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ORIGINAL RESEARCH ARTICLE

Modeling Time to Death using the application of Survival model among HIV/TB Co-infected Patients who are under ART Follow-up in Axsum-Hospital, Ethiopia.

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Abstract

The relationship between Human Immune Deficiency Virus (HIV) and Tuberculosis (TB) is complex, health problem resulting in the synergistic increases in patients" morbidity and mortality. The probability of being infected by both infections is attention seeking health issue worldwide. The application of combination of antiretroviral therapy (ARV) in 1996 has immense effect in extending the life span of infected patients by slowing the wasting period, and by boosting the CD4 cell count of an infected patient. This study aimed to identify factors that influence the survival status of HIV/TB co infected patients who are under ART follow-up and to assess the effectiveness of Cox PH model compared to parametric models in modelling time-to-death. The resulting data set comprises 210 cases all of them HIV-infected TB patients who are above the age of 15 years, and who have started anti-TB treatment between the years 2011 and 2015. The Cox proportional hazard model used to compare parametric models in modelling time-to-death. A total 210 participants 169 (80.5%) were died due to the disease, and 41 (19.5%) were not presented to follow-up during the time of data collection. From the total 210 ART followers, 88 (41.9%) were male while the rest were female. The study showed that the WHO clinical stage III is 1.27 ($p = 0.023$) indicating that WHO clinical stage III has the tendency to prolong the survival time of HIV/TB co-infected patient compared to stage IV. The study also revealed that the Accelerated failure time model has the best predictive power compared to the Cox model based on the AIC values. The best fitted model for survival analysis is the Generalized Gamma Accelerated failure time model. Among the several prognostic factors Age, CD4 cell count, and WHO Clinical Stages II and III were identified as significant prognostic factors.

Keywords: ART, Axum Hospital, HIV/TB co-infected, Risk factors, Survival Analysis

Introduction

The global HIV associated TB mortality was reached highest level in 2004 in which time 540,000 deaths were recorded. It declined to 360,000 in 2013, when 25% of all TB deaths and a quarter of an estimated 1.5 million of HIV-associated deaths were documented. Treatment with combination of Antiretroviral Therapy and TB/HIV collaborative works are possible reasons for this steady decline of mortality from 2004 mortalities. The risk of developing tuberculosis among people who are living with human immunodeficiency virus (PLHIV) is 30 times higher compared with HIV-uninfected (Raghavan, *et al*. 2012).

Globally, about 11% of new adult cases of tuberculosis are HIV/AIDS co-infected and in sub-Saharan Africa about 31% of new tuberculosis cases are HIV/AIDS co-infected (Rosas-Taraco *et al*., 2006). In 2007, WHO reported 9.27 million of the estimated new cases of TB infected of which 31% were in Sub-Saharan Africa, and about 1.37 million (14.8%) of these people who were living with human immunodeficiency virus (PLWHIV) (Lopez-Gatell *et al.,* 2007). In general, the majority of these cases, that is 79% HIV positive TB incident cases, were in Africa. In the same year, there were 456, 000 TB-related deaths out of which HIV-positive patients accounted 23% of the global HIV/AIDS mortality. Southeast Asia is the second most affected region with 11% of global new TB cases in 2007 (Lancioni *et. al*., 2011; Toor *et al*., 2014).

The high burden of TB in Ethiopia might in part be attributed to the rapid increase of HIV infection because available data indicated that HIV/ AIDS accounted for an estimated 32% or 141,000 total TB cases in 2005. Moreover, the WHO global report in 2008 estimates that in Ethiopia 40% of TB patients tested for HIV were HIV-positive. In Ethiopia routine data from 44 cities in the year 2005/6 showed 41% of TB patients were HIV positive. In addition another routine data collected in 2006/07 estimates that 31% of TB patients were HIV positive (WHO, 2011). According to WHO, TB was the cause of 76 thousands deaths in Ethiopia out of which 30% were HIV positive patients (WHO, 2008). Most importantly, the absence of studies by comparing Accelerated failure time with Cox PH methods of survival analysis that is on the basis of determining most significant factors affecting the length of life time of HIV/TB co-infected patients motivated the researchers to conduct this study in Axsum-Hospital, Ethiopia. Since parametric methods of statistical analysis is more powerful than non-parametric and semi-parametric method of analysis, provided that distributional assumptions are satisfied.

