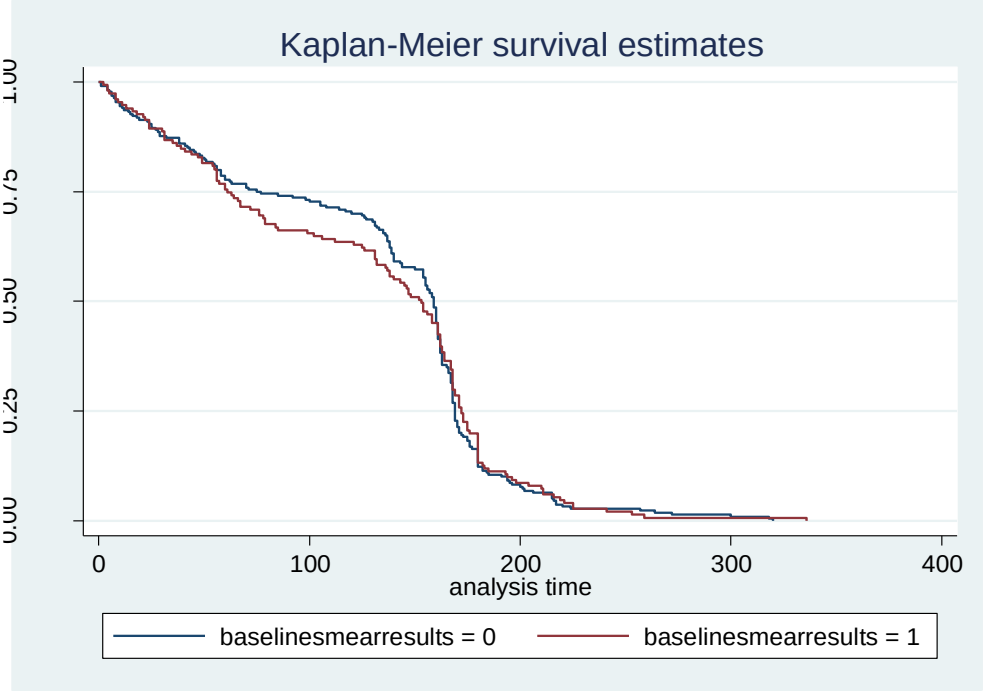
Appendix I: Kaplan-Meier survival curve of the TB patients of different covariates



