SURVIVAL STATUS AND ITS PREDICTORS AMONG PATIENTS WITH TUBERCULOSIS IN HOSANNA, SOUTHERN ETHIOPIA: RETROSPECTIVE COHORT STUDY

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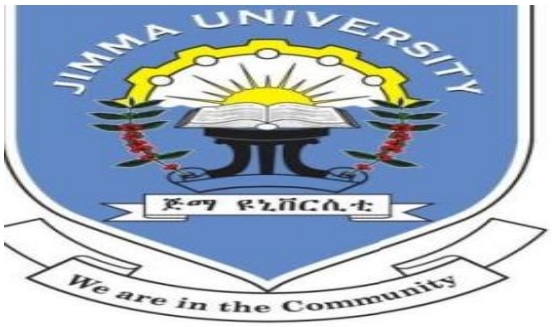

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Abstract

Background: Tuberculosis (TB) is chronic infectious disease contributed to morbidity and mortality of 9.6 and 1.5 million people worldwide respectively. Despite increased burden of death, time to death and its predictors among patients with TB not researched in the study area.

Objectives: To determine Survival status and identify its predictors among patients with TB in Hosanna, Southern Ethiopia, 2010-2015.

Methods: Retrospective cohort design was employed among patients treated for TB in Nigist Eleni Mohammad Memorial Hospital and Hosanna Health center located in Hosanna, Southern Ethiopia. Statistically determined 423 subjects were included in this study. Person-days time scale was used to measure survival time from treatment initiation until death or censoring occurred. Kaplan–Meier curves and log-rank test were used to assess survival time. Cox regression model was used to identify predictors of death. The 95% CI of Hazard ratio (HR) with corresponding P-value <0.05 were set to declare significance. Data was entered to Epi-Data 3.1 and exported to STATA 12.0 for analysis.

Result: Total of 423 TB patients were followed for 70608 Person-days. The mean survival time of the cohort was 269.8 Person-days. Out of the cohort 379(89.6%) patients survived to the entire 6 months follow up period. There were 44(10.4%) known deaths recorded in the follow up period. Incidence of death was 6.23 (*95% CI 4.6, 8.3*) per 10,000 Person-days. Majority, 27(61.4%) of deaths occurred within 30 days. Survival time significantly vary across status of TB/HIV co-infection (P<*0.001*), History of previous treatment (*P=0.02*), Residence (*P<0.001)* and weight change (*P<0.001*). TB/HIV co-infection (AHR =4.6, 95% CI: 2.41, 8.93, *P<0.001*) Previous history of treatment (AHR =4.8, 95% CI: 1.26, 18.59, P<*0.001*), Residence (AHR =3.1, 95% CI: 1.61, 6.21, P<*0.001*) and weight change (AHR=0.814 95% CI: 0.77, 0.85, P<*0.001*) were predictors of death.

Conclusion: Low survival time and higher incidence of deaths noted in this study. The existing treatment program should be strongly strengthened to reduce death during treatment.

Key words: Time to death, Tuberculosis, survival analysis, predictors of Tuberculosis death, Ethiopia

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I would like to thank Jimma University for overall technical and financial support. My appreciation and thank also goes to my advisors for their unreserved technical support. I would like also to thank NIMMH and Hosanna Health center staffs, data collectors and supervisors for providing records and collecting data.

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Acronyms Abbreviations

1. AHR: Adjusted Hazard Ratio
2. BMI: Body Mass Index
3. CI: Confidence Interval
4. COPD: Chronic Obstructive Pulmonary Disease
5. DM: Diabetes Mellitus
6. DOTS: Directly Observed Treatment Short course
7. HIV: Human Immune Deficiency Virus
8. HR: Hazard Ratio
9. MDG: Millennium Development Goals
10. MDR: Multiple Drug Resistance
11. TB: Tuberculosis
12. WHO: World Health Organization

1. Introduction

1.1. Background

Tuberculosis is chronic infectious disease caused by bacterium, *Mycobacterium tuberculosis* and *Mycobacterium bovines* which affects any parts of the body, mostly affects lung. [1].It is transmitted from patients with active tuberculosis through airborne droplet and from cattle infected with tuberculosis during raw milk consumption. Epidemiologically, it is a disease with well known risks factors, clinical features, diagnostic techniques and treatment modalities. The diagnostic technique are sputum smear microscopy developed 10 decades ago which detect bacteria from sputum sample, rapid molecular test to diagnose Tuberculosis (TB) and drug resistance TB. Countries with developed laboratory capacity diagnose TB using culture technique which is the current gold standard [2].

Tuberculosis is not self limited infection that more than 70 % of diseased cases die within 10 years if not treated. Anti-tuberculosis drug treatment developed in 1940s and currently , Isoniazid, Rifampin, Ethambutol and Pyrazinamide first-line drugs recommended for treatment of new drug susceptible TB for 6 months regimen to optimize cure[2-3].

World Health Organization (WHO) formulated indicators to measure burden and set targets for controlling TB globally, regionally and at national level. An incidence, prevalence and mortality of TB found to measure burden of TB. TB remains a growing global burden since recognized as public health problem since 1990s [2-4].

Case detection of all forms of TB, creating awareness on risks of TB transmission, accessing treatment in public and private health facilities are the major interventions to curtail TB burden in Ethiopia[5]. Regardless of these facts and efforts, TB treatment success and disease cure rate remains minimal in Ethiopia. Data on anti-tuberculosis treatment out comes not available for national average of Ethiopia [4-5]. Moreover; survival status and predictors of death among patients TB found to be un -recognized and under researched in the study area.

1.2. Problem statement

Unlike to most cancers and viral infections Tuberculosis is completely preventable and curable disease. It has preventive vaccination and curative chemotherapy. World Health assembly housed at WHO targeted to successfully treat TB cases in 2015. Directly Observed Treatment Short course (DOTS) launched in 1995 using standardized uninterrupted short course TB chemotherapy to optimize treatment outcomes. MDG also targeted to reverse incidence, prevalence and TB death. Furthermore; World Health Assembly adopted WHO End TB strategy in May 2014 to reduce catastrophic effects of TB in 2030[6].

Despite these international, regional and national responses; recent evidences notify that TB remains the major health problem of the world that poses devastating social, economical and health consequences. Global target for reduction of TB burden [1990-2015] was 47% which is below the target 50% reduction in 2015 [7].

WHO estimated 9.6 million people developed TB in 2014; one quarter of these is from Africa. About 1.5 million people died from TB and the highest rate of death also reported for Africa.[3] TB is top killer of children and young women age 20-59 years. Global TB report of 2015 show 3.2 million young women developed active TB and 480,000 died. Similarly, an estimated 1.0 million children developed TB disease and 140,000 children died from TB in 2014 globally [2].