Materials and Methods

Study Area and Data Source

The data used in this study was taken from Aksum Sanity Mary Hospital (ASMH) in Aksum town, central zone in Tigray regional state of Ethiopia. This hospital is used as referral Centre for different health centers and general hospitals in western and other central Tigray zones. In this case data regarding TB treatment and follow-ups was recorded according to the registration standards indicated by MOH. For this study, both ART and TB register were considered in order to record all persons who have been infected with HIV and who started ART and who have been under an anti-TB treatment. The resulting data set comprises all cases of HIV-

infected TB patients who were above the age of 15 years, and who have started anti-TB treatment between the years 2011 and 2015. The total number of cases included in the study were 210, and the collected information was secondary data type.

Study Variables

The response variable was survival time of HIV/TB co-infected patients who were under ART follow-up. The survival time is defined to be the length of time measured in weeks from the date of the anti-TB treatment's start to the date of the patient's death (event). Based on whether or not the patient died or alive, we used status measurement as dependent variable.

The independent Variables included**:** age, sex, marital status, Baseline weight, education, Substance abuse, Baseline CD4 cell count, TB type, WHO Clinical Stage, functional status, and Regimen type.

Non-Parametric Procedures

An initial step in the analysis of a set of survival data is to present numerical or graphical summaries of the survival times for individuals in a particular group. Such summaries may be of interest in their own right, or as a precursor to a more detailed analysis of data. Survival data are conveniently summarized through estimates of the survivor function and hazard function.

The Cox Proportional Hazards Regression Model

The Cox Proportional Hazard (PH) Model is a multiple regression method, and is used to evaluate the effects of multiple covariates on the survival (Aregay *et al.,* 2013). In Cox PH model analysis, a coefficient associated with continuous covariate is a change in the log hazard ratio due to a unit increase in the value of the variable under consideration keeping the values of other covariates constant. The corresponding Hazard Ratio can be calculated by exponentiation of the coefficient and it is an adjusted multiplicative effect on hazards of death for a unit change in the covariate value.

Parametric model

The Weibull Accelerated failure time model (AFT) Model

The Weibull distribution which includes the exponential distribution as a special case can also be parameterized as an AFT model, and it is the only family of distributions to have both PH and AFT property. The results of fitting a Weibull model can therefore be interpreted in either framework. Then the Weibull distribution is very flexible model for time-to-event data. It has a hazard rate which is monotonically increasing or decreasing and constant when the shape parameter g.The cumulative hazard can be computed as if

$Ti = exp\ (\mu + \acute{\alpha}xi)$ has a Weibull distribution.

The Log-Logistic AFT Model

The log-logistic distribution provides the most commonly used AFT model. Unlike the Weibull distribution, it can exhibit a non-monotonic hazard function which increases at early times and decreases at later times. It is similar in shape to the log-normal distribution but its cumulative distribution function has a simple closed form which becomes important computationally when fitting data with censoring (Derek *et al.,* 2014).

The Log-Normal AFT Model

If the survival times are assumed to have a log-normal distribution, the baseline survival function is given by

$$So(t) = 1 - \emptyset\left(\frac{logt-\mu}{\sigma}\right)$$

Where μ and σ are unknown parameters. Under AFT model, the survivor function for the i^{th} individual is then $Si(t) = So\left(e^{-\eta i}t\right)$,

where ηi = a1x1i + a2x2i + ... + apxpi. is a linear combination of the values of p explanatory variables for the i^{th} individual. Therefore

$$Si(t) = 1 - \emptyset\left(\frac{logt-\eta i-\mu}{\sigma}\right)$$

which is the survivor function of an individual whose survival times have a lognormal distribution with parameters ηi + μ and σ. The lognormal distribution therefore has the AFT property.

The Generalized Gamma AFT Model

In this section we introduce a regression model that is based on the general form of the gamma distribution. Therefore, in this study whenever we speak gamma AFT model, we mean that the generalized gamma AFT model since it includes relatively a wide range of family distribution as its special case. Let's first define some functions which may be used in the rest of this section. The gamma function is a well-known function which is

$$\Gamma(\gamma) = \int_0^\infty x^{\gamma-1}e^{-x}dx = (\gamma-1)!$$

defined as follows:

where γ is a positive integer.

The hazard function of the generalized gamma distribution is extremely flexible allowing for many possible shapes including as special cases the Weibull distribution when k = 1, the exponential when k = 1 and σ = 1, and the lognormal distribution when k = 0.

