COX PROPORTIONAL HAZARD MODEL TO ESTIMATE THE RISK FACTORS OF TUBERCULOSIS PATIENTS IN MAKURDI METROPOLIS

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Abstract: Tuberculosis is a chronic infectious disease that has been one of the major causes of mortality in Nigeria and Benue State in particular. The objective of this study is to identify the risk factors associated with Tuberculosis, estimate the survival time probabilities of the disease covariates, compare the survival time probabilities with respect to the risk factors and evaluate simultaneously the effect of these factors on survival using Cox Proportional Hazard model. This longitudinal epidemiological study selected two renowned Health Centers in Makurdi Metropolis. Kaplan Meier estimates and plots were used to assess the survival pattern for covariates under study. Multivariate analysis to test the association of independent variables with Tuberculosis mortality was performed using Cox Regression Analysis. Out of the registered patients, some died during the study while others were censored. The Wald, likelihood and Logrank Test were conducted to test for the significance of the model. The Schoenfeld residual and DFBeta plot were used to test the proportional hazard model assumptions and outliers respectively. Analysis of Cox regression parameters and hazard ratio show that age, HIV status, Initial weight and type of Tuberculosis diagnosed had statistically significant difference in survival experience of tuberculosis patients whereas patients' gender, Tuberculosis category and smear test result show no effect on patients' survival experience. It was recommended that special concern be given to Tuberculosis patients with HIV Positive status and middle age persons. Also, there is need to strengthen the follow up of patients with Tuberculosis treatment from the day of anti-TB treatment introduction to completion days.

Keywords: Cox Regression Analysis, dfbeta values, Kaplan Meier plots, Risk factors, Schoenfeld residuals, Survival, Tuberculosis.

Introduction

Tuberculosis popularly known as TB is the most challenging infectious disease that humankind faces. It is one of the major causes of death and the leading cause from a single infectious agent worldwide (WHO, 2020). Statistics show that more than 90% of new TB cases and deaths occur in developing countries. According to World Health Organization (2020), an estimated 10 million people fell ill with tuberculosis worldwide and about 1.4 million people died from TB in 2019 (including 208,000 people with HIV).

Nigeria is one among the eight countries that account for two thirds of the total infections worldwide (WHO, 2020).Furthermore, over 80% of TB cases in Nigeria are still undetected while the disease has been claiming millions of lives over the years in the country. Tuberculosis and Human Immunodeficiency Virus (HIV) co-infection and the emergence of drug resistant Tuberculosis are the drivers for the reemergence of Tuberculosis in Nigeria (Otu, 2013).

Benue State has the fourth highest TB prevalence rate in Nigeria behind Lagos, Kano and Oyo (WHO, 2018). The prevalence of HIV among TB patients increased from 2.2% in 1991 to 19.1% in 2001 and 25% in 2010. Benue State in Nigeria has high Tuberculosis prevalence which is worsened due to high rate of HIV/AIDS and poverty (Ejeh et al., 2013) The age groups commonly affected by TB are the most productive age groups, with the 25 – 34 age group accounting for 33.6% (15,303) of the smear positive cases registered in 2010 (Horne et al., 2010)

Tuberculosis is caused by *Mycobacterium tuberculosis* (Mtb), this bacillus is transmitted by the inhalation of infected aerosols generated by active TB patient. The inhalation of the bacilli will usually lead to the trigger of an immune response that can have one of the three different clinical outcomes: (1) Complete clearance of pathogen (2) latent TB infection (LTBI) or (3) progression to primary active disease (Oursler *et al.*, 2002). A latent infected host can be re-infected several times, thereby increasing the load of Mtb in its body and hence increasing the chance of progressing to active disease. According to the World Health Organization (2018), there was an estimated number of 2 to 3 billion people with LTBI in 2025, thus at the risk of developing an active disease. The control of the disease coordinated by the National Tuberculosis and Leprosy Control Program (NTBLCP) in-line with the End TB Partnership initiatives whose target is to eliminate TB as a public health problem by the year 2050. Despite current efforts to reduce TB, statistics of Nigeria's TB incidence is refusing to show any significant decline. Reducing death, eliminating disease and preventing the development of drug-resistant TB are the major goals of TB control (WHO, 2009), however, statistical analysis of the epidemiological relevant factors that affect the prognosis of patients with Tuberculosis is not well analyzed and packaged especially within Benue State that have varying patients' characteristics. For instance, what are the factors that mostly affect the survival pattern of TB Patients in Makurdi metropolis? Can it be Type of TB, HIV Status, Age group, gender, TB patient category, Smear Test result and body weight at initiation of patients? Therefore, to fill the gap, there is a need to study the factors that are affecting the survival of patients with Tuberculosis in Nigeria and Benue State in particular.

The main aim of the paper was to apply the Cox Proportional Hazard Model to estimate risk factors associated with tuberculosis patients in selected Health Centers in Makurdi Metropolis. The aim is better addressed using specific objectives stated as follows:

i. To identify the factors that are affecting the survival of the patients with tuberculosis
ii. To estimate survival time probabilities of the TB patients using Kaplan Meier plots
iii. To compare the survival time probabilities of the TB patients with respect to different risk factors and
iv. To identify the factors influencing death status of patient by using the Cox Proportional Hazards Model
v. To test the model assumptions and detect outliers.