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0.50
0.25
0.00
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100
200
300
400
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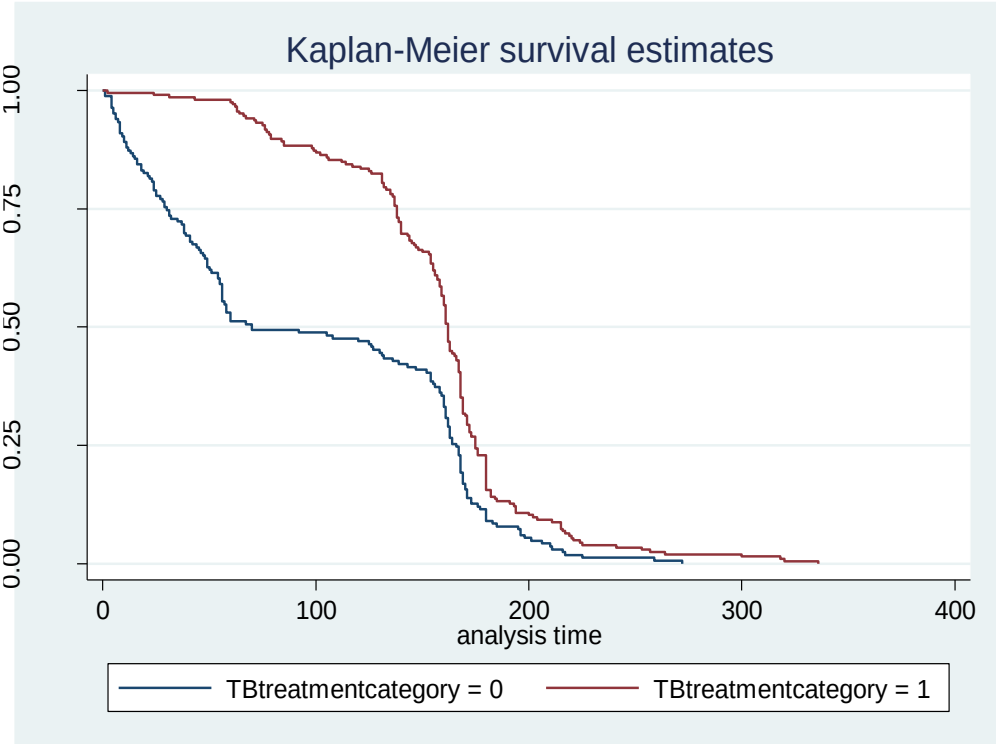
