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SURVIVAL AND PREDICTORS OF MORTALITY AMONG PATIENTS UNDER MULTI-DRUG RESISTANT TUBERCULOSIS TREATMENT IN ETHIOPIA: ST. PETER'S SPECIALIZED TUBERCULOSIS HOSPITAL, ETHIOPIA

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ABSTRACT

Background: Multi-drug resistance tuberculosis (MDR-TB) is an increasing global problem. The extent and burden of MDR-TB varies significantly from country to country. Survival of MDR-TB treatment is not described in Ethiopia. Therefore, examining a cohort who received second-line therapy for MDR-TB to determine overall survival has a great importance.

Objectives: To assess survival and predictors of mortality among patients under MDR-TB treatment in Ethiopia: St Peter's specialized TB Hospital, Addis Ababa, Ethiopia.

Methods: A retrospective analysis of records was conducted from Oct, 2011 - May, 2012 among cohorts of MDR-TB patients in St. Peter's specialized TB hospital that starts treatment from February 2009**.** Data were collected using checklist from 188 patients' record that is determined and analyzed using the STATA Statistical package, Version 11.0. Risk was estimated for the entire follow-up time corresponding to each event occurrence using Kaplan-Meier method and the covariates are fitted to Cox proportional hazard regression model.

Result: The 188 patients were followed for a total of 79,600 person-days. Median follow up time was 466.5 days or 1.28 years. Among the total subjects, 87 (46.28%) are male and the rest 101 (53.72%) are female with a median age of 27 years. There were 29 (15.43 %) known deaths (incidence rate: 3.6 per 10,000 person-days). Survival rate at 6, 12, 18, and 24 months of treatment were 88.53 %, 85.83 %, 82.71 % and 78.95 % respectively. The mean survival time for patients under MDR-TB was 9.7 years. Comparison of the groups showed that there is a significant difference in the probability of surviving between HIV status, smoking status, therapeutic delay, No. of first line resistant drugs at initiation, co-morbidities, region and clinical complication. In multivariate Cox proportional hazard regression, factors independently associated with mortality of patients were smoking (HR: 4.01, 95% CI 1.42 - 11.37, $P = 0.009$), therapeutic delay > 1 month (HR: 3.61, 95% CI 1.41 - 9.20, $P = 0.007$), HIV seropositive (HR: 5.94, 95% CI 2.40 - 14.72, $P < 0.0001$) and clinical complication (HR: 1.90, 95% CI 1.52 - 2.39, $P < 0.001$).

Conclusion and recommendation: Survival of patients was higher and higher hazard of death was noted in patients who started treatment after a month, smoker, HIV positive and patients who develop a clinical complication. Although survival is good, reinforcing the existing treatment program will further improve patients' survival in Ethiopia.

INTRODUCTION: According to World Health Organization (WHO) definition Multi drug-resistant tuberculosis (MDR-TB) is caused by bacteria that are resistant to the most effective anti-tuberculosis drugs (isoniazid and rifampicin). MDR-TB results from either primary infection or may develop in the course of a patient's treatment [1].

MDR-TB cases are classified into two categories: those who have primary resistance and those who have acquired resistance, consisting of the majority of cases. Insufficient previous treatment is a strong prognostic factor in the development of MDR-TB. Many of the MDR-TB patients had been taking anti-TB drugs for a long time, and often irregularly, which resulted in treatment failure [2, 3].

MDR-TB patients respond poorly to short course chemotherapy and need to be treated intensively for up to 24 months with a regimen based on reserve anti-tuberculosis drugs [4].

MDR-TB is an increasing global problem. The extent and burden of MDR-TB varies significantly from country to country. Globally, the proportion is higher in patients who had previously received anti-tuberculosis (anti-TB) treatment reflecting the failure of programs designed to ensure complete cure of patients with tuberculosis [5].

WHO estimates that, 440 000 people had MDR-TB in 2010 and that result a 150 000 deaths from MDR-TB worldwide. In 2010, the largest WHO MDR-TB survey reported the highest rates ever of MDR-TB, with peaks of up to 28% of new TB cases in some settings of the former Soviet Union, including regions sharing borders with the European Union [1].

Asia bears the burden of the epidemic as almost 50% of MDR-TB cases worldwide are estimated to occur in China and India [6]. High prevalence of MDR-TB was also found among new cases in Ecuador, and Israel. Central Europe and Africa, in contrast, reported the lowest median levels of drug resistance [6].

In Africa, where little data is available, an estimated 69 000 cases emerged in 2009, but the vast majority of them went un-diagnosed [7].

In 2002, MDR TB in Ethiopia was also reported in about 1.2% of new cases and 12% of re-treatment cases [8]. According to WHO 2009 report there are 1.6% MDR-TB patients among all new TB cases & 12% MDR-TB patients among previously treated TB cases in Ethiopia [9].

Of the 27 countries with a high burden of MDR-TB and extensively drug resistant TB (XDR-TB), 13 countries with data on treatment outcomes for MDR-TB cases reported a success by 25%-82% among patients that started on treatment in 2007 [7]. However, it should be remembered that increases in the prevalence of resistance can be caused by poor or deteriorating TB control, the immigration of patients from areas of higher resistance, outbreaks of drug-resistant disease, and variations in surveillance methodologies [10].

Expanding access to MDR-TB therapy is urgently needed, yet poor implementation of such therapy can worsen the problem of XDR-TB. Understanding risk factors for poor treatment outcomes (death) among MDR-TB patients is necessary to improve treatment outcomes [11].

Outcomes of MDR-TB treatment are not described in Ethiopia. Therefore, examining a cohort who received a standardized second-line therapy and management of MDR-TB to determine the overall survival rate has a great importance.