Africa highly affected by TB burden that 46 per 100,000 population of TB patients under treatment died which is by far higher than reported for six WHO regions and global average [16 per 100,000 population] in 2014[2-4]. The 2015 target assessment finding report reveal WHO African region attain under the targeted 50% reduction of both prevalence rate and TB mortality rate by 2015 compared to 1990[2]. Epidemiologically TB is predicted to kill more than 35 million people in the region in the next 20 years if the current trend continues[2].

Ethiopia share similar profile with majority of African countries and hardly hit by TB burden. It ranked 3rd in Africa and 7th from 22 highest TB burdened countries in the world, with incidence of 207 per 100,000 and cause annual death of 33 per 100,000 populations in 2014 [4].TB death is incomparably higher than east African countries with relatively similar socio-economic status, Egypt 0.25, Somalia 7 , Kenya 21 deaths per 100,000 population [2].

Tuberculosis claimed to be the most sever disease and cause avoidable death. It has ability of spreading at higher rate, one person per second and higher potential of drug resistance. It kills young most productive and reproductive segment of the society that, the world biggest killer of young women. More often, TB tightly grip most productive society and hamper development of the nation through reducing productivity and increasing cost for treatment. Study findings demonstrate, TB death higher among women age15-44. Biologically, this age is the most important time for women to reproduce and continue generation, losing women could potential derange the natural balance of human resource of the country. Furthermore; this also increase risk for children without parents [3-4].

Moreover; TB burden more sever in Ethiopia due to the fact that factors adversely affect TB treatment outcome remains quite vast in Ethiopia. Therapeutic delay, fail to initiate anti-TB treatment after signs and symptoms seen increase risk of death. It is significantly high in Ethiopia [7]. All of studies among cohort of TB patients reported TB /HIV co-infection predictor of death among TB patients. Seventy nine percent of TB patients HIV co-infected in the region which is the highest of all nations [3].

Similarly, prevalence of substance use in Ethiopia, Tobacco use [6.5-10.8%], harmful alcohol use [44.7-54.6%] and Khat chewing [11.0-27.6%] behaviors also challenge treatment success rate in Ethiopia [8]. Tobacco use greatly increase TB death, more than 20% of TB deaths attributable to smoking. Ethiopia is the least urbanized country; 84% of population lives in rural settings which is predictor of TB death [8-10].

Genesis and complication of TB affected by nutritional status of patients. However; 37% of men and 26.9% of women were undernourished [BMI< 18.5Kg/m^2] in Ethiopia 2011 [8]. Molecular and epidemiological investigations show TB death found to be avoidable and most of predictors amenable to interventions. Large portion of knowledge and finance invested to avoid TB death. Regardless of these responses, TB death still high in Ethiopia.

1.3. Significance of the study

This study is important to generate evidence on currently existing survival status of patients under TB treatment and on identified gaps uncovered by other studies. The findings will benefit patients with tuberculosis and their family by providing information when death occurs and factors predispose for death. The findings will also benefit researchers by providing baseline information on current survival status and important predictors in the study area.

Moreover; findings of this study will add benefit of health workers and TB control program officers to assess success of TB control programs. An increased death, default and treatment failure provide message for health workers in TB treatment and care centers to strengthen their role in counseling for adherence and follow-up. Importance of findings and demand for current data justify this study.

2. Literature review

2.1. Responses to Tuberculosis burden

The existing knowle1edge on survival time and predictors of death among TB patients exhaustively addressed through thorough review of relevant and recent literatures. World health organization formulated strategies and set indicators to measure tuberculosis burden and evaluates the impact of programs and policy on Tuberculosis control. Vaccination against tuberculosis, case detection, preventive treatment of people at high risk, early diagnosis and treatment of people with tuberculosis are pillars of global tuberculosis control/"End TB" strategies [6]. Treatment out comes; death, disability, default, treatment failure, cure and treatment complete are the most important indicators of tuberculosis control. Cure and death found to be the best and worst outcomes of tuberculosis respectively [9].

2.2. Survival time

Tuberculosis is the major public health insult that attribute to 16 people per 100,000 populations. Mortality due to TB 1.7 death per 100,000 populations in WHO American region, which is the lowest of six WHO regions. The figure for European regional average is 3.7 per 100,000 populations [2]. Study among sample cohort of TB patients in Ireland reported the median survival time 51 days after completion of treatment [10]. Similar study in Barcelona reported mortality 3.4 per 100 person years during follow up period [11].

Countries in WHO Eastern Mediterranean region are also highly affected by TB death which contributes for death of 14 TB patients per 100,000 populations [2]. Iran from this region reported 15.5 % of TB patients died during the follow-up period in 2014. The median survival time of TB patients on anti-TB treatment was 10.5 years after treatment [12].

WHO Global TB report of 2015 shows WHO South-east Asian region remains the second highly TB burdened region and TB mortality 24 per 100,000 population [2-4]. Study findings from different parts of India in this region also reflect burden in the region. Geeta P. undertook survival analysis among TB patients in India in 2009. The findings reveal survival rate by the end of intensive phase was 96 %, 93% & 99% in categories I, II, & III respectively [13]. Similar study from South India in 2008 reported 98%, 94% and 97% of TB patients survive after completion of treatment from three categories respectively [14].

Africa highly affected by TB burden and contribute larger portion of illness and death to the world. WHO African region contain 12% of global population however, contribute 31% of global TB burden. Moreover; WHO global TB report of 2015 for WHO African region reveal death of 46 individuals per 100,000 populations in the region, which is the highest for all regions [2].

Study in Nigeria 2014 reported 9.9% and 9.4% of TB patients on treatment were died and defaulted respectively. Nearly 36 % (35.7%) of defaults and 91.5% of death occurred during intensive phase of treatment in this study [15]. K Peltzer also undertake study among TB patients in primary health care facilities in South Africa and the result showed 70% of TB patients on TB treatment cured or completed treatment by the end of 6 months[16]. Similarly Dominique J reported 5.3 % of TB patients on treatment died during follow-up period in South Africa in 2015[17].

Survival analysis findings among MDR (Multiple Drug resistance TB) in Mekele reveal mean survival time of MDR patients 7.9 year and incidence of death 3.6 per 10,000 person years [18]. Similarly, Balewgizie from Northwest Ethiopia reported 29.3% of TB patients died during follow-up period [19].

Cohort study aimed to assess treatment outcomes of tuberculosis treatment in Addis Ababa July 2004-June 2009 reported only 18.1% were reported as being cure and 3.7% died during the follow-up periods [20]. Ashenafi S., Goitom W. and Gebremedhin reported 94% of tuberculosis patients survived at the end of treatment and 58.3% died within 2 months of starting treatment [21].