RESULTS

A total of 210 participants with full record of variables were included in the study. From these patients 169 (80.48%) were died due to the disease, 19.52% (41) were not presented to follow-up during the time of data collection. Out of the total 210 ART followers, 88 (41.9%) were male, but the rest were female. Among 210 patients, 40 (30%) were at clinical stage IV, 167 (30.5%) were at clinical stage III, and 3 (23.4%) were at clinical stage II. And there were 65 (31%) patients who were able to work, 81 (38.6%) were ambulatory and 64 (30.4%) were bedridden. The average baseline weight of the patients was 40.5 kilograms (with a standard deviation of 7.1 kilograms). From the Kaplan Meier graph, there were significance differences among those who abuse drugs and those who do not abuse drugs. Those who abuse drugs died earlier than those who do not.

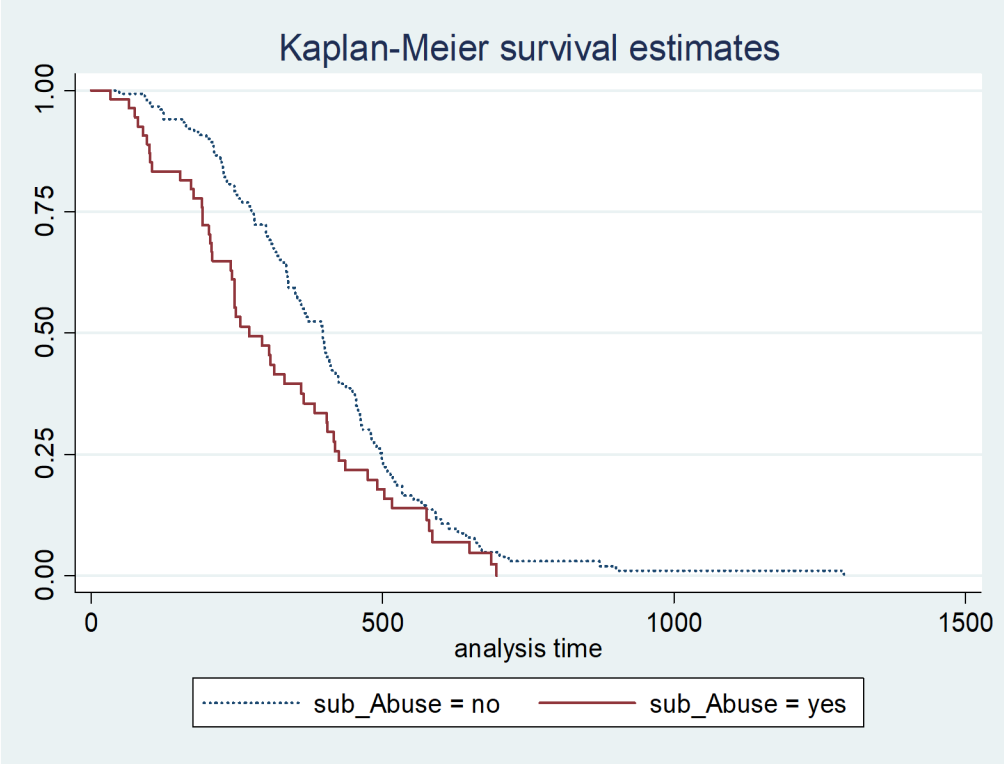

Figure 1: K-M Estimate of the Survivor Function for Categories of substance abuse (smoker, alcohol), (ASMH, 2017).

Table 1: Log rank test for equality of survival time of HIV/TB co- infected Patients among different groups of covariates, (ASMH, 2017).

Categorical Covariates	**Chi-Square**	**Df**	**P-value**
Sex	4.072	1	0.044
Marital status of patients	0.207	2	0.902
Education	0.560	3	0.905
Substance abuse(Smoking, alcohol)	5.724	1	0.017
Regime type	3.124	1	0.049
TB type	0.961	1	0.327
WHO clinical stage	18.965	2	0.000
functional status	6.258	2	0.044

According to the results in table1, to identify, the categorical levels should have an effect on the HIV/TB co-infected patients. Using log-rank test for equality of survivor function between Male and Female, the p-value was 0.044. Therefore, there is statistically significant difference in the distribution of survival time between male and female at 5% level of significance. Furthermore, substance abuse, regimen type, WHO clinical Stage, Functional Status were identified to have statistically significant effect by Non-Parametric analysis.