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300
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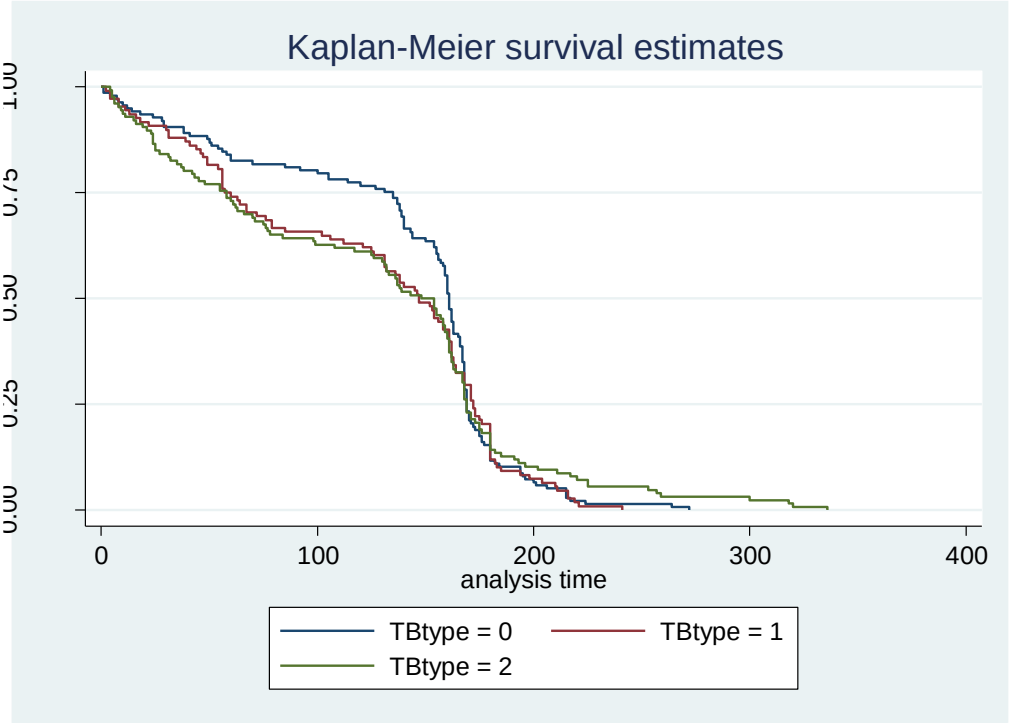
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