2.3. Factors affecting survival time and mortality

Majority of study findings claimed that death among TB patients while on treatment is not at random. Similar to survival time and rate of mortality, predictors of death among TB patients vary across six WHO regions in the world. Available evidences reveal Intra-venous drug use, advancing age, alcoholism, smoking , HIV – co-infection, previous history of treatment and MDR TB were predictors of death among WHO European region as reported by studies from Ireland, Barcelona in Spain and Russian federation[11, 20,22].

Oursler KK from Maryland assessed molecular and epidemiological predictors of death among 139 adult TB patients in 2012 and identified DNA finger print, patients with unique pattern DNA finger print, underlying illness DM, renal failure, chronic obstructive pulmonary disease and HIV co-infection as important predictors of death among TB patients [23].

Demographic, behavioral and co-infection found to affect survival time in most of WHO East-Asian countries. Studies from different parts of India identified (age > 60 HR=21.54), type of disease, previous history of treatment, alcoholism, drug misuse, smoking and co-infection predictors of death among TB patients on ant-TB treatment in India [13, 14, 24].

Mortality was significantly higher among extra pulmonary TB cases, smear negative TB patients, rural residents, HIV co-infected and under retreatment regimen in Nigeria [15]. Furthermore, findings from South Africa and republic of Tanzania show, co-morbidity, prior history of TB, poor adherence, MDR TB and Diabetes Mellitus, predictors of death among TB patients treated for TB in 2015[16,17].

Case-control study in western Ethiopia reported Divorce/widowed, no formal education, underweight (BMI< 18.5Kg/m^2), history of Diabetes Mellitus, TB/HIV-Co infection significantly associated with death among TB patients [25,26]. Moreover; retrospective cohort studies from Mekele, Dangila, Addis Ababa, and Yirgalem reported therapeutic delay and smoking significant predictors of death among TB patients [27-32]. Most studies not clearly explained time to death and reported death rate/incidence of death. All were among

adults/children missed and in urban settings and on small sample. This study emphasis on the identified gaps to generate evidences for improvement.

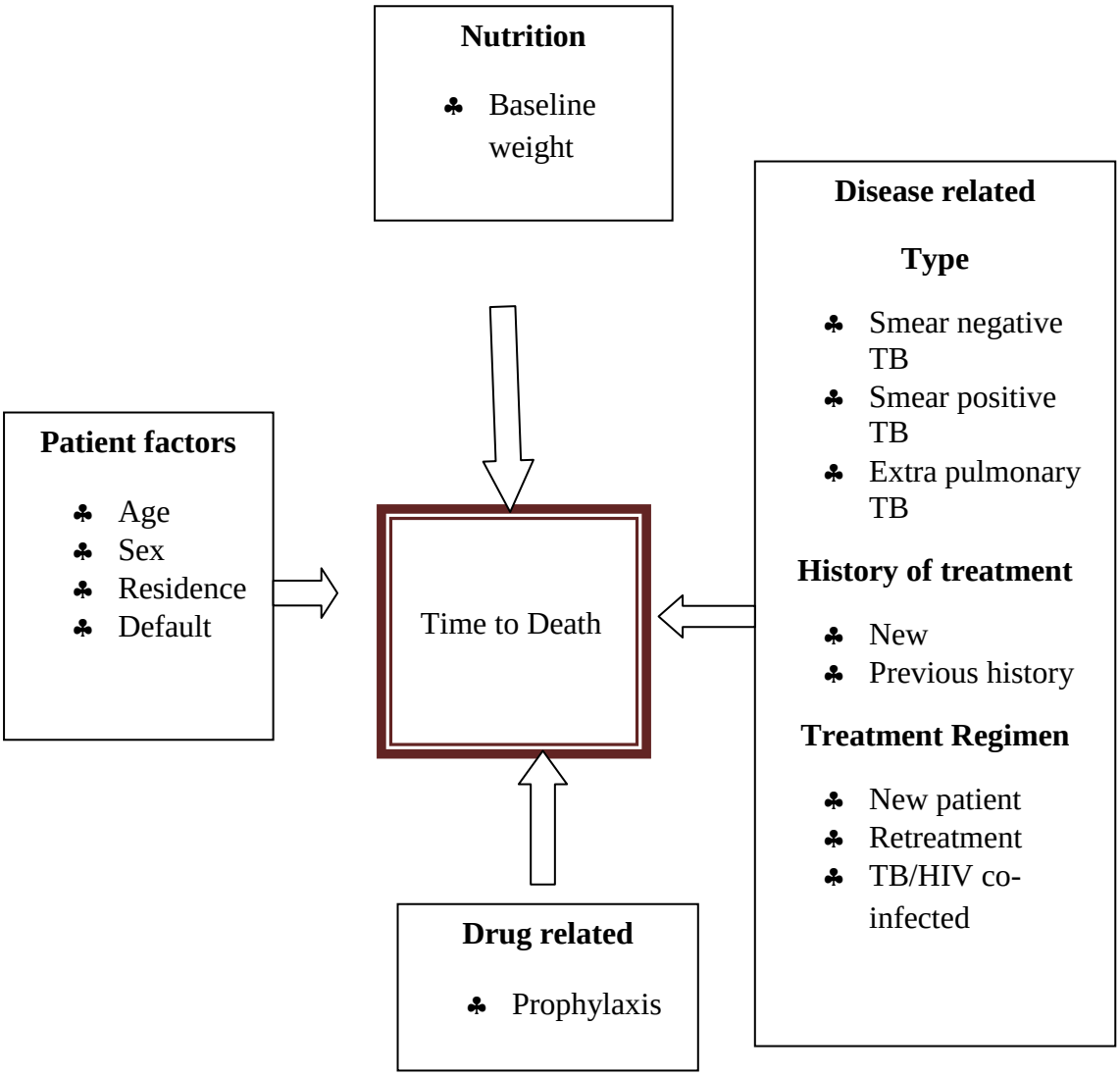

Fig 1. Conceptual framework of survival status and predictors of death among patients with TB treated between 2010-2015 in Hosanna, Southern Ethiopia

Sources: Developed by reviewing relevant literatures

3. Objective

3.1. General objective

To determine Survival status and identify its predictors among patients with TB treated between 2010-2015 in Hosanna, Southern Ethiopia.