Isoniazid, the most powerful mycobactericidal drug available, ensures early sputum conversion and helps in decreasing the transmission of TB. Rifampicin, by its mycobactericidal and sterilizing activities is crucial for preventing relapses.

Thus, isoniazid and rifampicin are keystone drugs in the management of TB. While resistance to either isoniazid or rifampicin may be managed with other first-line drugs, resistant to both isoniazid and rifampicin (MDR-TB) demands treatment with second-line drugs. These drugs have limited sterilizing capacity and are not suitable for short course treatment.

Thus, patients with MDR-TB require prolonged treatment with drugs that are less effective and more toxic [12].

Since the treatment of MDR-TB in Ethiopia started recently, the survival rate and its determinant factors among patients under MDR-TB treatment are not described. Identification of survival rate and risk factors of mortality in MDR-TB cases is essential for proper planning and effective implementation of MDR-TB treatment.

Hence, the objective of this study is to assess the survival and predictors of survival time among patients under Multi-drug resistant tuberculosis in Ethiopia.

METHODS:

Study settings: MDR-TB treatment was started for a total of 218 patients in St. Peter's specialized TB Hospital, Gondar University Hospital and Dire Dawa Dil Chora Hospital [22]. Gondar Hospital has started the treatment in 2011 and Dil Chora Hospital does not start the treatment till the end of September. Therefore both are excluded from this study because there is no longer follow up period to determine the outcome of interest. Only patients in St. Peter's specialized TB Hospital are included in this study. Ethiopia has a total of three Hospitals that render MDR-TB treatment with 119 trained health professionals [22]. St Peter's specialized Hospital is one of the three health facilities which provide the service in Addis Ababa, the Capital City of the Federal Democratic Republic of Ethiopia starting from 2009 designed to give the treatment for patients who are referred from different part of the country [23].

Study design and participants: A cross sectional study was conducted from October, 2011 up to May, 2012 among cohorts of MDR-TB patients that starts treatment from February 2009 in Addis Ababa St. Peter's specialized TB hospital. The study population was patients who are confirmed MDR-TB patients and referred to St. Peter's specialized TB hospital from different part of the country and started treatment with second line drugs and those patients records found in this hospital.

The sample size was determined by assuming a 2.33 hazard ratio (effect size) [18] associated with a one-unit increase in covariate of interest which is HIV co-infection when other covariates are held constant, the default 0.5 standard deviation of covariate of interest is used, the probability of failure (death) observed is 0.234 [18], giving any particular outcome to be with 5% marginal error and 95% confidence interval of certainty ($\alpha = 0.05$). The number of subjects needed to achieve a power of 80% and assuming no subjects anticipated to withdrawal from the follow up.

Based on this assumption, sample size estimation for the assessment of survival time under the Cox-proportional hazards model is computed using the STATA Statistical package, Version 11.0. The total sample size required is 188 to achieve 80% power. Simple random sampling without replacement technique using the lottery method was employed to fulfill the desired patient's record.

Data Collection procedure and Quality Assurance: Data were extracted from Medical records by health professionals, working at the hospital through a uniform checklist and variables on socio-demographic factors, clinical factors and time of the event was recorded. Data entered into a password protected computer to maintain the confidentiality by the data clerk after checking for completeness and coding. Regular and daily supervision of the data collection process was done by the principal investigator. Data collectors were oriented and employed for one day on how to appropriately extract the data and on-site supervision and feedback was given to them. Data were checked on a daily basis for consistency, completeness, clarity and accuracy.

Analysis variable: The dependent variable is the time of death. On the basis of previous work and literature review, a set of variables is selected for the analysis. Considering the potential importance, the following variables were taken as likely covariates: Socio-demographic factors: sex, age, weight, region.

Clinical factors: HIV co-infection, No. Of anti-TB drug taken, MDR category, presence of chronic disease, clinical complication, radiological findings, No. Of resistant drugs at initiation, therapeutic delay, smoking status and smear positivity.

We do not have any prior knowledge of specific interactions that must be included so all the possible interactions were considered. There was no any interaction term found in the model and were not included in the model.

Data Management and Statistical Analysis: Death is the outcome variable (event) that was measured (coded as 1 for death and 0 for censored). The patient surviving till end of the cohort study contributed a censored cases. Censorship includes cured, treatment completed, treatment failure, treatment stopped, transfer out & study time completion. Time to event data (survival times) was calculated by subtracting date of treatment (t_o) started from date of event occurred (t_1). Some of the continuous variables (age, weight, No of resistant drugs) are categorized for the ease of Cox-proportional hazard regression model and age was considered as time dependent covariate.

Data was analyzed using the STATA Statistical package, Version 11.0. Relative risks (hazard ratio) with 95% CI and two-sided test of significance was used to measure the association of dependent and independent variables. Survival curves were compared between different exposure groups using log-rank test (Chi-square test with 1 df under H_o). Survival trend over the follow up time was calculated using the Kaplan Meier (KM) method and the covariates were fitted to Cox proportional hazard regression model and Collett's Model selection approach [Annex III] was used. After fitting the Cox proportional hazard regression model to a set of survival data, the adequacy of the fitted model to the survival data was checked using (Generalized) Cox-Snell residuals and martingale residuals.

An assumption to Cox-proportional hazard model that is the hazards remaining proportionately constant is checked using graphical representation (Log-log plot) and a statistical test. No violation of the assumption was found, therefore no stratified Cox model or incorporate a time-dependent term were not used. The statistic -2 log L was used to measure the extent to which the data are fitted by a particular model is required. It is the summary measure of agreement between the model and the data.