Cox PH Model

Using PH model, the estimated hazard ratio for clinical stage III is 0.668 with a 95% C.I. [0.452, 0.986]. Thus, a patient whose clinical stage III has approximately 0.668 times the hazard faced by patient whose clinical stage is IV. And also, the estimated hazard ratio for clinical stage II is 0.436 (with a 95% C.I. 0.568 - 0.992).

Table 2: Adjusted Semi-Parametric Analysis of Covariates Effect (Cox PH Model) Variables in the Equation (ASMH, 2017).

							95.0% CI for Exp (B)	
	B	SE	Wald	Df	Sig.	Exp (B)	Lower	Upper
Age	0.0234	0.01070	4.988	1	0.026	1.024	1.003	1.046
Stage			8.457	2	0.012			
Stage (2)	0.2347	0.48144	3.351	1	0.048	0.436	0.568	0.992
Stage (3)	-0.4037	0.19871	3.332	1	0.042	0.668	0.452	0.986
CD4	-0.0044	0.00119	14.081	1	<0.001	0.995	0.993	0.998

Furthermore, the continuous covariate's age (P-Value = 0.026) and CD4 cell count (P < 0.001) were significant covariates. The adjusted hazard of experience death for age is 1.024; 95% CI: [1.003, 1.046]. This means log hazard ratio died of HIV/TB patients increased by 2.4 for every single year in age of patients. Similarly, the other continuous covariate CD4 count (p-value < 0.001) the hazard experience death for CD4 is 0.995; 95% CI: [0.993, 0.998]. This implies that the log hazard ratio decreases by 0.005 for an increase in CD4 cell count of patients who adjust other covariates constant.

We also assess the effectiveness or fitness of the Cox-Snell residuals against the cumulative hazard of Cox-Snell residuals by a plot which is presented in Fig. 2.

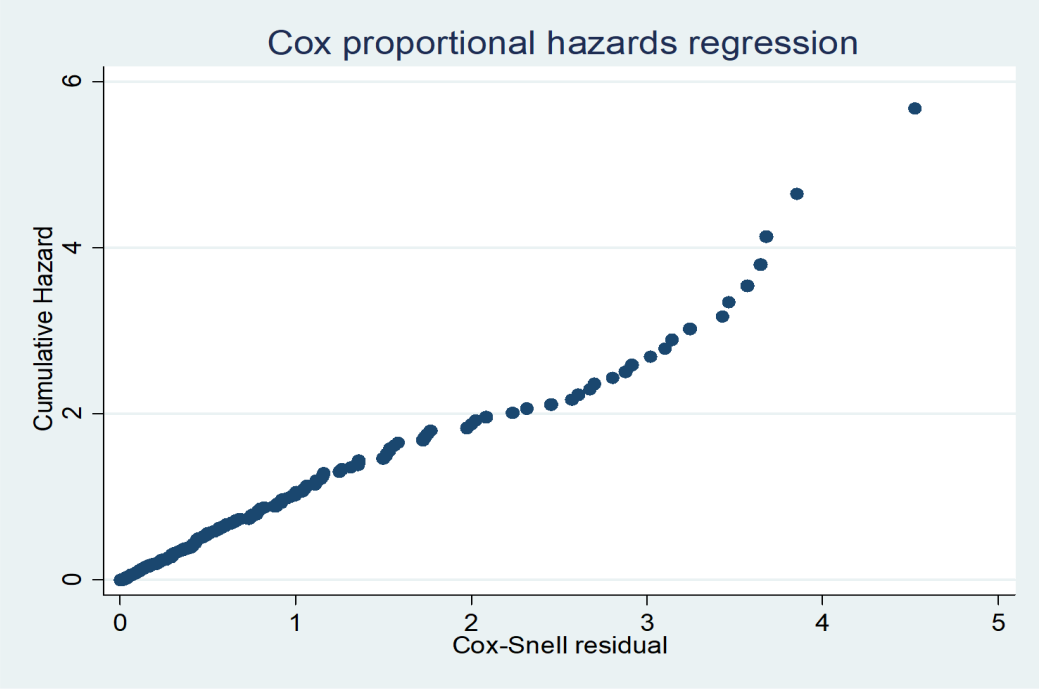

Figure 2. Cumulative hazard plot of the Cox-Snell for cox proportional hazard model, (ASMH, 2017).