3.2. Specific objectives

3.2.1. To determine survival status of patients with TB treated between 2010-2015 in Hosanna, Southern Ethiopia

3.2.2. To compare survival time among different strata in cohort of TB patients treated between 2010-2015 in Hosanna, Southern Ethiopia

3.2.3. To identify predictors of death among different strata in cohort of TB patients treated between 2010-2015 in Hosanna, Southern Ethiopia

4. Methods

4.1. Study Area and Period

The study was carried out in Hosanna located in Hadiya Zones in Southern Ethiopia. Hosanna is located 232 km Southwest from Addis Ababa, the capital of Ethiopia and 196 Km west to Hawassa, the capital of Southern regional state of Ethiopia. This study was undertaken from March 2 – April 14 2016. There is one General Hospital, Nigist Elemini Mohammad Memorial Hospital (NIMMH) and 3 Health centers in Hosanna Town. Only NIMMH and Hosanna Health center initiated TB treatement since 2010. Total of 760 TB patients treated for TB from 2010-2015.

4.2. Study Design

Retrospective cohort design used.

4.3. Source population

All TB patients initiated treatment among facilities in Hosanna

4.4. Study Population

Selected TB patients treated in NEMMH and Hosanna Health center from 2010- 2015.

4.5. Inclusion and exclusion criteria

Records lacked data on death, time when treatment was started, time when event or censoring were occurred and transferred out were excluded. Total of 62 records of patients were excluded.

4.6. Sample size determination

Sample size was determined for Cox proportional Hazard model by using Schoenfeld formula for survival analysis.

$$n = \frac{(Z\alpha + Z\beta)^2}{[\log(HR)]^2\,[(1 - \ P\ )\psi(1 - \rho 2)]} \quad ------ \ [\mathbf{35}]$$

Where,

- ♣ n= Sample size
- ♣ Significance level (α) =0.05
- ♣ Power 80 %,(β)=0.8 , Zβ=0.84
- ♣ HR: Effect size=**0.46** [50, 51]

- ψ-: probability of event (death) =0.123 [21, 33]
- P: The proportion of variability among co-variates of interest =**0.5** [34]
- ρ2= Square of correlation of independent variables with time to death=0.5 [35]
- The final sample size n=**423**

4.7. Sampling technique

Simple random sampling technique employed to recruit study participants. List of Medical record (MRN) Numbers assigned to each study population in sampling frame were selected. Record numbers range from 02 - 77761 of 698 patients seed in to IBM SPSS version 20.0. Random sample of 423 from list of 698 cases was selected. Records of patients exactly attached to selected MRN were collected and included in analysis.

4.8. Data collection technique

Data were extracted from patient follow-up records and clinical requests by Health officers working in TB clinic. Structured data sheet developed by reviewing relevant literatures was used to collect data. Principal investigator and assigned supervisors monitored the overall data extraction. Completed data sheets were counter checked for consistency with the selected MRN and examined for completeness. Four Heath officers and 2 MPH holders were enrolled to data collection and supervision. Half day orientation was given on basic principles of research ethics and data collection tool for data collectors and supervisors.

4.9. Variables and measurement

4.9.1. Dependent variable

Time to death

4.9.2. Independent variables

Type of tuberculosis: Smear negative TB, Smear positive TB, EPTB

History of treatment: New, Previous history

Treatment Regimen: New patient, Retreatment, TB/HIV co-infected

Baseline characteristics and underlying illness: Weight, Co-morbidity, adherence.

Socio-demographic factor: Age , Sex **Drug related**: Prophylaxis drug use

4.10. Data quality

Data collectors and supervisors were took orientation on overall technique of data collection to adhere on the protocol. Computer assisted data cleaning undertaken by data exploration, simple frequency, tabulating for consistency and sorting techniques. Data need transformations were re-coded to meaningful information. Appropriate statistical models were used and assumptions were checked for each model.

4.11. Data analysis

Data was entered in to Epi Data and exported to Stata software package for analysis. Data set declared to survival-time data. Duration: time from starting treatment until death occurred in days set as time variable. Status: death occurred or censored was set as failure variable and "1" defines death and "0". Mean/Median and percentages were used to describe baseline characteristics of participants. Survival was expressed in terms of cases per person-days of follow-up. Survival times assessed using Kaplan–Meier curves and log-rank test. Cox regression model used to identifying predictors of death. Findings were presented using 95% CI of HRs with the corresponding P-value. P-value <0.05 set for significance. Epi-Data 3.1 and STATA 12.0 for windows were used for data analysis.

4.12. Dissemination plan

The manuscript of this study will be submitted to Jimma University department of epidemiology and presented to Jimma University Public Health staff as scheduled by the department. The manuscript will be submitted to international journals for publication

4.13. Ethical considerations

This study was approved by institutional review board of JU. Official letters that allow conducting the investigation and data collection to study area were received from JU. Identifiers such as name, cell phone were eliminated from data collection tool to ascertain confidentiality

4.14. Operational definition

Time to Death: Time from date of starting treatment to died or censored measured in days.

Death: A TB patient who dies for any reasons during the course of treatment. **Censored**: TB patients not recorded as death but recorded as cure, treatment completed and defaulted. **Retreatment:** Treatment category that is recommended for patients after treatment failure, default, and relapse. **Treatment failure:** A patient whose sputum smear or culture is positive at 5 months or later during treatment.

5. Result

5.1. Socio-demographic and baseline characteristics of patients

The mean age of participants was 29.7± SD (15.1) year. Large portion of participants 272 (64.3%) and 223 (52.7%) were in age group 18-40 and male respectively. Majority of participants 324 (76.6%) were from urban settings. The mean weight of patients immediately before initiating treatment was 49.53 ± 11.78 kg *95% CI, (48.8, 50.6*). The mean weight during follow-up was 51.46 ± 11.62 kg. The mean change in weight, the difference between weight at baseline and at the end of two months was 2.0±3.3kg.

Regarding tuberculosis type 239(56.5%) was pulmonary negative followed by pulmonary positive 123(29.1%). Three hundred seventy nine 89.6% were under new category of tuberculosis treatment. All of participants' undergone HIV test and findings demonstrate 54(12.8%) TB/HIV co- infected and 369(87.2%) were not. Reason to stop treatment of most patients defined and findings show that 235 (55.6%) defined under treatment completed and 102 (24.1%) cured. Out of the cohort 102(24.1%) claimed to be cured and 235(55.56%) treatment completed resulting over all treatment success rate of the 79.6%.

Incidence rate of death in Men was 7.04 per 10,000 Person-days , which is higher than incidence rate in Women (5. Per 10,000 Person-days). But the difference is not statistically significant HR=0.75, 95% CI: (0.39, 1.43). The incidence of death in Rural residents 14.8 Per 10,000 Person-days higher than incidence for Urban residents 4.2 Per 10,000 Person-days HR=3.53, 95% CI: 1.85, 6.67). (Table $_{1}$ and figures $_{1\text{-}4}$).