Operational definition:

Died - Patient who dies during the course of treatment [24].

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

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

Therapeutic delay – A confirmed MDR-TB patient who starts treatment after one month.

Previously NOT treated for TB - A patient who denies having had any prior anti-TB treatment.

Previously treated case - A patient who admits having been treated for TB for one month or more. Chemoprophylaxis should not be considered as treatment for TB.

Ethical consideration: The ethical clearance was obtained from Mekelle University, College of Health Science, Health Research Ethics Review Committee (HRERC) and St. Peter's Specialized TB Hospital ethical clearance committee. There was no any harmful action imposed to patients and the researcher does not photocopy or remove documents from the hospital. Anonymity of individual patient was maintained absolutely. The study has a benefit to patients by providing improved management and effective implementation of MDR-TB treatment. Therefore, the study was carried out after getting permission from the independent ethical clearance committee.

RESULTS:

Study Population: There are around 300 confirmed MDR-TB cases that start the treatment in St. Peter's specialized Tb hospital. The analysis was done on the 188 patients with complete data. More than half of the patients had missing data on smear positivity at the time of MDR-TB diagnosis; therefore the variable smear positivity is excluded from analysis. Except region which has 2 (1.06%) missing data and radiological findings which has 12 (6.38%) missing data all other variables have complete data. Since both are less than 10%, considered as they have no effect on the result and deletion method was used to treat the missing data.

Socio-demographic and Clinical characteristics: Of the total study units, 87 (46.28%) of them are male and the rest 101 (53.72%) are female. Among the total subjects, there were 29 (15.43 %) known deaths, of them 30.3 % (10/33) in HIV positive and 12.3 % (19/155) in the HIV negative group occurred.

The incidences of death among patients under MDR-TB treatment were 0.03643 % that is approximately there were 4 deaths /day /10,000 after the patient started the treatment. The majority of MDR-TB patients were younger aged less than 35 years (81.38 %) with median age of 27 years living in Addis Ababa (75.27 %), Oromia (11.29 %), Tigray (5.38 %), with a median weight of 47 Kg and nonsmokers (94.68 %). 7.98 % and 4.26 % of patients had clinical complication due to Cor pulmonale and pneumonia respectively.

Around 146 (82.95 %) of patients had unilateral or bilateral lung damage due to cavities (61.93%) and infiltration (21.02%) identified on radiographs. All patients were tested for HIV infection as testing is imposed by national policies and 33 (17.55 %) were positive. Only 7 (3.72 %) were not treated for anti-TB drugs the rest 181 (96.28 %) were treated previously for anti-TB drugs. In addition to resistance to isoniazid and rifampicin 65.96 % were resistant to other first line drugs [**table 1**].

TABLE 1: SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTIC OF MDR-TB CASES (N=188) IN ST. PETER'S SPECIALIZED TB HOSPITAL, 2012

Characteristics	Frequency, (%)	Median (SD)
Death		
Dead	29, (15.43)	
Censored	159, (84.57)	
Sex		
Male	87, (46.28)	
Female	101, (53.72)	
Age		**27 (10.11676)**
Region		
Tigray	10, (5.38)	
Amhara	2, (1.08)	
Oromia	21, (11.29)	
SNNP	7, (3.76)	
Dire Dawa	2, (1.08)	
Addis Ababa	140, (75.27)	
Others*	4, (2.16)	
Weight		**47 (10.81128)**
HIV co-infection		
Negative	155, (82.45)	
Positive	33, (17.55)	
MDR category		
Previously treated	181, (96.28)	
Previously NOT treated	7, (3.72)	
Co- morbidities		
No	172, (91.49)	
Diabetes Mellitus	5, (2.66)	
Myocardial Infarction	6, (3.19)	
DM & HTN	3, (1.60)	
Asthma	2, (1.06)	
Clinical complication		
No complication	155, (82.45)	
Pneumothorax	7, (3.72)	
Pneumonia	8, (4.26)	
Hemoptysis	3, (1.60)	
Cor pulmonale	15, (7.98)	
Radiological findings		
Unilateral cavity	7, (3.98)	
Bilateral cavity	102, (57.95)	
Unilateral infiltration	23, (13.07)	
Bilateral infiltration	14, (7.95)	
Non-cavity	26, (14.77)	
Bronchiectasis	2, (1.14)	
Effusion	2, (1.14)	
No. of first line drugs resistant at initiation		
INH & RIF only	64, (34.04)	
More than INH & RIF	124, (65.96)	
Therapeutic delay		
< 1 month	93, (49.47)	
> 1 month	95, (50.53)	
Smoking status		
Yes	10, (5.32)	
No	178, (94.68)	

* Others include Somalia=1, Benishangul Gumuz=1, Gambella=1 & Harari=1

Summary of Survival time: The 188 patients were followed for a total of 79,600 person-days. Median follow up time was 466.5 days or 1.28 years. The median survival time or the survival time at which the cumulative survival function is equal to 0.5 was undetermined. Because the largest observed analysis time was censored, the survivor function does not go to zero [**Figure 1**]; in this case the mean is the best estimate of survival time.

The cumulative survival probability at the end of 2.29 years was 78.95 % (95 % CI; 67.84 % - 86.59 %). In HIV positive patients, the overall cumulative survival probability at the end of 2.29 years was 59.9 % (95 % CI; 36.16 % - 77.24 %) and in HIV negative patients, the overall probability of survival was 82.13 % (95 % CI; 66.88 % - 90.82%). The cumulative survival probability at the end of the years was summarized in **Table 2**. The restricted mean underestimate the result, therefore the extended mean were used which is an ad hoc approximation that extends the survivor function from the last observed time to zero by using an exponential function and computes the area under the entire curve [26].