This plot reveals that there is little evidence of a systematic deviation from the straight line which gives us only some concern about the adequacy of the fitted model.

AFT Model

The results from the different AFT models applied to HIV/TB co-infected data set are presented in Table 3. Accordingly, Age, CD4, Weight, Educational level, TB status and WHO Clinical Stage resulted the minimum possible loss of information for all parametric models except Exponential AFT Model (See Table 3).

Table 3. Results from AFT models for HIV/TB co-infected patient, (ASMH, 2017).

Covari-ates	Exponential			Weibull			Log -normal			Log-logistic			Generalized Gamma		
	Coef.	TR	P	Coef.	TR	P	Coef.	TR	P	Coef.	TR	P	Coef.	TR	P
Age	-0.02	0.981	0.19	-0.01	0.986	0.013	-0.015	0.9848	0.027	-0.016	0.983	0.011	-0.014	0.98	0.014
CD4	0.002	1.00	0.04	0.002	1.00	< .001	0.002	1.001	<0.00 1	.0015	1.01	<0.001	0.0019	1.002	<0.001
Weight	0.006	1.00	0.59	0.009	1.01	0.078	0.008	1.008	0.175	0.0104	1.01	0.080	0.009	1.009	0.079
Sex	-0.04	0.956	0.83	-0.03	0.963	0.683	-0.029	0.9712	0.775	-0.038	0.96	0.692	-0.036	0.963	0.684
Marital status (reference: others)															
0	-0.22	0.799	0.69	-0.28	0.752	0.227	-0.057	0.9444	0.837	-0.342	0.71	0.256	-0.290	0.748	0.225
1	-0.04	9514	0.92	-0.24	0.786	0.297	0.091	1.095	0.736	-0.188	0.83	0.517	-0.241	0.785	0.299
Educational status (reference : college)															
0	0.3	1.35	0.44	0.13	1.14	0.402	0.241	1.272	0.201	0.2197	1.25	0.254	0.142	1.15	0.396
1	0.35	1.42	0.26	0.15	1.16	0.241	0.298	1.347	0.058	0.319	1.38	0.049	0.161	1.17	0.249
2	0.33	1.4	0.31	0.12	1.12	0.397	0.206	1.229	0.207	0.2459	1.28	0.135	0.126	1.13	0.391
Substance Abuse (Alcohol, Smoking) (reference: yes)															
0	.13	1.13	0.56	0.11	1.12	0.195	0.116	1.123	.228	.0778	1.08	0.460	.117	1.24	0.200
TB types (reference: pulmonary)															
0	0.15	1.16	0.5	0.18	1.2	0.05	0.174	1.19	0.129	0.1786	1.2	0.118	0.19	1.21	0.051
WHO Clinical Stage (reference: stage IV)															
2	-0.52	0.594	0.5	-0.61	0.542	0.053	-0.639	0.5277	0.07	-0.582	0.56	0.118	-0.61	0.543	0.054
3	0.19	1.21	0.47	0.243	1.27	0.022	0.278	1.321	0.037	0.2555	1.29	0.057	0.243	1.27	0.023

Table 3. Continued ....

Covariates		Exponential			Weibull			Log -normal			Log-logistic			Generalized Gamma		
		Coef.	TR	P	Coef.	TR	P	Coef.	TR	P	Coef.	TR	P	Coef.	TR	P
Functional status(reference: bedridden)																
0		0.06	1.07	0.78	-0.02	0.983	0.873	0.003	1.003	0.976	-0.008	0.99	0.946	-0.02	0.983	0.879
1		0.07	1.07	0.75	0.022	1.02	0.819	0.035	1.036	0.744	0.056	1.06	0.599	0.023	1.02	0.806
Regimen(reference: AZT)																
0	-0.05		0.947	0.8	0.072	1.07	0.408	-0.056	0.9451	0.586	-0.074	0.93	0.491	0.065	1.06	0.496
_cons	5.55	256. 7		<0.01	5.64	283.1	<0.001	5.12	167.8	<0.001	5.421	226.2	<0.001	5.639	281.3	<0.001
/ln_sig								-0.677		0				-0.904		
Sigma								0.508						0.404		
Kappa														0.955		
ln_p					0.917											
p					2.5											
1/p					0.399											
ln_gam											-1.27		<0.001			
Gamma											0.2807					

The log likelihood and the Akaike's Information Criteria (AIC) values are presented in Table 4. In addition to finding significant covariates, we make model comparison to identify which model can express the relationship between dependent and independent variables.