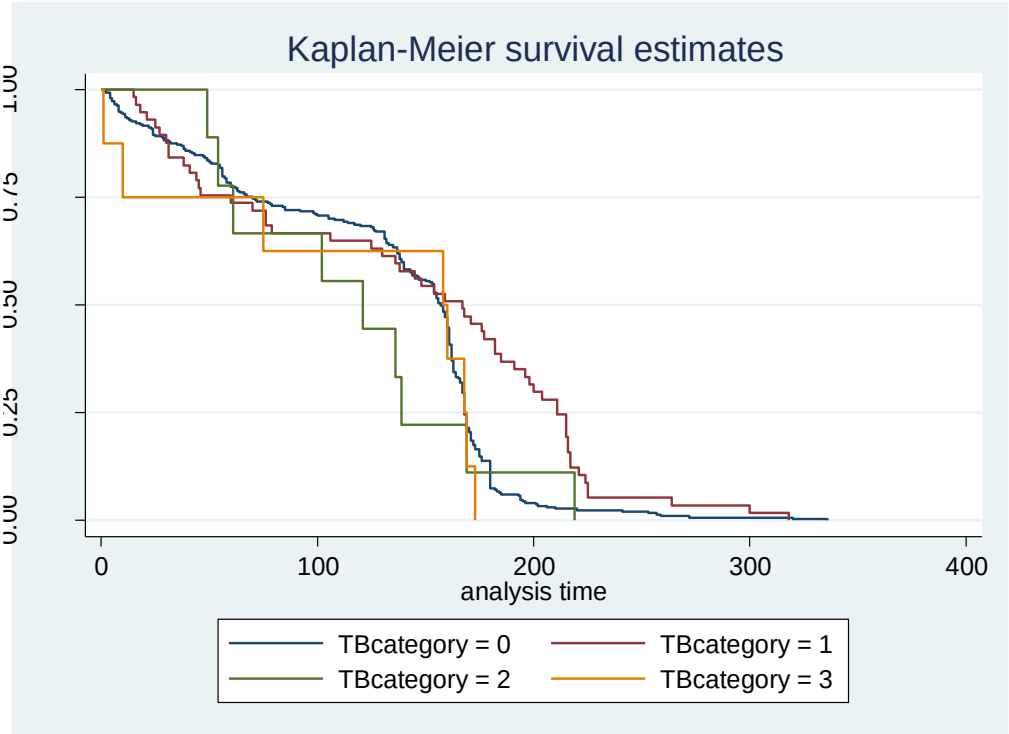
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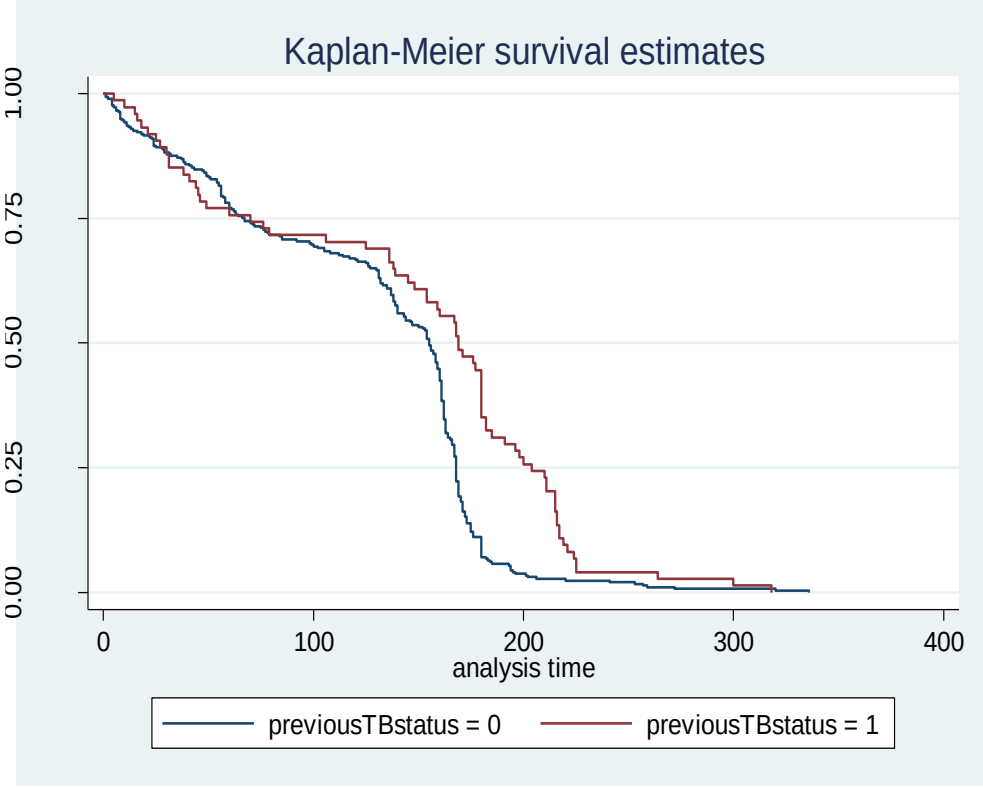
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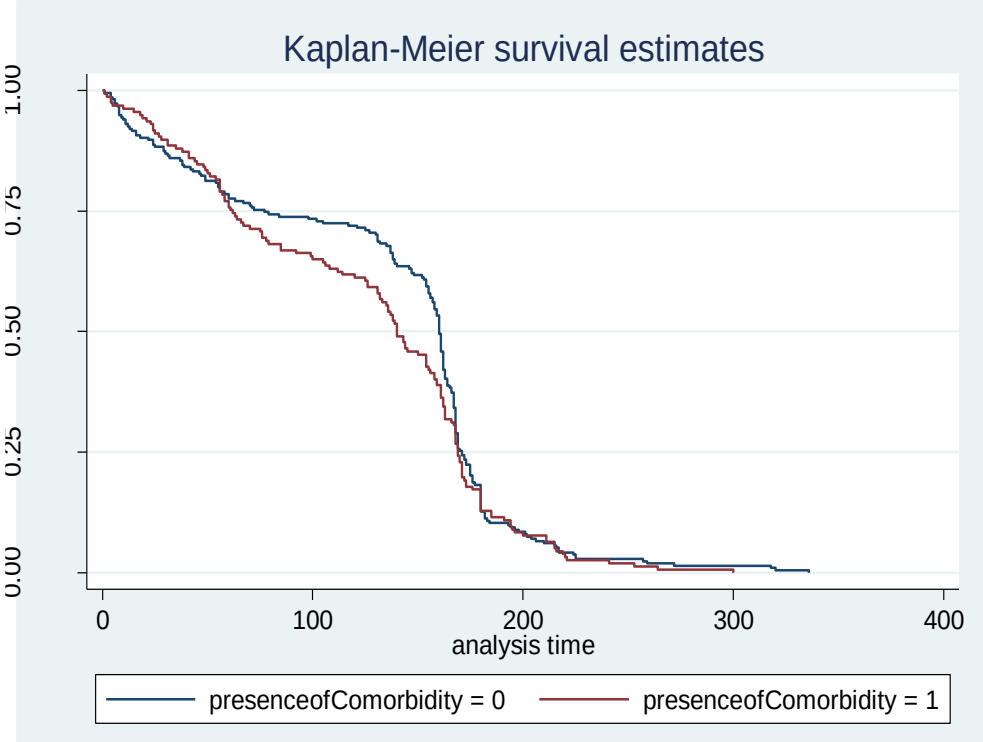