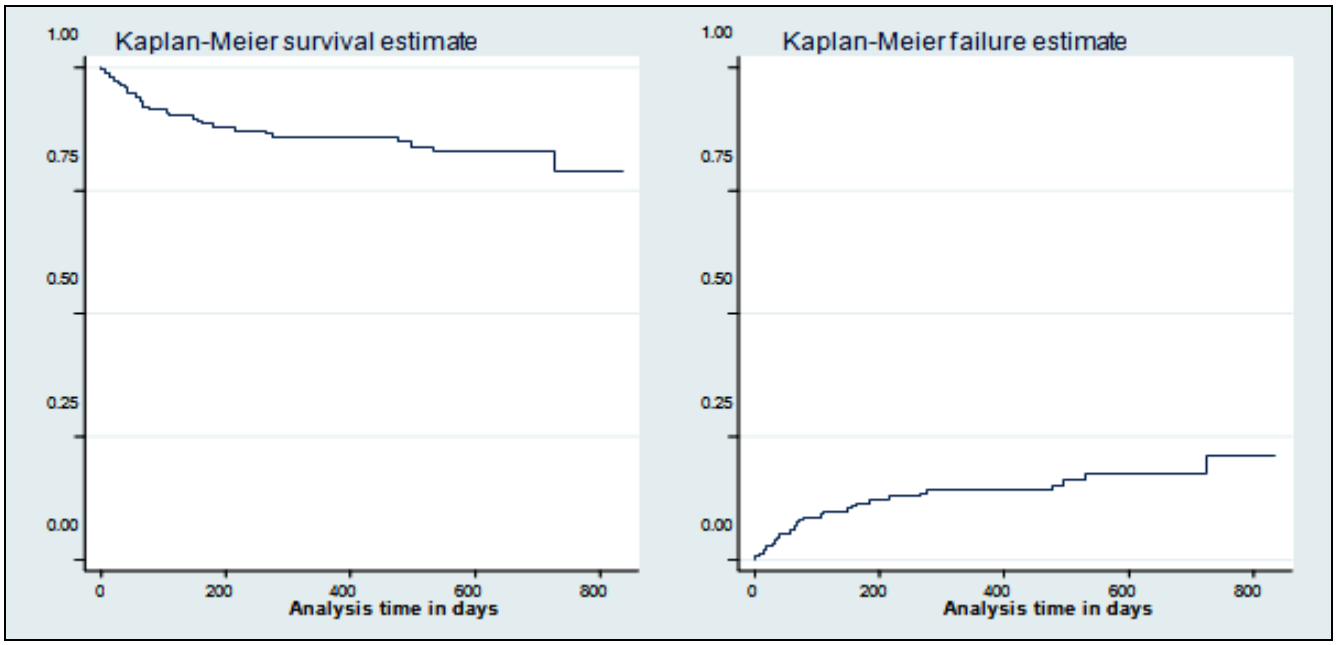

FIGURE 1: KAPLAN-MEIER SURVIVAL AND FAILURE ESTIMATE OF PATIENTS UNDER MDR-TB TREATMENT IN ST. PETER'S SPECIALIZED TB HOSPITAL, 2012.

TABLE 2: SUMMARY PROBABILITY OF SURVIVING OF PATIENTS UNDER MDR-TB TREATMENT OVER THE YEARS ST. PETER'S SPECIALIZED TB HOSPITAL, 2012

Time in year	Survival rate up to the end of the year (CI)
0.5 years	88.53 % (82.95% - 92.37%)
1 year	85.83 % (79.69% - 90.22%)
1.5 years	82.71 % (75.60% - 87.91%)
2 years	78.95 % (67.84% - 86.59%)

The mean survival time for MDR-TB patients under the treatment were 3541.267 days or 9.7 years [**Figure 2**]. The mean survival time for HIV positive MDR-TB patient were 1588.379 days or 4.35 years and for HIV negative MDR-TB patient were 3996.926 days or 10.95 years.

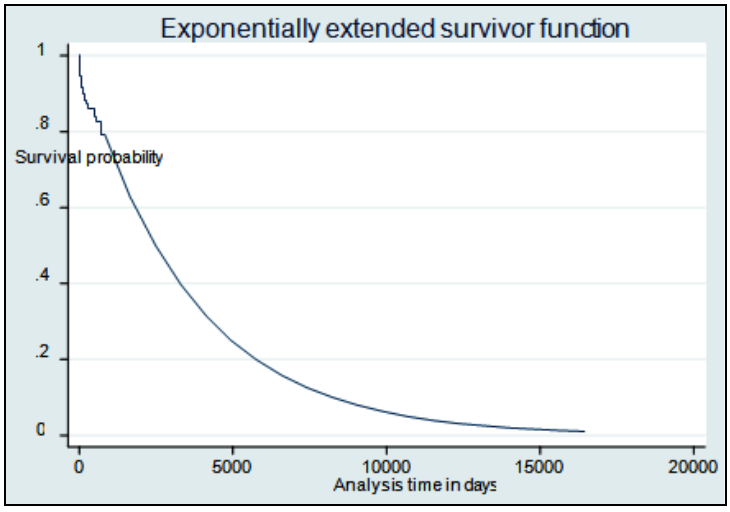

FIGURE 2: EXPONENTIALLY EXTENDED MEAN SURVIVAL FUNCTION OF PATIENTS UNDER MDR-TB TREATMENT IN ST. PETER'S SPECIALIZED TB HOSPITAL, 2012

Predictors of Mortality: Efron method was used to handle a tied failure time which is a more accurate approximation of the exact marginal likelihood than Breslow's. Factors that might be expected to have a potential impact on the death of MDR-TB patients are shown by univariate Cox proportional hazard regression analysis in **Table 3.** Smoking, therapeutic delay of > 1 month, HIV serpositivity, No. of first line resistance drugs > 2, baseline weight and clinical complication were factors significantly associated with the outcomes of death in the univariate analysis.

