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# SURVIVAL TIMES OF TUBERCULOSIS PATIENTS USING COX PROPORTIONAL HAZARDS

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***ABSTRACT***

***Tuberculosis (TB) is an infectious bacterial disease caused by Mycobacterium Tuberculosis (MTB), persistently to be an important global public health problem and one of the major causes of mortality in Africa. This study is aimed at applying cox proportional hazards model for multivariable analysis with a view to identifying the factors that affect the survival and influence death status of patients with tuberculosis. The result of the analysis showed that 36 (22.4%) patients died during the study period and 123 (77.4%) were censored out of the total 159 registered TB patients. Multivariable cox hazard regression analysis revealed that the covariate HIV was significant risk factors associated with death status in TB patient. Death of individuals with disease especially HIV co-infected cases was high. Therefore, there is need to strengthen the follow up patients with TB treatment from the day of ante-TB treatment initiation to completion days.***

***Key word:*** *Cox Model, HIV-Infected, Maiduguri, Tuberculosis*

## INTRODUCTION

Tuberculosis is one of the important major causes of deaths worldwide. The World Health Organization (WHO) estimate indicate that 8.8 million new cases of the disease and 1.6 million deaths per year (WHO, 2006) with 50% of reported cases in 2012, occurred in just 22 countries. TB affects all age groups and all parts of the world, however, the disease mostly affects young adults and people living in developing countries. In 2012, 1.3 million people died from the disease with 8.6 million falling ill (WHO, 2014).

Tuberculosis continues to be public health problem, intensified by the human immunodeficiency virus (HIV) epidemic, the HIV/TB have a synergistic interactions each propagates progression of the other (Elenga et al., 2013). It was estimated that one third of HIV-infected people are estimated to be co-infected with Mycobacterium tuberculosis (TB) which can activate or reactivate during the citation of antiretroviral therapy (ART) due to immune reconstitution inflammatory syndrome (IRIS) (WHO, 2012).

The proportion of active TB in HIV-infected patients with latent TB infection incidence is about 10% per year compare to 10% per infective for an HIV uninfected individual. It was estimated that about 1.1 million (range 0.9-1.2m) deaths from TB among HIV-negative people and additional 0.35 million (range 0.32-0.39) deaths from HIV associated TB (WHO, 2012).

Tuberculosis (TB) in human immunodeficiency virus (HIV) positive persons remain a great challenge for physician globally. Survival rates of HIV-positive persons with active TB (TB-HIV Patients) very substantially around the global and depend on several factors relating to the management of both HIV infection and TB disease (Podlekareva, 2013).

Globally sub-Saharan Africa has the largest rate of tuberculosis as well as HIV/AIDS (WHO report, 2006). Today almost 70% of those co-infected with TB/HIV live in Africa. The high rates of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) have caused a sharp rise in the prevalence of tuberculosis (UNAID 2004).

Nigeria as the most populous country in sub-Saharan African carries the highest burden of tuberculosis and has placed it among the top five of the WHO 22 high burden tuberculosis countries (WHO report, 2006). Available data reported that about 200, 000 of all types and 100,000 of new sputum positive tuberculosis is occur each year with an estimated 2% annual risk of infection in Nigeria (Daniel et al., 2006). A study in Nigeria showed a median HIV prevalence of 17.0% (range 4.2% - 35.1%) among the TB patients. The highest prevalence was recorded in the North central state of Benue and the least was at the south west state of Oyo and in that study Kano recorded 12.4% (Ekanem et al., 2004). In a study in Maiduguri, Nigeria about 69.4% Mycobacterium infection among HIV-seropositive patients was reported (Ajayi et al., 1999).

## SOURCE OF INFORMATION

The data was a retrospective cohort study based on TB/HIV patients that were registered in TB registers in the Medical Record Department of the University of Maiduguri Teaching Hospital. Maiduguri. In this research we used secondary data which was retrieved from patient follow up records. Information for this study was carefully extracted from a document of TB cases registered from the years 2011 to 2013 are treated.

## VARIABLE IN THE STUDY

The response variable: this is the waiting time until the occurrence of an event (dead: 1, censored: 0) individuals who died were considered failure and those who remained until the end of the study were considered censored; observations are censored in the sense, that for some units, the event of interest has not occurred at the time the data analyzed.

Predictor variable: predictors or independent/explanatory variables which are called covariates are those effects on the waiting time we wish to asses. The covariate variables which are assumed to influence the survival of TB patients included in the model are: (a) age (b) gender (c) TB clinical presentation, that is, Pulmonary and extra pulmonary (d) HIV status

## METHOD OF DATA ANALYSIS

The independent effects of each coverable were measured using the Cox proportional risk model (Harris EK, Albert A. 1991) and the importance of each coverable in the model was evaluated with the Wald test.