Table 4: Statistical Information Criteria for Comparison of Models by Stepwise Selected Covariates for Possible Reduction of Loss of Information, ASMH, 2017.

Stepwise Covariates selection	PH Models Only		Both PH and AFT Models				AFT Models Only					
	COX		Exponential		Weibull		Log-logistic		Log-normal		Generalized gamma	
	-2l	AIC	-2l	AIC	-2l	AIC	-2l	AIC	-2l	AIC	-2l	AIC
Null	1438.3	1442.3	443.2	445.3	320.2	324.2	332.6	336.6	342.6	346.6	318.6	322.6
Age	1429.3	1435.3	440.2	440.2	312.2	318.2	323.4	329.4	333.6	339.6	310.4	316.4
CD4	1404.3	1412.3	432.6	438.6	282.6	290.6	303.1	311.1	311.9	319.9	282.6	290.6
WHO Stage	1397.8	1407.8	430.2	438.2	276.2	286.2	291.8	301.8	295.4	305.4	275.9	285.9

Therefore, based on the results in Table 4, all parametric models appeared to fit better than Cox PH. The Generalized Gamma model appeared with the minimum statistic and seemed to fit better. After identifying the best model to identify factors affecting the survival of HIV/TB co- infected patients under ART follow-up, the suitability of the model to be fitted was checked using residual plots. The cumulative hazard plot of the Cox-Snell residuals in Generalized Gamma model is presented in Fig. 3.

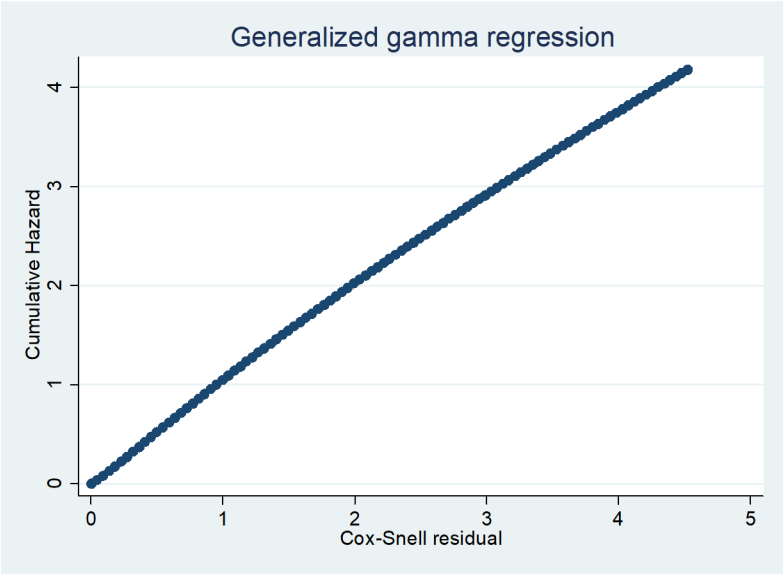

Figure 3: cumulative hazard plot of the Cox-Snell for generalized gamma AFT model, (ASMH, 2017)

The plotted points lie on a line that has a unit slope and zero intercept. So there was no reason to doubt the suitability of this fitted Generalized Gamma model. Generally, for every combination of the covariates we fit, the Generalized Gamma model resulted a minimum value of AIC suggesting that the Generalized gamma AFT model may provide a better description of the data set for any combination of variable in the dataset. Hence, we use the Generalized gamma parametric model with a combination of covariates with the smallest AIC to discuss the effect of covariates on the survival time of HIV/TB co-infected patients.

Table-5: Generalized gamma model with combination of variables yielding smallest AIC value variables, ASMH, 2017.