TABLE 3: UNIVARIATE ANALYSIS OF COVARIATES ASSOCIATED WITH RISK OF DEATH DURING MDR-TB TREATMENT IN ETHIOPIA: ST. PETER'S SPECIALIZED TB HOSPITAL, 2012

Covariates	HR [95% CI]	*P*-value
Male sex	1.24 [0.60 - 2.58]	0.559
Smoker*	4.63 [1.76 - 12.17]	0.002
Therapeutic delay > 1 month*	3.19 [1.36 - 7.46]	0.008
No. Of first line resistant drugs > 2*	0.39 [0.19 - 0.80]	0.011
HIV seropositive*	2.63 [1.22 - 5.67]	0.014
Previously treated for TB	6.20e+14 [0 - .]	1.000
Baseline weight*	0.95 [0.91 - 0.99]	0.013
Age	0.99 [0.98 - 1.00]	0.593
Clinical complication*	1.78 [1.46 - 2.18]	< 0.001
Radiological findings	0.97 [0.73 - 1.29]	0.826
Co-morbidities	1.17 [0.83 - 1.63]	0.369

*Variables to be included in the model

Further analysis was carried out using multivariate Cox proportional hazard model, Covariates are then allowed to shift this baseline hazard [**Figure 3**] proportionally, so that the factors investigated were controlled for one another and parameter estimates for the final model were selected using the stepwise selection method.

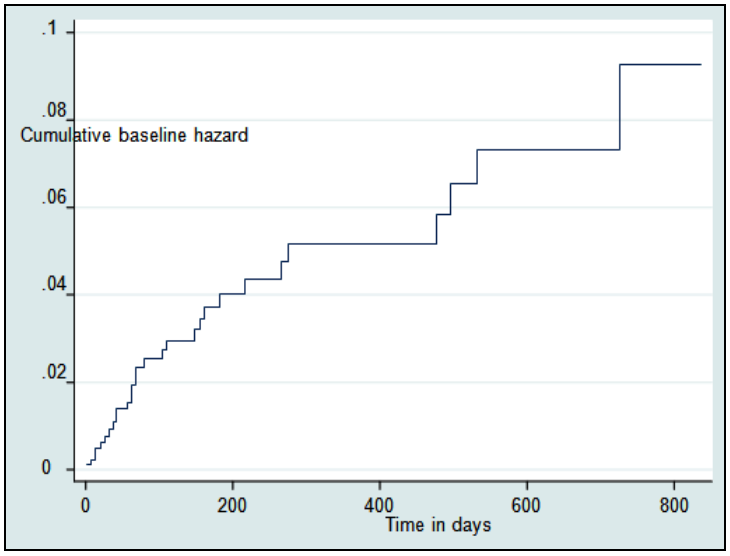

FIGURE 3: BASELINE CUMULATIVE HAZARD

PH assumption was not found to be violated by any covariates; therefore further stratification has not been made to estimate the hazard. In multivariate Cox proportional hazard regression [**Table 4**], factors independently associated with survival after adjusting for other patient characteristics were smoking, therapeutic delay > 1 month, HIV seropositive and clinical complication. When we compare patient mortality among those who smoke with those who do not smoke, the difference was statistically significant. High mortality occurred in those who smoke (HR 4.01; 95%; CI 1.42 - 11.37, *P* = 0.009) than do not smoke.

The other factor that showed significant association was therapeutic delay of more than one month. When we compare patient survival who starts treatment a month delay after diagnosed as MDR-TB was observed to have a higher hazard of death (HR= 3.61; 1.41- 9.20, *P* = 0.007). HIV seropositive individuals also have a higher hazard of death (HR 5.94, 95% CI 2.40 - 14.72, *P* < 0.0001) compared to HIV negative individuals. Patients who have clinical complication also have a higher hazard of mortality (HR 1.90, 95% CI 1.52 - 2.39, *P* < 0.001) than who do not have the complication.

Even though it is not statistically significant, a one Kg increase in baseline weight has a protective effect, that is 3% lower hazard of death (HR= 0.97; 0.93 -1.02, *P* = 0.224).

This study revealed that survival of patients under MDR-TB treatment was not associated with age, sex, baseline weight, radiological findings, previous Tb treatment, No. of first line resistant drugs and co-morbidity.

TABLE 4: ANALYSIS OF FINAL MODEL OF COVARIATES ASSOCIATED WITH RISK OF DEATH DURING MDR-TB TREATMENT IN ETHIOPIA: ST. PETER'S SPECIALIZED TB HOSPITAL, 2012.

Covariates	HR [95% CI]	β [95% CI]	P-value
Smoker	4.01 [1.42 - 11.37]	1.39 [0.35 - 2.43]	0.009
Therapeutic delay > 1 month	3.61 [1.41 - 9.20]	1.28 [0.35 - 2.22]	0.007
No. Of first line resistant drugs > 2	0.53 [0.24 - 1.19]	-0.63 [-1.43 - 0.18]	0.126
HIV seropositive	5.94 [2.40 - 14.72]	1.78 [0.87 - 2.69]	< 0.001
Baseline weight	0.97 [0.93 - 1.02]	-0.03 [-0.07 - 0.02]	0.224
Clinical complication	1.90 [1.52 - 2.39]	0.64 [0.42 - 0.87]	< 0.001

Overall assessment of Model Adequacy: The value of Harrell's *C* is 0.8725, which indicates that we can correctly order survival times for pairs of patients 87 % of the time on the basis of measurement of fitted variables in the model. The *C* index is defined as the proportion of all usable subject pairs in which the predictions and outcomes are concordant.