Patients were censored at the time of TB diagnosis or at the rate of death or date of last visit in cases lost to follow up. The factors associated with tuberculosis were analyzed using a cox proportional model (Elenga et al., 2013). Univariate analysis was carried out to study the covariates and their relation to response variable and also to study the significance of all the variables in the model, the omnibus test was carried out at 5% level of significance. The covariate that were associated with the outcome p ($<0.05$) were then included in the multivariate cox model yield adjusted hazard ratios.

## SURVIVAL ANALYSIS

Survival analysis techniques are employ methods to investigate the amount of study time an experiment unit contributes to a study period from the entry until event (Tyler 2000). Non parametric survival analysis techniques are often used in clinical and epidemiological research to model time at risk until event without parametric assumption. The term ‘’survival’’ analysis may be misleading because the techniques are applicable to any well-defined event although traditionally death was the event of interest and the study period consisted of the following period before death. Event in survival analysis (also referred to as endpoint or outcomes) are defined by transition from one discrete state to another at an instantaneous moment of time.

## THE SURVIVAL FUNCTION

Let $T > 0$ have a Probability Density Function (PDF) $f(t)$ and Cumulative Density Function (CDF) $F(t)$. Then the survival function takes on the following form: $S(t) = P\{T > t\} = 1 - F(t)$.

The survival function gives the probability of surviving or being event-free beyond time t. Because $S(t)$ is a probability, it is positive and range from 0 to 1. It is defined as $S(0) = 1$ and as $t$ approaches $\infty$, $S(t)$ approaches 0. Thus, $S(10)$ is the probability that an individual survives longer than 10 units of time, while $F(10)$ is the probability that an individual survives no more than 10 units of time.

## THE PROPORTIONAL HAZARDS MODEL

This is used for multivariate analysis to identify factors associated with death from tuberculosis and cox proportional hazards (PH). The model is given by

$$\mathrm{X}(t/z) = \lambda_o(t) e^{Z^T \beta}$$

Where $Z = (Z_1, ..., Z_P)^T$ and $\beta = (\beta_1, .., \beta_p)^T$, $Z$ is a $p \times 1$ vectors of covariate such as treatment indication and prognostic factors and $\beta$ is a $p \times 1$ vectors of regression coefficient which are age, TB type etc.

The parameters was estimated by using partial likelihood function, the score test, but in this study we use two different test to access the significance of the coefficient in cox proportional hazards models, the Wald test and Omnibus test.

Survival and hazard function for HIV status to access the overall patterns of Cox proportional hazards regression model by plotting the cumulative survival versus the time to death (survival) times.

## RESULTS

The statistical package SPSS Version 16.0 has been used to analyze data. The data show that out of the total 159 registered TB patients 36 (14 male and 22 female) or 22.6% died during the study period and 123 (77.4%) were censored. The age group (40 and above) showed the highest percent 14.5% with respect to death proportions among the other two age groups.

**Table 1. Case Processing Summary**

| | | N | Percent |
|---|---|---|---|
| Cases available in analysis | Event[a] | 36 | 22.6% |
| | Censored | 123 | 77.4% |
| | Total | 159 | 100.0% |
| Cases dropped | Cases with missing values | 0 | 0.0% |
| | Cases with negative time | 0 | 0.0% |
| | Censored cases before the earliest event in a stratum | 0 | 0.0% |
| | Total | 0 | 0.0% |
| Total | | 159 | 100.0% |

a. Dependent Variable: Time

**Table 2. Characteristics of tuberculosis patient data of UMTH, from 2011 to 2013**

| Summary of the number of death and censored values | | | | | |
|---|---|---|---|---|---|
| Patients characteristics | Total | Death | Percentage of Death | Censored | percent censored |
| Gender | | | | | |
| Male | 59 | 14 | 8.8 % | 45 | 28.3 % |
| Female | 100 | 22 | 13.8 % | 78 | 49.1 % |
| Age categories | | | | | |
| 0-19 | 41 | 3 | 1.9 % | 38 | 23.9 % |
| 20-39 | 60 | 10 | 6.3 % | 50 | 31.4 % |
| 40 and above | 36 | 23 | 14.5% | 35 | 22.0 % |
| Type of TB | | | | | |
| Pulmonary | 110 | 17 | 10.7 % | 93 | 58.5 % |
| Extra Pulmonary | 49 | 19 | 11.9 % | 30 | 18.9 % |
| HIV Status | | | | | |
| Negative | 133 | 16 | 10.1 % | 117 | 73.6 % |
| Positive | 26 | 20 | 12.6 % | 6 | 3.8 % |