Table 1: Socio-demographic and baseline medical profile of patients on anti-TB treatment between 2010-2015 in Hosanna, Southern Ethiopia

Variables		Died N=44(%)	Censored N=379 (%)	N=423 (%)
Age group	Below 18	6(7.6)	73(92.4)	79(18.7)
	18-40	29(10.7)	243(88.3)	272(64.3)
	Above 40	9(12.5)	63(87.5)	72(17.0)
Sex	Male	26(11.7)	197(88.3)	223(52.7)
	Female	18(9.0)	182(91.0)	200(47.3)
Address	Urban	24(7.4)	300(92.6)	324(76.6)
	Rural	20(20.2)	79(79.8)	99(23.4)
Type of TB	Pulmonary positive	10(8.1)	113(91.9)	123(29.1)
	Pulmonary negative	31(13.0)	208(87.0)	239(56.5)
	Extra pulmonary	3(4.9)	58(95.1)	61(14.4)
Treatment category	New	35(9.2)	344(90.8)	379(89.6)
	Relapse	8(33.3)	16(66.7)	24(5.7)
	Treatment after failure	0(0)	2(100)	2(0.5)
	Treatment after lost	1(14.3)	6(85.7)	7(1.7)
	Transfer in	0(0)	2(100)	2(0.5)
	Others	0(0)	9(100)	9(9.0)
HIV status	Reactive	16(29.6)	38(70.4)	54(12.8)
	Non-reactive	28(7.6)	341(92.4)	369(87.2)
Previous History of treatment	New	35(9.2)	344(90.8)	379(89.6)
	Re-treatment	9(20.5)	35(79.5)	44(10.4)
Site of infection	Pulmonary	41(11.3)	321(88.7)	362(85.6)
	Extra-pulmonary	3(4.9)	58(95.1)	61(14.4)

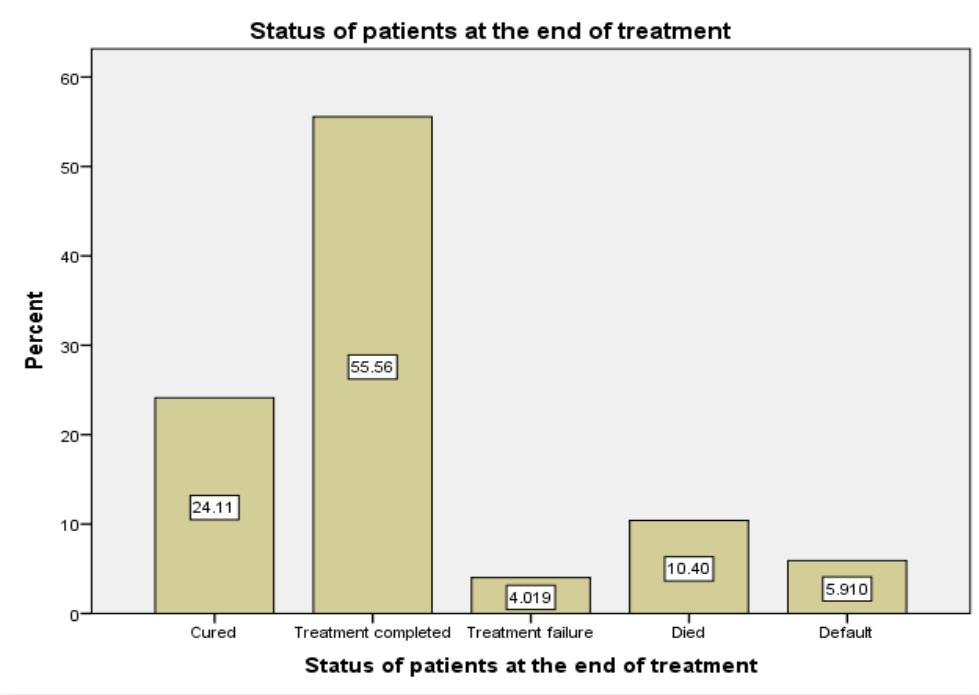

Figure $_1$: Status of TB patients treated for TB in NIMMH and Hosanna Health center in Hosanna, Southern Ethiopia ,2010-2015

5.2. Survival status of patients

Four hundred twenty three subjects were followed for total of 70608 Person-days. There were 44 (10.4%) known deaths in follow up period. Incidence rate of death was 6.23 per 10,000 Person days. The mean survival time of the cohort was **269.8** Person-days. Out of the cohort, 379 (89.6%) survived during the entire follow up period. Majority 27(61.4%) of deaths were occurred within 30 days of treatment initiation.

Survival time was compared graphically using Kaplan-Meier curve and statistically tested using Log rank tests. The mean survival time of male was 266.58 person- days and female was 252.88 person-days, however; the difference was not statistically significant ***[P=0.38***]. Mean survival time for subjects from rural settings was 199.5 Person-days which is significantly lower than urban residents 278.7 person-days [X^2***=18.25, P<0.001***] (Fig.$_3$)

Similarly HIV sero-status was associated with estimated survival time of the cohort that, TB/HIV co-infected (189.14 Person-days) Patients have lower survival time compared to not co-infected (277.9 Person-days) [X^2***=29.8, P<0.001 (***Fig. 4***).*** Survival time was also significantly different among patients in different treatment category. Subjects in repeat treatment category have lower survival time [X^2***=16.2, P=0.006***] (Fig. 5).

Table 2: Kaplan Meier Survival status of patients treated for TB in Hosanna, Southern Ethiopia, 2010-2015

Time in days	Number of patients under observation	Number of death	Probability of survival in the cohort	Probability of death in the cohort
30	397	27	0.933	0.064
60	383	8	0.914	0.083
90	376	3	0.909	0.090
120	372	2	0.904	0.095
150	297	1	0.901	0.098
210	104	2	0.889	0.110
240	54	1	0.878	0.121

The KM cumulative survival curve at mean of covariates of patients treated for TB in NEMMH and Hosanna Health center from 2010 to 2015 is steep, slowly progressing down. This is typical feature of low survival rate and short survival time.