Checking the Proportionality Assumption: Assumptions to Cox-proportional hazard model were checked using graphical representation and covariate specific PH assumption test. No covariates violate the proportional-hazards assumption. Therefore stratified Cox model or time dependent terms were not used. Covariate specific PH assumption global test [**Table 5**], we can see that there is no evidence that the proportional-hazards assumption has been violated

TABLE 5: COVARIATE SPECIFIC TEST OF PROPORTION ACOVARIATES ASSUMPTION OF COVARIATES FITTED IN THE FINAL MODEL, ST. PETER'S SPECIALIZED TB HOSPITAL, 2012.

Covariates	chi^2	Df	*P*-value
Complication	1.26	1	0.2618
HIV	1.62	1	0.2037
Delay	1.52	1	0.2183
Smoking	0.19	1	0.6600
Weight	0.36	1	0.5492
No Res. Drugs cat	0.12	1	0.7313
Global test	4.91	6	0.5556

Comparing alternative models:

Log Likelihood: The log likelihood statistic for the survival model that contains variables which is not dummied (Model I) and the model which contains dummied variables (Model II) was almost similar [**Table 6**]. The goodness of fit statistics for the final survival regression model gives for the two comparative models were a Log likelihood value of -116.5031 and -115.0344 which implies *p*-value of 0.000 which signifies a significant decrease in deviance thereby implying an equal good fit of the models but the model which contains dummied variables have a wider CI and large SE value, therefore dummying of categorical variables were not necessary.

Akaike's information criterion (AIC) and Bayesian information criterion (BIC): The AIC and the BIC were done to measure the models fit and complexity. Given two models fit on the same data, the model with the smallest value of the information criterion is considered to be better. Based on the above information Model I has a smallest AIC and BIC [**Table 6**], therefore Model I was selected as a final model as it has a good fit and less complexity and Model II were considered as an over fitted model because it has a large SE.

In an over fitted model, the estimated values of some of the *β*-coefficients were highly dependent on the actual data. A very slight change to the values of one of these variables could then have a large impact on the estimate of the corresponding coefficient. This is the reason for such estimates having large standard error. An over fitted model is one that is more complicated than is justified by the data, and does not provide a useful summary of the data. This is another reason for not including the dummied variables in the model for the hazard of death from MDR-TB.

TABLE 6: VALUES OF MAXIMUM LIKELIHOOD, AIC AND BIC FOR MODELS FITTED TO THE DATA IN DIFFERENT MODELS, ST. PETER'S SPECIALIZED TB HOSPITAL, 2012

Model	Variables in the model	LL	AIC	BIC
Model I	HIV, Smoking, Delay, Complication	-116.5031	241.0062	253.9519
Model II	HIV, Smoking, Delay, Pneumonia, Hemoptysis, Cor pulmonale	-115.0344	244.0687	266.7238

Checking residuals:

Cox-Snell residual: If the Cox regression model fits the data, these residuals should have a standard censored exponential distribution with hazard ratio [1]. The hazard function follows the 45 degree line very closely except for large values of time [**Figure 4**]. It is very common for models with censored data to have some twisting at large values of time and it is not something which should cause much concern. Overall we would conclude that the final model fits the data very well.

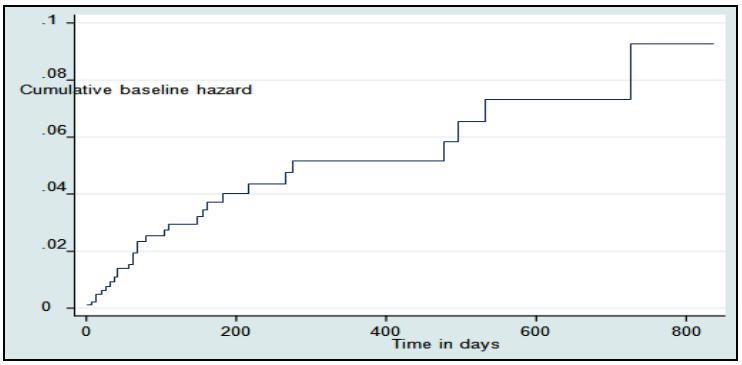

FIGURE 4: COX-SNELL RESIDUAL CUMULATIVE HAZARD GRAPH FOR PATIENTS (N=188) UNDER MDR-TB TREATMENT IN ST. PETER'S SPECIALIZED TB HOSPITAL

Martingale Residuals: Martingale residuals are useful in assessing the functional form of a covariate to be entered in to a Cox model. Sometimes the covariate may need transforming so that the transformed variable will satisfy the assumptions of the proportional hazards model. The smooth appears nearly linear [**Figure 5**], supporting the untransformed version of weight and age in our Cox model.