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0.25
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300
400
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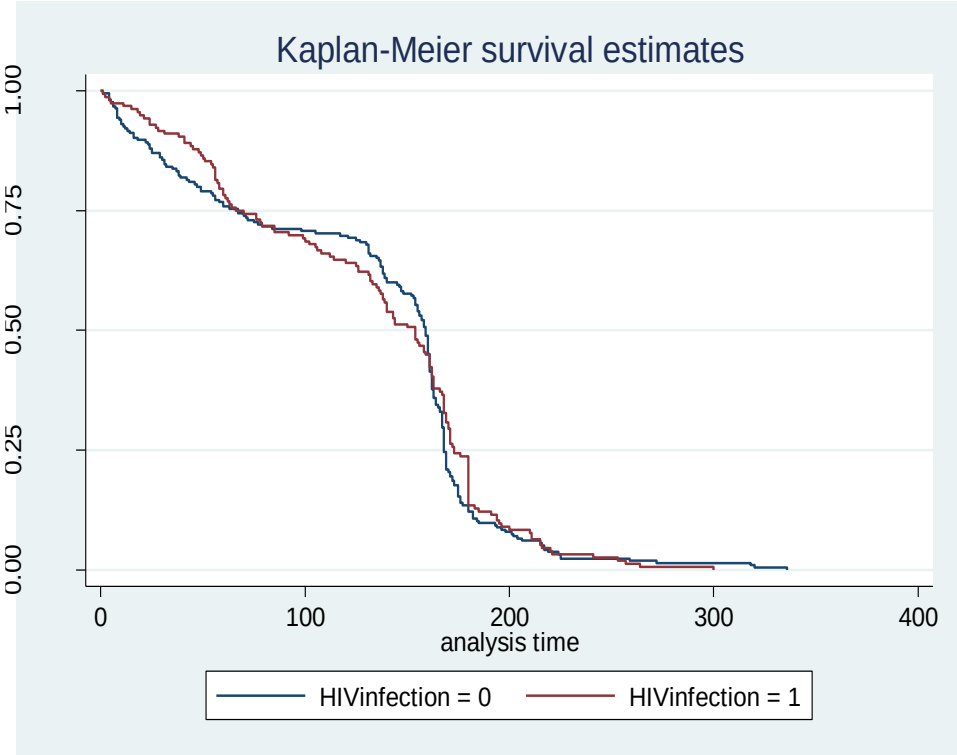