**Table 3. Categorical Variable Codings [a,d,e,f]**

| | | Frequency | (1)[c] | (2) |
|---|---|---|---|---|
| HIV[b] | .00=Negative | 133 | 1 | |
| | 1.00=Positive | 26 | 0 | |
| TB[b] | .00=Pulmonary TB | 110 | 1 | |
| | 1.00=Extrapulmonary TB | 49 | 0 | |
| Sex[b] | .00=Female | 59 | 1 | |
| | 1.00=Male | 100 | 0 | |
| Group[b] | .00=0-19 | 41 | 1 | 0 |
| | 1.00=20-39 | 60 | 0 | 1 |
| | 2.00=40 and above | 58 | 0 | 0 |

a. Category variable: HIV (HIV Status)

b. Indicator Parameter Coding

c. The (0,1) variable has been recorded, so its coefficients will not be the same as for indicator (0,1) coding.

d. Category variable: TB (Type of TB)

e. Category variable: Sex (Gender)

f. Category variable: Group (Age)

**Table 4. Omnibus Tests of Model Coefficients[a]**

| | | |
|---|---|---|
| -2 Log Likelihood | | 283.601 |
| Overall (score) | Chi-square | 36.966 |
| | Df | 5 |
| | Sig. | .000 |
| Change From Previous Step | Chi-square | 27.825 |
| | Df | 5 |
| | Sig. | .000 |
| Change From Previous Block | Chi-square | 27.825 |
| | Df | 5 |
| | Sig. | .000 |

a. Beginning Block Number 1. Method = Enter

The percentage of death 10.7% and 11.9% occurred in patients with pulmonary and Extra-pulmonary type 2 of TB respectively. HIV positive TB patients are the highest risk group for death is 12.6%. Table 2 showed that out of 159 TB patients 123 patients were censored (77.4% and 36 patients died (22.6%). Table 6 also depicts an omnibus test of the model coefficient that contains the entire variable which was significant in the univariate cox proportional hazard model at 5% level.

**Table 5. Variables in the Equation**

| | B | SE | Wald | df | Sig. | Exp(B) |
|---|---|---|---|---|---|---|
| HIV | -1.533 | .396 | 15.019 | 1 | .000 | .216 |
| TB | -.144 | .374 | .149 | 1 | .700 | .866 |
| Sex | .203 | .352 | .332 | 1 | .564 | 1.225 |
| Group | | | 1.489 | 2 | .475 | |
| Group(1) | -.796 | .663 | 1.442 | 1 | .230 | .451 |
| Group(2) | -.218 | .407 | .289 | 1 | .591 | .804 |

Table 5 showed the summary of four covariate variables in the univariate analysis. The most appropriate subset of these predictors was selected in the multivariate model based on their contribution to the model; it was also found that the exogenous variable coefficient of HIV status was the only found to be significant at 5%. While TB, sex and age group were found not significant.

In fitting the multivariate cox proportional model, the predictor's type of TB, sex and age group become the first to be removed from the multivariate model so at this stage a model that includes HIV status only.

**Table 6. Omnibus Tests of Model Coefficients[a]**

| -2 Log Likelihood | Overall (score) | | | Change From Previous Step | | | Change From Previous Block | | |
|---|---|---|---|---|---|---|---|---|---|
| | Chi-square | df | Sig. | Chi-square | Df | Sig. | Chi-square | Df | Sig. |
| 285.778 | 35.372 | 1 | .000 | 25.648 | 1 | .000 | 25.648 | 1 | .000 |

a. Beginning Block Number 1. Method = Enter

**Table 7. Variables in the Equation**

| | B | SE | Wald | df | Sig. | Exp(B) |
|---|---|---|---|---|---|---|
| HIV | -1.798 | .342 | 27.621 | 1 | .000 | .166 |

Figure 1 exhibit that there were difference among survivor cases of HIV status for TB patients, this implies that HIV positive patients have low survival curves compare to the HIV negative patients, because they are more likely to have shorter time to death.