Covariates	Coef.	TR	Z	P > z	[95% Conf. Interval]	
Age	-0.0089	0.99116	-1.98	0.047	-0.0177	-0.0001
CD4	0.00186	1.00186	3.97	0	0.00094	0.00277
Stage						
Stage II	-0.0937	0.91059	-0.47	0.642	-0.4883	0.30103
Stage III	0.18072	1.27	2.05	0.023	0.00801	0.35342
_cons	5.92048		32.02	0	5.55808	6.28289
/ln_sig	-0.8637		-11.26	0	-1.0141	-0.7133
/kappa	0.92394		4.43	0	0.51515	1.33274
Sigma	0.42161				0.36274	0.49003

Based on the generalized gamma AFT model, the acceleration factor for WHO clinical stage III is 1.27 (p = 0.023) indicating that WHO clinical stage III has the tendency to prolong the survival time of HIV/TB co-infected patient as compared to stage IV. Similarly, the estimated acceleration factor for a year increase in age considering the effect of other covariates in the model constant was 0.991 which indicates that older patients were more likely to die earlier than patients who were relatively younger. In a similar way, it was 1.0018 for an increase in CD4 count providing evidence that patients with relatively larger CD4 count were more likely to survive as compared to patients with relatively smaller CD4 counts.

Discussion

Survival model shows that parametric AFT model was better than Cox Ph model. So, we analyzed these covariates that are significant for HIV/TB co-infected patients using Parametric AFT model. From these covariates CD4 cell count is the most important marker of HIV/TB co-infection disease progression, and it is a strong predictor of survival HIV/TB co-infected patients. When the CD4 count of the patient become very low, and the survival time of the patient will be short. A study by Fauci *et al*. (2005) and Mashimbye (2010) reported that patients with low baseline CD4 cell count were at a high risk factor for early mortality of HIV/ TB co-infected patients. Similarly, a

previous study which is done in Barcelona between the years 1996 and 2006 showed that survival was at improbable situation among patients that have low baseline CD4 count (Catala *et al*., 2011). WHO clinical stage was one of the risk factor of HIV/TB co-infected patients. When the patients' clinical stage move from lower stage to the next higher stage, their probability of die increased. Similarly, a retrospective study that was conducted in Ethiopia, Hawassa referral hospital (Tarekegn, 2011), supported that the low risk of mortality was happened among patients that have WHO stages II and III compared to those patients who have WHO clinical stage IV. The study also revealed that age of patients was one of the covariates that influence the survival time of HIV/TB co-infected patients. When the age of the patients' increased, their probability to die also increased. Other studies also show consistency with previous studies. For example, a study which was conducted in South Africa and dealt with TB treatment outcomes in adult TB patients who were attending the Rixile HIV clinic in Tintswalo hospital, in Bushbuckridge, showed similar result. In this study, age, sex, and ARV treatment were found to predict mortality related to TB in multiple logistic analysis (Mashimbye, 2010). Another retrospective cohort study that was conducted between June 2007 and December 2009 on HIV-infected patients who had started anti-tuberculosis treatment in the state of Pernambuco, Brazil, showed consistency with the above studies. Survival data were analyzed using the Kaplan-Meier estimator, the log-rank test and Cox model. The study indicated that the risk factors for death in the study population were females who were above the age of 30 years, and who have anemia, and also who were not using Highly Active Antiretroviral Therapy (HAART) during treatment for TB. Not only this, but also females whose CD4+ lymphocyte count below200 cells/mm3 (Mazura *et al., 2012*). Previous studies shows that Cox regression and parametric models based on AIC and standardize of Parameter estimates reveled similar studies (Pourhoseingholi *et al*., 200). It is a fragment sentence. Please reconsider it again. In our case, the generalized gamma AFT model produced a value which is far from zero parameter as compared to the other parametric model as well as Cox PH suggesting that the generalized gamma AFT model was better than the rest parametric as well as semi parametric models.

Conclusion

Comparing the Cox model with the AFT model based on the AIC showed that the Generalized Gamma model has the lowest value. The Cox-Snell residual plot further confirmed that the Generalized Gamma model was well fitted for evaluating the survival of HIV/TB co-infected patients. The average survival time of the patients was 338.37weeks. It was also observed that age, CD4 cell count and WHO clinical stage were significant determinants of the patients' survival at 5% significance level. The result revealed that the generalized gamma model provided was a better fit to the studied data than the Cox proportional hazards model. Health authorities should be very cautious, and they should give extra attention to patients who have higher WHO stage (III and IV) and who have lower CD4 cell counts because it is observed from the above studies that these factors significantly affect the survival of the patients while closely monitoring the WHO clinical stages and the age as well. Hence, it is better for researchers

who study on HIV/TB Co-infection to consider AFT model even if the proportionality assumption of the Cox model is satisfied.