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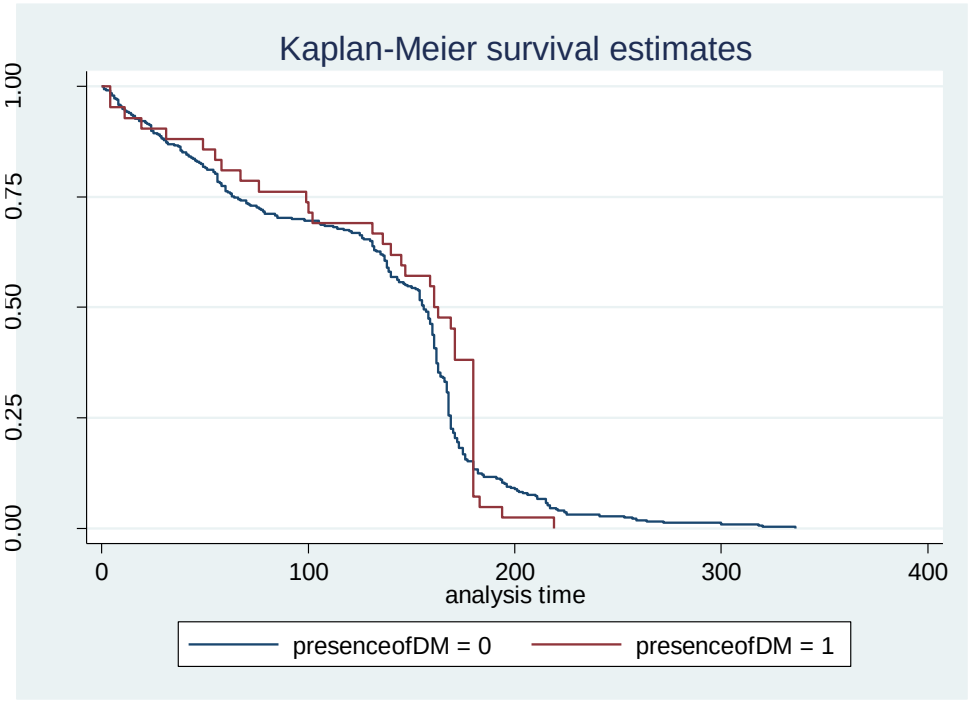
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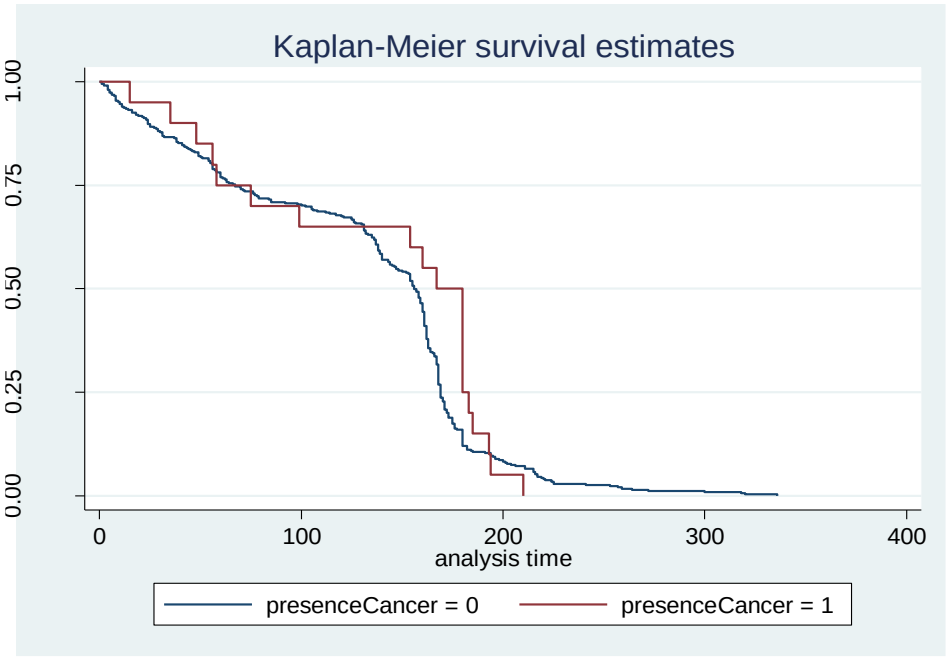