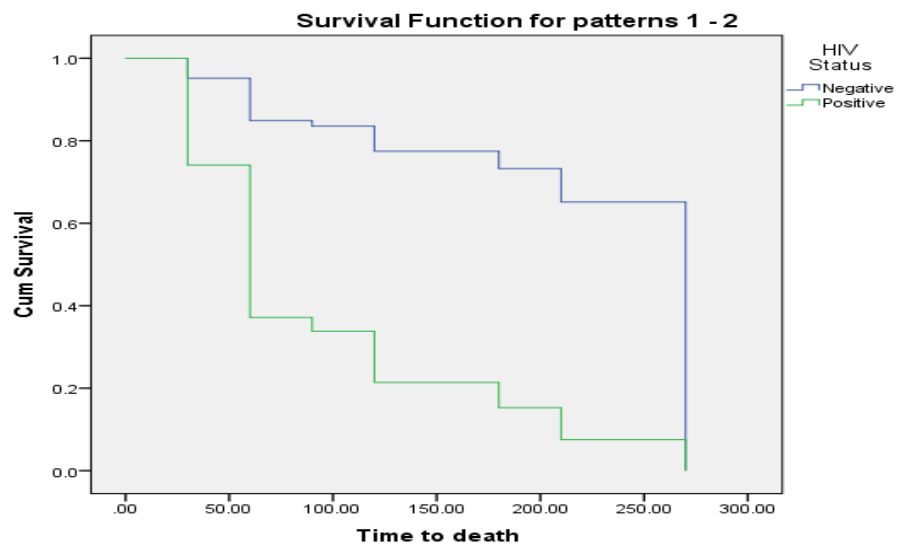


**Figure 1: survival function for HIV status**

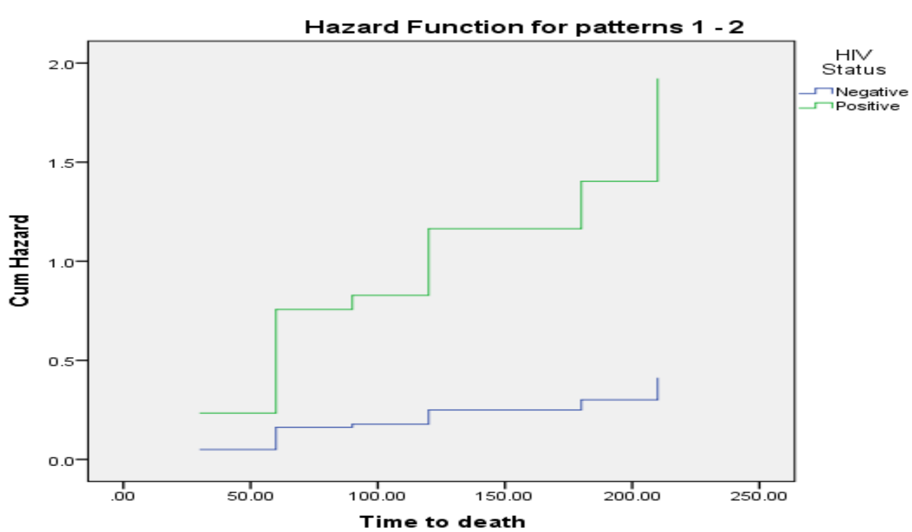


**Figure 2: Hazard function for HIV status**

Figure 2 shows the hazard function of HIV status with TB, which indicate that HIV positive patients have high probability of time to death than the patients with HIV negative as shown on the graph curves.

## SUMMARY AND CONCLUSION

This study is an attempt to identify factors that affect the survival and influence death status of the patients with tuberculosis. However there was significant difference among survival curves of HIV status. The multivariable Cox proportional hazards regression results analysis indicated that the covariates age group, gender and type of TB were not found to be factors that affect the survival of patients with TB and HIV is significantly not associated with factor that are affecting the survival of patients with tuberculosis, and the covariate HIV status was found significantly associated with death among TB patients.

It was also observed that females were at higher risk factors for death of TB patients which account for 13.8% and types of tuberculosis (extra-pulmonary tuberculosis) were identified as the significant factors for mortality of tuberculosis patients among females. The study also shows that for the past three years (2011-2015) the survival of TB patients increase especially among men with the collaboration of Government, WHO and other agencies.

A similar study by Oursler et al., (2002) showed that a total of 29 (29%) of the 139 patients died during treatment, the median time to death among these patients was 39 days and follow up for survivors was 202 days.

A similar study carried out by Mirian et al (2011) to analyze survival probability and identifying risk factors for death from tuberculosis in a cohort of patients living in Recipe who started treatment for tuberculosis during with HIV positive was statistically significant in multivariable cox regression. HIV confection was statistically significant risk factor for death in TB patients and this means the risk of death in TB patients with HIV infection was higher than in those without HIV infection in multivariate cox proportional hazard regression model.

## RECOMMENDATION

The study suggests a high increase in the hazard of death of individuals associated with HIV positive co-infected and extra pulmonary TB cases among female patient. Therefore, there is needs to strengthen the follow up of patients with treatment from the day of anti-TB treatment to completion days.

It is also recommended that the management of UMTH Maiduguri should strengthen patient follow-up, especially for females with TB, in order to improve survival rate. Since more death occurred between the age group 40 and above, efforts should be made to strengthen and orient old people in this age interval since they contribute to the death of TB patients.

It is also pertinent to the Government, WHO, NGOs and other stake holders to formulate a policy program to control and protect the disease and also to broaden their enlightens and education of TB patients especially the age group 40 and above which contribute significantly to the death of TB patients so as to eradicate the disease among TB patients.

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