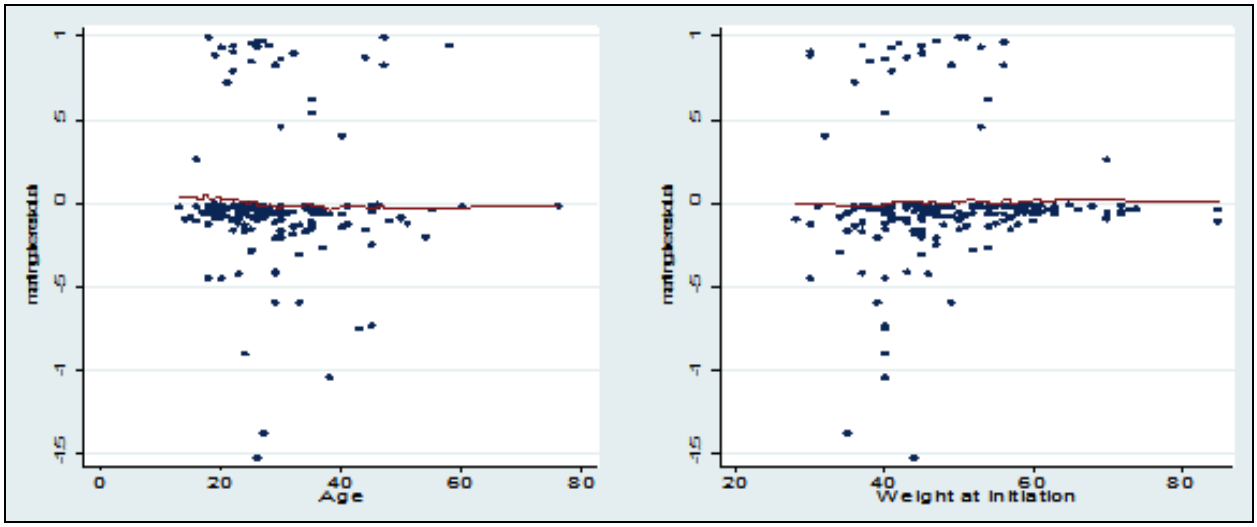

FIGURE 5: MARTINGALE RESIGROUP OF WEIGHT AND AGE GRAPH FOR PATIENTS (N=188) UNDER MDR-TB TREATMENT IN ST. PETER'S SPECIALIZED TB HOSPITAL

Checking influential cases: Influential observations were checked using the delta beta-estimated |dfbeta| change in the regressor's coefficient because of deletion of that subject indicates that there is no suspicious influential observation (|dfbeta| < 1). [**Figure 6**]. Thus, all in all we can say that our model fits the data very well.

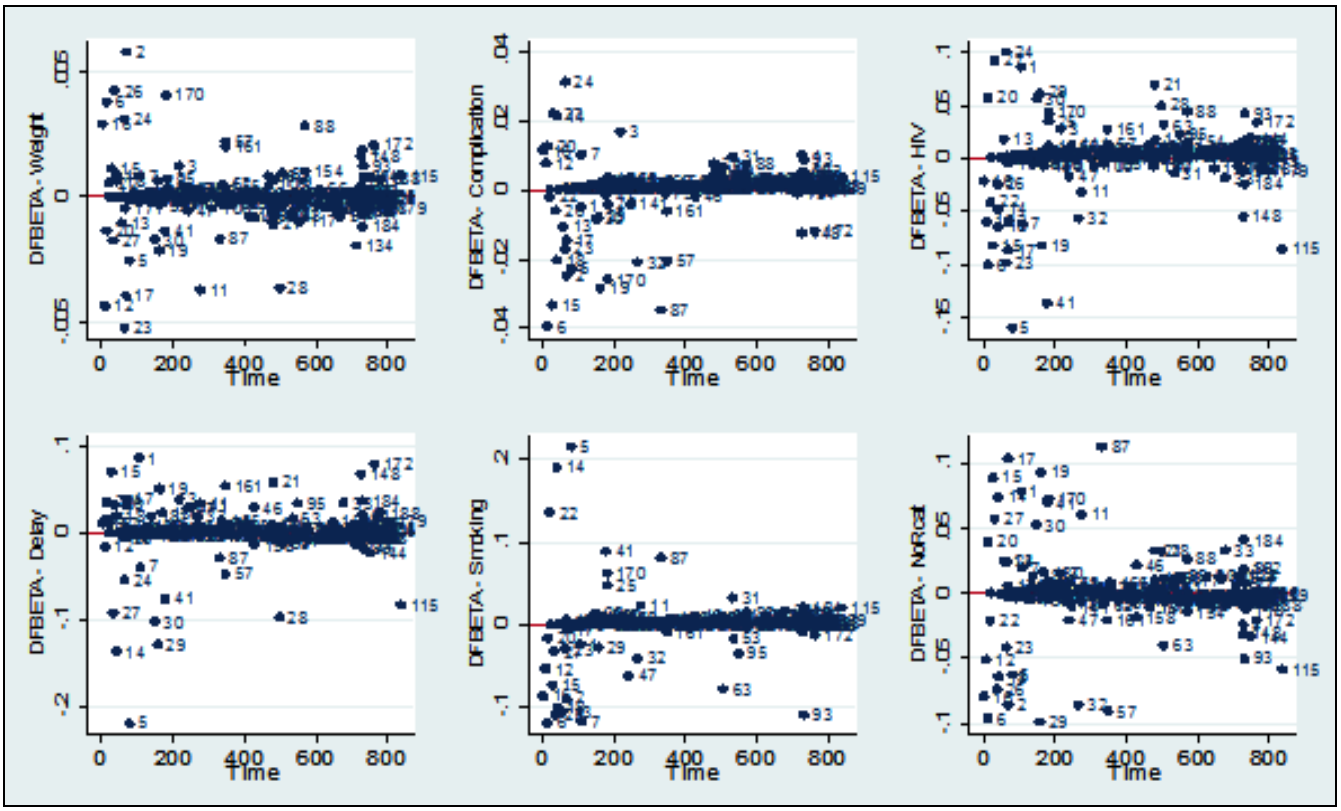

FIGURE 6: DELTA COVARIATESATE OF FITTED COVARIATES FOR PATIENTS (N=188) UNDER MDR-TB TREATMENT IN ST. PETER'S SPECIALIZED TB HOSPITAL

DISCUSSION: This study was conducted to examine survival time and predictors of mortality in a cohort of patients with MDR-TB treatment. PH assumption was not found to be violated by any covariates; therefore further stratification has not been made to estimate the hazard. We found higher hazard of death or lower survival rate in patients who started treatment after a month of period diagnosed as MDR-TB, smoker, HIV positive and patients who have clinical complications during the treatment period.