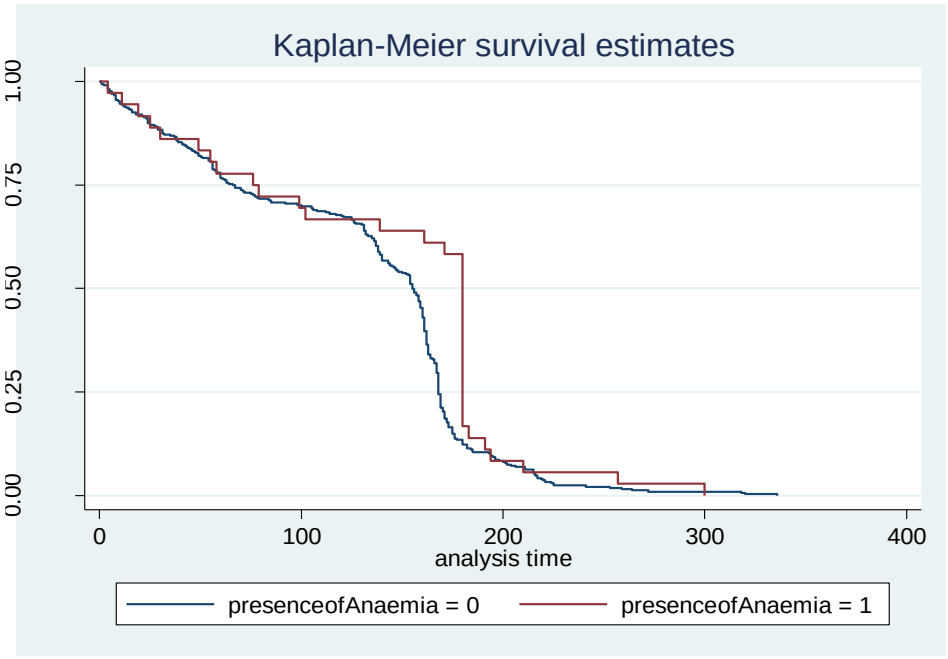
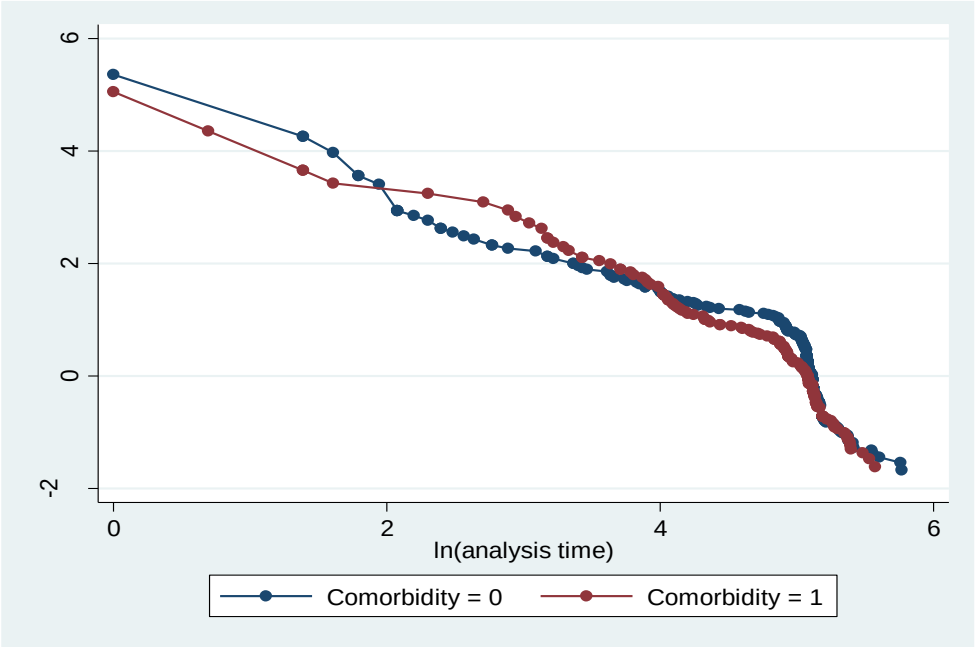