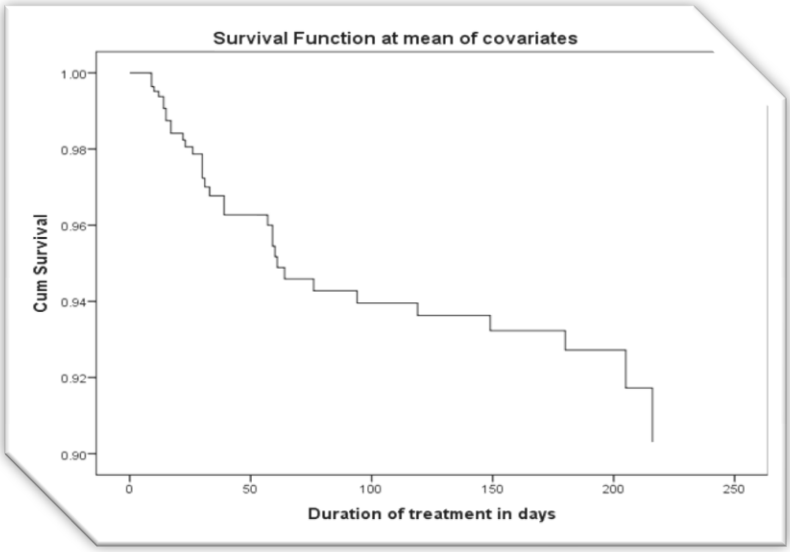

Figure 2: KM survival curve estimates of patients on anti-TB treatment in Hosanna, 2010-2015

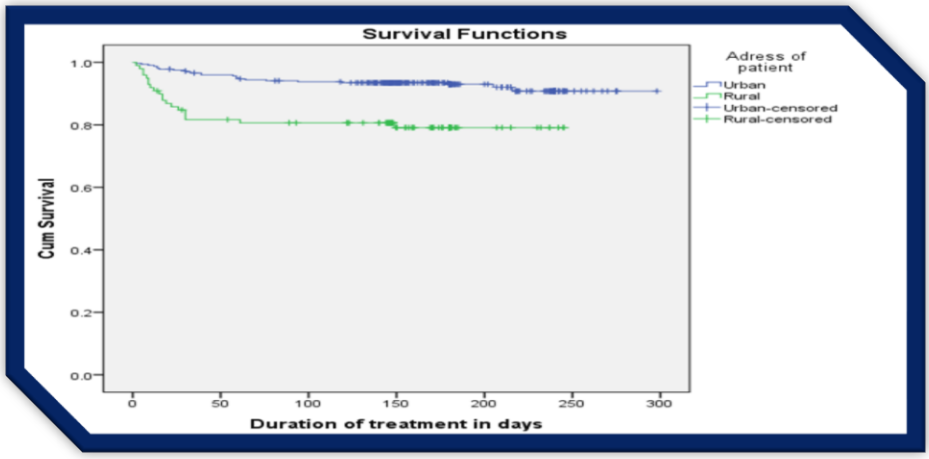

Figure 3: KM survival curve estimates of patients on anti-TB treatment in Urban and Rural settings in Hosanna, 2010-2015

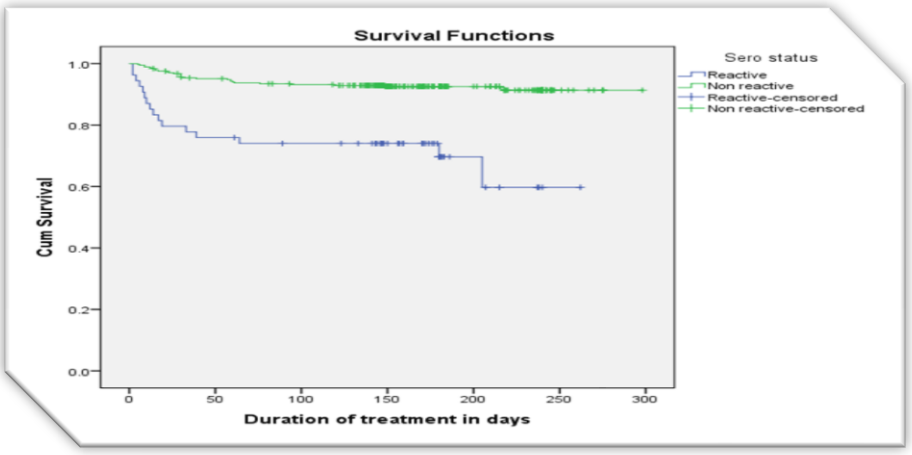

Figure 4: KM survival curve estimates of patients on anti-TB treatment having reactive and Non-reactive sero status in Hosanna, 2010-2015

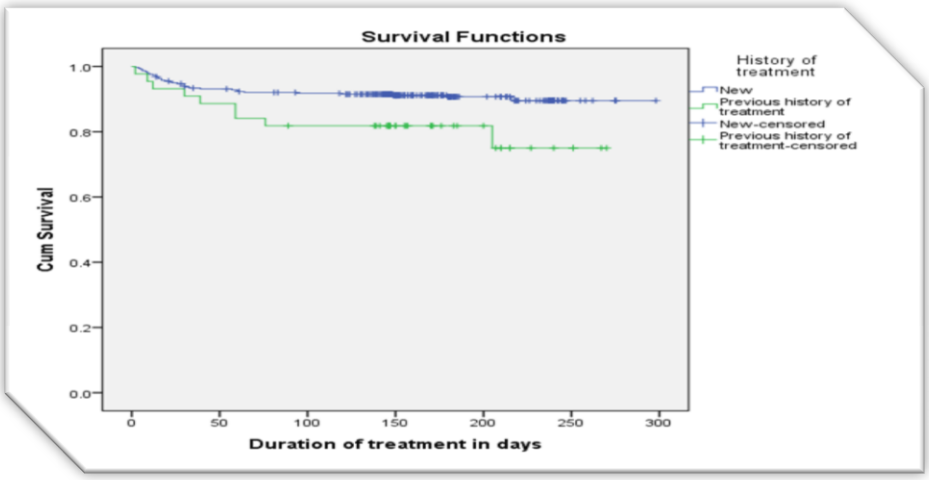

Figure 5: KM survival curve estimates of patients on anti-TB treatment with Previous history of tuberculosis in Hosanna, 2010-2015

5.3. Predictors of death among patients

Candidate variables which were significantly associated with survival in KM test were entered in to Cox proportional hazard model. Proportional- hazards assumption test based on Schoenfeld residual was satisfied (global test $X^2=8.27$, $P=0.76$). Akaike's information criteria (AIC) and Schwartz's Bayesian information criteria (BIC) were used to select model. Model with lowest AIC (435.92), and BIC (484.49) score was defined as optimal and selected.

Address, change in weight, previous history of treatment and HIV/AIDS co-infection were predictors of death in this study (***P<0.05***). Tuberculosis patients from rural settings were 3.1 times hazardous to die compared to those from Urban settings (AHR=3.1, 95% CI: 1.61,6.21 ***P<0.001)***. One kg increase in weight from time starting treatment until completion was found to reduce risk of death by 81.4% across entire range of weight of the cohort by controlling for age and sex (AHR=0.814 95% CI: 0.77,0.85 ,***P<0.001***).