The median survival time was undetermined. Because the largest observed analysis time was censored, the survivor function does not go to zero; in this case the mean is the best estimate of survival time.

We found that Model II was an over fitted model because it has a large SE. In an over fitted model, the estimated values of some of the *β*-coefficients were highly dependent on the actual data. A very slight change to the values of one of these variables could then have a large impact on the estimate of the corresponding coefficient. This is the reason for such estimates having large standard error. An over fitted model is one that is more complicated than is justified by the data, and does not provide a useful summary of the data.

The hazard function of Cox-Snell residuals follows the 45 degree line very closely except for large values of time. It is very common for models with censored data to have some twisting at large values of time and it is not something which should cause much concern.

The probability of survival at the end of two years in this study which is 78 % were similar to a study conducted in South Africa, UK and Lithuania, where by approximately similar percentage of patients were surviving at the end of two years of MDR-TB treatment, irrespective of other categories [18, 22, 25].

The study conducted in UK and Lithuania they used the mean to describe the survival time but in our study the extended mean was used because the restricted mean underestimate the result, therefore the extended mean were used which is an ad hoc approximation that extends the survivor function from the last observed time to zero by using an exponential function and computes the area under the entire curve [26] so it is not possible to make a comparison.

In the UK and Lithuania study, the median survival time of treatment initiation to death was 3.78 (95% CI 3.66 to 6.89) years and 4.1 (95% CI 3.7 to 4.4) years respectively [22, 25].

Survival time of MDR-TB patients in this study is relatively long enough to establish a large pool of individuals potentially infectious for others and facilitate further transmission of drug-resistant strains in the community and in hospital settings where patients spend up to three months.

In our study, total death rate was 15.43% for the cohort is similar to other study like the death rate for Uzbekistan cohort which is 15% [27] but different from the death rate of 7% and 23.4% reported for the Latvian cohort [17] and South African cohort [18] respectively. This difference may be due to different follow up period in those studies.

In our study HIV seropositivity was significantly associated with death. Similar finding was observed in Lithuania and France in which HIV seropositivity was a significant risk factor of death during MDR-TB treatment period [25, 20]. On the other hand, a study in the UK reported that among persons who were immunocompromized was associated with an increased risk of death but HIV seropositivity was not a significant factor of death [22].

In our study treatment category was not associated with death particularly previously treated for TB patients. It is also similar to Latvian study the mortality amongst the patients with previously treated for TB was not statistically different [17]. This finding might not reflect the devastating effect of MDR-TB on survival and highlights the fact that almost all patients in our country started the treatment after taking repeated the first line drugs.

We do note that the majority of our cohort (96.28%) were re-treatment cases. Although we did not evaluate this, a possible cause for this high rate of MDR-TB among this group is that the DOT infrastructure requires strengthening in early identification of drug susceptibility pattern at all levels of the health facilities.

One system level issue that has a significant contribution to mortality is the delay of patients more than one month from MDR-TB diagnosis to treatment initiation. We believe there are many factors that contribute to this delay.

First, delays may have been encountered in detecting the patient and referring him/her to the MDR-TB treatment facility due to the shortage of health facilities which perform DST; second, the limited number of health facilities that render the service in Ethiopia and the availability of drugs in the MDR-TB facility may have resulted in additional delays. The high early mortality seen in this cohort argues strongly for early initiation of second-line TB drugs in MDR-TB patients.

The strength of this study was availability of relevant exposure data like HIV status and allows direct measurement of incidence of death. This study is not without limitations. The data were extracted from medical records of those already visited and registered at the hospital. In the present study, the analyses included all deaths, irrespective of the cause of death, so misclassification of the cause of death might not have a major influence on the results and as the nature of secondary data, some of the data are incomplete to gather some variables such as sputum smear result at initiation, BMI. It is possible that some patients do not remember their history of previous anti-tuberculosis treatment at the time of diagnosis and were inappropriately classified under different category.

CONCLUSION AND RECOMMENDATION:

CONCLUSION: In view of the above discussion points, the following conclusions are to be drawn and the research has shown clinical factors are critical in determining survival of patients under MDR-TB treatment than socio-demographic factors.

- The overall survival rate in this study population was high.
- Higher hazard of death or lower survival rate was noted in patients who started treatment after a month of period diagnosed as MDR-TB, smoker, HIV positive and patients who have clinical complications during the treatment period.

RECOMMENDATION:

1. The strong associations of worse survival with social factor like smoking emphasize an urgent need for non-medical interventions on cessation of smoking to improve survival of patients.
2. Although survival time is good, reinforcing the existing treatment program to include all MDR-TB patients for patients who start treatment after a month have a high rate of death.
3. Early administration of appropriate treatment to decrease clinical complications.
4. Early identification of MDR-TB is important for HIV positive individuals in particular (who will die earlier than HIV negative) and adequate infection control measures to minimize the opportunity for cross infection.
5. Expansion of culture and drug susceptibility testing are necessary to improve patients' survival of MDR-TB in Ethiopia.

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