Figure 10: The Kaplan-Meier survival curve of the TB patients of different covariates in **Addis Ababa, Ethiopia, May 2016 to May 2017**

Appendix II: Graphical assessment of Cox assumption



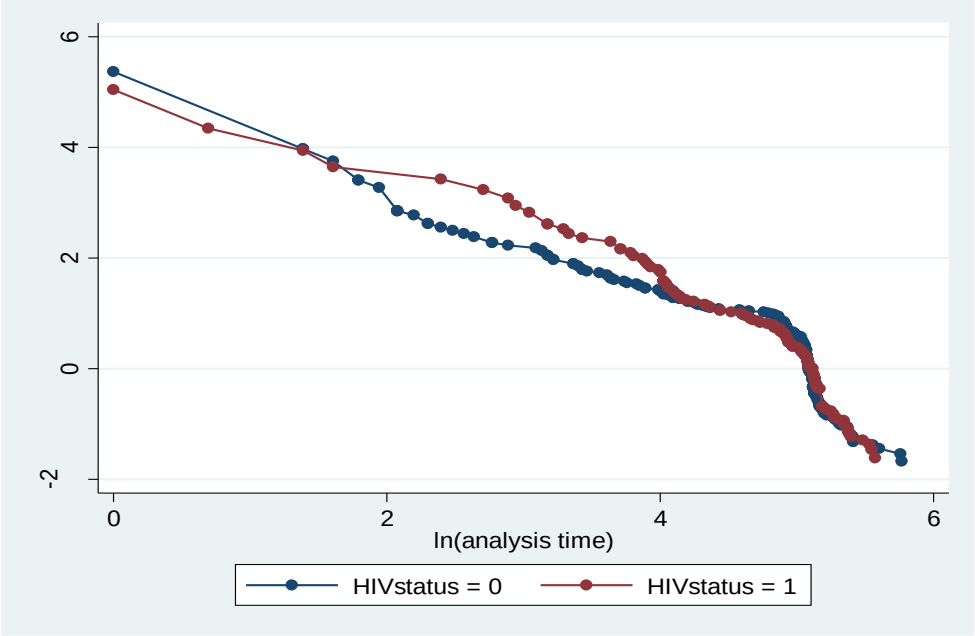


Figure 11: Graphical assessments of covariates for Cox PH assumptions in Addis Ababa, Ethiopia, May 2016 to May 2017.

Appendix III: Covariate (predictor) variables and their description

Predictor variables	Description	Code
Sex	Sex of a patient	0=male,1=female
Age	Age of a patient	Continuous
Residence	Residence of a patient (sub cities)	1=Yeka,2=Nifas Silk 3=Kolfe Keraniyo, 4= Kirkos, 5= Bole 6= Akaki Kality, 7=Lideta, 8= Addis Ketema
Weight	Weight of a patient	Continuous
Baseline smear result	Smear result at diagnosis	0= positive, 1= negative
TB type	Type of tuberculosis	0=SPTB, 1=SNTB, 2= ETB
TB treatment category	Phase of TB treatment	0= intensive phase, 1= continuation phase
TB category	Tuberculosis category	0=New, 1= relapse, 2= other
Previous TB status	Previous TB history	0= no, 1=yes
Presence of comorbidity	Co infection of other disease with TB	0= no, 1=yes
HIV infection	TB/HIV coinfection	0= no, 1=yes
Presence of DM	TB/DM coinfection	0= no, 1=yes
Presence Cancer	TB/cancer coinfection	0= no, 1=yes
Presence Anemia	TB/anemia coinfection	0= no, 1=yes
Final status	Event occurred	0= censored, 1= death

Appendix IV- Check lists for data extraction

Addis Ababa University

College of Health Sciences

School of Pharmacy

Department of Pharmaceutics and Social Pharmacy

Check list for data collection of time to death and its predictors among TB patients in selected health centers of Addis Ababa.

Name of the data retriever: _____Sign. _____

Name of the supervisor: _____Sign. _____

Date of data retrieving _____ E.C

Part I: Socio demographic characteristics

101. MRN _____

102. Sex 1. Male 2. Female

103. Age (in years): _____

104. Place of residence (sub cities) _____

105. Name of health facility _____

Part II: Baseline clinical factors

201. Date of TB diagnosis (DD/MM/YY _____

202. Date of TB confirmed (DD/MM/YY) _____

203. Anti TB start date (DD/MM/YY) _____

204. Anti TB end date (DD/MM/YY) _____

204. Type of TB 1. Pulmonary positive 2. Pulmonary negative

3. Extra pulmonary 4. Other, specify_____

205. TB category (registration group) 1. New 2. Relapse 3. Failure
4. Defaulter

206. Base line smear results 1. Smear negative 2. Smear positive

207. Baseline weight_____

208. Presence of comorbidity 1. Yes 2. No

209. If yes, types of comorbidity_____

2010. Outcome of TB treatment 1. Cured 2. Completed 3. Failure 4. Died

Part III: Clinical information of previous TB treatment

301. History of Previous TB 1. Yes 2. No

302. Outcome of TB treatment 1. Cured 2. Completed 3. Failure

4. LTFU 5. Transferred out

DECLARATION

I, the undersigned, declare that this thesis is my original work, has not been presented for a degree in this or any other university and that all sources of materials used for the thesis have been fully acknowledged.

Name: Girma Teketelew Signature: _____

Name of the institution: Addis Ababa University, Date of submission: _____

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

Name of the first advisor: Prof. Teferi Gedif, Signature: _____

Name of the Co-advisor: Dr Girmay Medhin, Signature: _____