The Hazard of death was significantly higher among tuberculosis patients with previous history of treatment compared to those newly initiated treatment (AHR=4.8, 95% CI: 1.26, 18.59 ***P=0.021***). Tuberculosis patients co-infected with HIV/AIDS were 4.6 times likely to die compared to those not infected with HIV/AIDS (AHR=4.6, 95% CI: 2.41, 8.93, P<***0.001***).

Table 3: Predictors of death during tuberculosis treatment among patients with tuberculosis in Hosanna, Southern Ethiopia, 2010-2015

Variables		Died N=44 (%)	Censored N=379 (%)	AHR(95%:CI)	*P - value*
Sex	Male	26(11.7)	197(88.3)	**1**	
	Female	18(9.0)	182(91.0)	0.51(0.26,1.04)	0.055
Address	Urban	24(7.4)	300(92.6)	**1**	
	Rural	20(20.2)	79(79.8)	3.1(1.61,6.21)	***0.001***
Facility	H Hospital	16(10.5)	136(89.5)	1.43(0.73,2.78)	0.288
	Hosanna HC	28(10.3)	243(89.7)	1	
Type of TB	P positive	10(8.1)	113(91.9)	**1**	
	P negative	31(13.0)	208(87.0)	2.69(1.18,6.13)	***0.018***
	EP	3(4.9)	58(95.1)	0.63(0.17,2.31)	0.49
HIV status	Reactive	16(29.6)	38(70.4)	4.6(2.41,8.93)	***0.001***
	NR	28(7.6)	341(92.4)	1	
Previous History of treatment	New	35(9.2)	344(90.8)	1	
	Has history	9(20.5)	35(79.5)	4.8(1.26,18.59)	***0.021***

NB. **1**=Reference, **P positive**-Pulmonary positive, **P negative**-Pulmonary negative, **EP**-Extra Pulmonary, **NR**-Non-reactive (not infected), **HC**-Health Center

6. Discussion

This study assessed survival status and predictors of mortality among patients with tuberculosis initiated treatment in Nigist Eleni Mohammad Memorial Hospital and Hosanna Health center from February 2010-December 2015. Findings reveal 89.6% of participants survived to the entire follow up time with mean survival time of 269.88 Person-days. The proportion of participants survived in this study is by far lower than reported for cohort of patients with tuberculosis in Yirgalem Hospital 94.1% [2012-2013] (21) and Sidama Zonal Health facilities in Southern Ethiopia 91.1% [1998-2006] (29).

In this study 10.4% subjects died during follow up period, with incidence of death **6.23** Per 10,100 Person-days. Majority (61.4 %) of deaths occurred within 30 days of starting treatment. Mortality rate in this study is higher than reported for range facilities, Mizan Aman General Hospital in Southern Ethiopia 1.22% (41),Felege Hiwot Hospital in Bahirdar, Yirgalem Hospital 1.02 Per Person-month(21) and Health facilities in Dangila Woreda North west Ethiopia 7.4%(27).

In contrast, overall mortality in this study is lower than study finding from center for Tuberculosis research in Baltimore Maryland 21%. The more likely elucidation for the observed difference could be, the previous study included only Pulmonary TB cases among age above 18 years and used death certificate and considered all deaths before, during and after treatment.

Large portion of previous reports from Ethiopia, Nigeria and Cameroon claimed that majority 56.7 %(27), 91.5 %(15) &36.5 %(47) of deaths occurred within the first 2 months of treatment, which in line with the current study finding. Consistency in reports suggests death among tuberculosis patients occur within short period of starting treatment. Chronic respiratory failure and progressive damage of organs remains the major causes of death among pulmonary and Extra-pulmonary tuberculosis respectively.

Delay in treatment found to pose these fatal consequences and have poor prognosis in clinical course of tuberculosis treatment (7). Thus early deaths more likely imply delay in initiating tuberculosis treatment.

Address, weight change, previous history of treatment and HIV/AIDS sero-status were identified predictors of mortality among patients with tuberculosis during treatment. Risk of mortality was significantly higher among rural residents in this study, which is supported by previous comparative studies from Bahirdar in Ethiopia (43) and Nigeria (15).

Success in treatment of tuberculosis requires advanced care besides taking medication. Possibly, people from rural residents have lower socio-economic status and level of awareness to ascertain these important supports. This could be the likely elucidation for the observed risk. However; reasons risk for death among rural resident tuberculosis patients warrant further study.

Change in weight significantly affects survival status of patients with tuberculosis and predictor of mortality in this study. This finding is in line with range of reports from Ethiopia and Africa [20, 27, 50, 37]. Similarly, Studies on mechanism of tuberculosis infection explained that, tuberculosis adversely affect nutritional status by altering appetite regulatory hormone and increases metabolic activity due to prolonged inflammatory process[38]. Weight is an important indicator of acute change in nutritional status that, finding of this study indirectly suggest the need for nutritional support during tuberculosis treatment.

Prior history of TB treatment in category of TB was associated with survival time and predictor of mortality among patients with tuberculosis in this study. This finding is in agreement with reports from Ethiopia (20), South Africa (17) and Russia (22). Unlike to this, study from Hawassa city and Yirgalem town health centers reported no significance risk difference among relapse and new cases [21]. The previous study defined only relapse cases as repeat, which could explain the difference in findings. Consistency in most of findings better explain previous history of treatment important predictor of mortality among TB patients during treatment.

Sero-status of the cohort was analyzed for its independent effect on survival status of TB patients in our sample. Findings demonstrate sero-status was an important predictor of TB mortality that, risk of mortality significantly higher among patients with positive sero-status compared to their negative counterparts. This is consistent with report of Balewgizie S. from Bahirdar (19), Getahun A from Gambella Hospital [39] and Muhabaw J. from Metema Hospital [42].

This implies HIV/AIDS still remains the major public health insult and challenge TB treatment due to its combined immune-compromising effect. Overall treatment success rate was 79.7%

which is lower than reported for 15 districts in Tigray region 89.2%[44] but higher than findings from Metema Hospital 65..3%[42]. The difference could be due methodological and variation in the population.

7. Limitations of the study

The data extracted from secondary data which is subject to missing important characters such as height and incompleteness. Specifically, the data lack height which is important to compute Body mass index (BMI) an important indicator of mass change during treatment. Records and measurements were undertaken by different individuals risk for introduction of observer bias. This study used death during treatment to estimate TB mortality which is limited indicator of TB mortality.

8. Conclusion

Low Survival time and high mortality identified among patients treated for TB in Hosanna Hospital and Hosanna Health center. Most of deaths occurred within 30 days of treatment initiation. This implies delay in initiating treatment in the study area. The study also sought survival time varies among different strata in the cohort. Tuberculosis patients from urban residence and those with previous history of treatment have relatively shorter survival time. Moreover, TB/HIV co-infected found to have short survival time compared no infected.