Declarations

Ethics approval and consent to participate

The ethical approval and permission for the study was obtained from Ethical Review Board of University of Gondar, Gondar, Ethiopia.

Consent for publication

Not applicable

Availability of data and materials

Data can be found from the corresponding author based on request.

Competing Interests

Authors declare that there is no conflict of interest.

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No fund was obtained from any source to conduct the study as well as in processing of the manuscript for publication.

Authors' Contribution

HA: Developed the idea of the study, collected the data and analyze results. KMY: Involved in designing the methods, supervising data collection, write up the study and manuscript. TJL: involved in the analysis and interpretation of the result. KMY: involved in the design of methods and interpretation of the result. All authors read and approved the final manuscript.

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References

Aregay G, Solomon G, Fisaha H, Berhe W and Carla D.(year?) Predictors of mortality among HIV infected children on anti-retroviral therapy in Mekelle Hospital, Northern Ethiopia. BMC Public Health. 2013;13: 1047.

Catala L, Orcau A, Garcia de Olalla P, Millet J-P, Rodriguez-Mondragon A and Cayla J.A. Survival of a large cohort of HIV-infected tuberculosis patients in the era of highly active antiretroviral treatment. The International Journal of Tuberculosis and Lung Disease. 2011;5(2):263-269.

Derek NN, Albert L, Timothy A. Performance of Cox Proportional Hazard and Accelerated Failure Time Models in the Analysis of HIV/TB Co -infection Survival Data ,Department of Statistics University for Development Studies.2014. Navrongo, Ghana.

Fauci AS, Lane HC, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL. Harrison's Principles of Internal Medicine (16th Edition) McGraw-Hill. New York. 2005; 1076-139.

Lancioni CL, Mahan CS, Johnson DF, Walusimbi M, Chervenak KA, et al. Effects of antiretroviral therapy on immune function of HIV-infected adults with pulmonary tuberculosis and CD4+ >350 cells/ mm3. J Infect Dis. 2011; 203: 992-1001.

Lopez-Gatell H, Cole SR, Hessol NA, French AL, Greenblatt RM, et al. Effect of tuberculosis on the survival of women infected with human immunodeficiency virus. Am J Epidemiol. 2007; 165: 1134 -1142.

Mashimbye L. Tuberculosis (TB) treatment outcomes in adult TB patients attending arural HIV clinic in South Africa (Bushbuckridge). 2010. Website:http:// hdl.handle.net/10539/7982.

Mazura, M; Albuquerque, M. F. P. M; Braga, M. C; Barbosa, M. T. S; Byington, R;Coimbra, I; Moura, L. V; Batista, J. D. L; Diniz, G. T. N; Miranda-Filho, D. B;Lacerda, H. R; Rodrigues, L. C; Ximenes, R. A. A. Survival of HIV-infected patientsafter starting tuberculosis treatment: a prospective cohort study. International Journal of Tuberculosis and Lung Diseases. 2012; 16 (5): 618-624.

Pourhoseingholi M A, Hajizadeh E, Moghimi B et al. Comparing Cox Regression And Parametric Models For Survival Of patients With Gastric Carcinoma.Asian Pacific J Cancer Prev. 2007; 8: 412-416.

Raghavan S, Alagarasu K, Selvaraj P. Immune genetics of HIV and HIV associated tuberculosis. Tuberculosis Edinb. 2012; 92 (1):18-30.

Rosas-Taraco AG, Arce-Mendoza AY, Caballero-Olin G, and Salinas-Carmona MC. Mycobacterium tuberculosis upregulates coreceptors CCR5 and CXCR4 while HIV modulates CD14 favoring concurrent infection. AIDS Res Hum Retroviruses. 2006; 22:45-51.

Tarekegn S. The effect of HAART on incidence of tuberculosis among HIV infected patients in Hawassa university referral hospital, South Ethiopia. Addis Ababa University unpublished MPH thesis. 2011.

Toor JS, Singh S, Sharma A, Arora SK. Mycobacterium tuberculosis modulates the gene interactions to activate the HIV replication and faster disease progression in a co-infected host. PLoS One. 2014; 9: e106815.

WHO/HTM/TB/2009.420. World Health Organization. Global Tuberculosis Control. 2011.

World Health Organization, Global Tuberculosis Control: surveillance, planning, financing. Geneva, Switzerland. WHO/HTM/ TB/2008.393.