Change in weight at baseline and during follow up period, address, history of previous treatment and HIV/AIDS sero-status were important predictors of mortality among patients with TB. Higher risk of death is noted in patients from rural residents, low change in weight, previous history of TB treatment and HIV/AIDS co-infection. Over all treatment success is low in this study.

9. Recommendation

Low survival and higher rate of TB mortality among facilities in Hosanna requires urgent clinical, managerial, and public health intervention. Clinicians and front line Health workers are recommended to regularly assess co-morbidity and drug sensitivity among TB patients taking chemotherapy particularly to patients from rural residence and with previous history of treatment. The existing case detection strategy would better be strengthened in order to identify, diagnose and initiate tuberculosis treatment without delay particularly from rural community. Supervision and monitoring should be reinforced to improve counseling particularly during intensive phase of treatment. Nutritional assessment and counseling are important during tuberculosis treatment and should be considered as major part of treatment in the existing DOTS program for better treatment outcome. Specifically:

1. Health facilities

- ♣ Nutritional assessment and counseling are important during TB treatment and should be considered as major part of treatment in the existing DOTS program
- ♣ Strengthen patient follow-up to adhere on treatment and regularly check until cure.

2. Media

- ♣ Communicate the need for earlier initiation and adherence to treatment and risks of delay treatment initiation and treatment after default.

3. Program owners

- ♣ Strengthened case detection strategy in order to identify, diagnose and initiate TB treatment without delay particularly from rural community.
- ♣ Supervision and monitoring should be reinforced to improve counseling particularly during intensive phase of treatment.

4. Researchers

- ♣ Undertake further study to explore causes of death particularly in the beginning of initiating treatment and reasons why people from rural are risk for death

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Annexes

Annex $_1$: Assurance of Principal Investigator

The undersigned agrees to accept responsibility for the scientific ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the College of Health Sciences in effect at the time of grant is forwarded as the result of this application.

Name of the student: **Likawunt Samuel**

Date: **January 2016** Signature: _____

Approval of the Advisors

Name of the first advisor: **Desta Hiko**

Date._____ Signature: _____

Name of the second advisor: **Abiyot Girma**

Date._____ Signature: _____

Annex 2: Consent form

My name is_____I am working in TB clinic Hosanna Hospital/ Hosanna Health center / Shurmo Health center in Southern Ethiopia and now collecting data for research entitled " Survival analysis and Predictors of Death among Patients with Tuberculosis in Southwest Ethiopia: Retrospective Cohort Study" by Likawunt Samuel for fulfillment of MPH in Epidemiology from Jimma University. Your organization is selected by chance. Data on tuberculosis record from your organization will provide evidence on survival status of patients with tuberculosis and predictors of death. Data from your organization is strictly confidential and used only for research purpose. Data will be collected from TB log books, laboratory request, in-patient cards and patient referral papers.

For any question contact the principal investigator of this article Likawunt Samuel, on phone: **+251 911 549009**, at Email: samuelliku@gmail.com

Are you willing to let me collect the data? Yes _____ No _____

Annex 3: Questionnaire

Survival analysis and Predictors of Death among Tuberculosis Patients in Southern Ethiopia: Retrospective Cohort Study

Date of data collection: _____/_____/_____

Name of health facility: _____

Name of data collector: _____date: _____sign:_____

Name of field supervisor: _____date: _____sign:_____

Time of data collection: Start: _____ Stop: _____

Patient registration code ☐

101. Source of data: TB DOTS Registration at Health center/Clinic/Hospital ☐ In-patient cards ☐ Laboratory requests ☐ Referral papers ☐

Part I	***Socio-demographic Characteristics***	***Response***	***Skip***
102	Age of participant	_____year	
103	Sex	Male ☐ Female ☐	
104	Religion	Orthodox ☐ Islam ☐ Protestant ☐ Others: specify_____	
105	Ethnicity	Hadiya ☐ Kembata ☐ Amhara ☐ Oromo ☐ Others :specify _____	

106	Marital status	Married ☐ Divorced ☐ Widowed ☐ Separated ☐ Not ever married ☐	
107	Educational level	Primary ☐ Secondary ☐ Higher education ☐ Not educated formally ☐	
108	Occupation	Government employee ☐ Non-government employee ☐ Merchant ☐ Driver ☐ Daily laborer ☐ Commercial sex worker ☐	
109	Monthly income	_____Birr.	
110	Residence	Urban ☐ Rural ☐	
Part II	***Behavioral factors***		
201	History of substance use	Yes ☐ No ☐	If no →301
		Tobacco use ☐ Alcohol use ☐ Other : Please specify:_____	
Part III	**Baseline characteristics**		

301	Source of referral	Self ☐ Health post ☐ Health center ☐ Other : specify :_____	
302	Functional status	Working ☐ Ambulatory ☐ Bedridden ☐	
303	Underlying illness	Diabetes Mellitus ☐ Renal failure ☐ Chronic pulmonary disease ☐ Other : please specify:_____	
304	Diagnosis	Clinically diagnosed ☐ Bacteriologically confirmed ☐	
305	Weight in Kg	_____Kg	
305	Height	_____m	
306	Body mass index[BMI]	_____Kg/m^2	
Part IV	**Disease category and treatment regimen**		
401	TB category/Type	Smear positive TB ☐ Smear negative TB ☐ Extra pulmonary TB ☐	
405	History of treatment	New ☐ Previous history of treatment ☐	
406	Treatment regimen	New patient ☐	

		Retreatment ☐ Multi-drug resistant ☐ HIV- Co-infected regimen ☐	
Part V	***Patient follow up data of recent results***		
501	Duration	Duration after initiation of treatment:_____day/Month	
502	Recent weight	_____Kg	
503	Height	_____m	
504	Recent BMI	_____Kg/m^2	
505	Lost to follow-up	Yes ☐ No ☐	If no →507
506	If yes, reasons to lost follow-up	Drug side effects ☐ Too ill ☐ Forgot ☐ Felt better ☐ Travel problem ☐ Others: Please specify:_____	
507	Recent functional status	Working ☐ Ambulatory ☐ Bedridden ☐ Not known ☐	
508	Evidence of new infection	Yes ☐ No ☐	If no →510

509	If yes	Please specify:_____	
510	Drug side effect seen	Yes ☐ No ☐	If no→512
511	If yes	Please specify:_____	
512	Drug regimen change	Yes ☐ No ☐	If no →514
513	If yes reasons for change	Drug side effect ☐ Pregnancy ☐ Treatment failure ☐ Other: please specify:_____	
514	Recent test findings	Pleaase list:_____	
515	Current status/Event	0. Alive ☐ 1. Died ☐	

Thanks