In clinical investigations, there are many situations, where several known covariates potentially affect patient prognosis. Suppose two groups of patients are compared: those with and those without a HIV, Pulmonary result or Smear result. If one of the groups also contains older individuals, any difference in survival may be attributable to other variables or both. Hence, when investigating survival in relation to any one factor, it is often desirable to adjust for the impact of others. Statistical model is a frequently used tool that allows us to analyze survival with respect to several factors simultaneously.

The Cox proportional-hazards model is one of the most important methods used for modelling survival analysis data. Cox proportional-hazards model (Cox, 1972) is essentially a regression model commonly used in medical research for investigating the association between the survival time of patients and one or more predictor variables. The purpose of the model is to evaluate simultaneously the effect of several factors on survival of patients living with Tuberculosis. In other words, it allows us to examine how specified factors influence the rate of a death of tuberculosis patients at a particular point in time. This rate is commonly referred as the hazard rate. Predictor variables (or factors) are usually termed *covariates* in the survival-analysis literature.

Many studies in literature have been carried out to identify and estimate the effects of the risk factors associated with tuberculosis patients, some of the researches are summarized below;

Oursler *et al*. (2002) researched on the survival experience of patients among the three different pulmonary tuberculosis types (positive, negative and extra-pulmonary), their findings showed that patients with positive pulmonary has the lowest risk of death followed by patient with extra-pulmonary tuberculosis.

Lo *et al*. (2003) wrote on the risk factors associated with death in tuberculosis patients for a period of 12 months. Findings from this study show that about 50% of deaths occurred during the first 2 months. Their analysis show that most of the deaths occurred in the earlier months of Tuberculosis treatment initiation.

A study conducted by Pardeshi (2009) showed that the survival curves of TB patients among age group are significantly different whereas there was no significant difference in gender and type of tuberculosis.

A study by Getahun *et al.* (2011) conducted in Addis Ababa, Ethiopia showed that the survival status was significantly different between patients' age, weight in initiation of anti-TB treatment, patient category, year of enrolment and treatment center.

Age has been identified as important risk factors for death in tuberculosis patients. Different studies showed that age was a factor that is affecting the survival of tuberculosis patients. According to Horne *et al.* (2010), in Washington State, mortality was independently associated with increasing age. Also a research conducted by Oursler et al. (2002) showed that age was strongly associated with the risk to death.

Also HIV co-infection was statistically associated with increased risk of death in tuberculosis patients during treatment as discovered by the works of Horne *et al*. (2010), and Domingos *et al*. (2008)

Despite the intensive research work conducted by scholars to estimate the effects of risk factors associated with death of tuberculosis patients, there has been limited research that has captured the effects of various covariates on the survival probability of patients due to tuberculosis in Makurdi Metropolis of Benue State. Hence this work seeks to address this gap.

Materials and Methods

Data

The data used for this research is a comprehensive cohort study based on TB patients that were registered in unit tuberculosis registers in three major Health Centres providing DOTS in Makurdi Metropolis, Nigeria. These are Benue State University Teaching Hospital, Bishop Murray Hospital, High Level, Makurdi and Federal Medical Centre both from Benue State – Nigeria.

The input data for the survival-analysis features are duration records: each observation records a span of time over which the subject was observed, along with an outcome at the end of the period. A record of covariates collected over time per subject will be considered. It was extracted from patient follow up record from all registered tuberculosis cases for a period of two years (December, 2018 – December, 2020) in the selected hospitals.

Variables in the Study: The response variable is the length of time of treatment for tuberculosis patient. It is the waiting time until the occurrence of an event which in this case is dead (represented by 1) and censored (represented by 0). The independent variables of interest in this study will include the disease characteristics, demographic and medicine related factors. These are the covariates that influences or affect the survival of tuberculosis patients. The covariates that will be considered in this work are

i. HIV status (positive or negative)
ii. Age (<24 years, 24 – 44 years and >44 years)
iii. Gender (male and female)
iv. Type of Tuberculosis (pulmonary positive, pulmonary negative and extra pulmonary)
v. Smear test result (positive and negative)
vi. Initial weight of patient (<35 kg and ≥ 35 kg)

Method of Data Analysis

The study will focus on time to event (time to death of patient due to tuberculosis complications). The appropriate method of analysis that will be considered for this research is survival analysis using proportional hazard to develop a model that will estimate the effect of the risk factors associated with death in patients with Tuberculosis.

The Kaplan Meier plot was used to study the survival pattern and estimate the survival probability and statistical significance of categorical covariates. The Kaplan Meier plot will show the shape of the survival distribution. This figure shows if the pattern of survivorship function lies above or below another. If it lies above, it means the group defined by the upper curve lived longer or had a favorable survival experience than the group defined by the lower curve.

Cox proportional hazards model*:* A Cox proportional hazards model assumes that the underlying hazard *rate* (rather than survival time) is a function of the independent variables (and covariates). The model is expressed as follows:

$$log\left[\frac{h(t_i)}{h_0(t_i)}\right] = \beta_0 X_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots + \beta_k X_k$$

Where $h(t_i)$ is called the hazard function, i.e., the probability of having the event of interest at time t_i given the subject survived at and beyond the time t_i. The term $h_0(t_i)$ is called the *baseline hazard*; it is the hazard for the respective individual when all independent variable values are equal to zero. X_1 X_2, X_3, … ,X_k are covariates and β_1, β_2, … β_k are the corresponding regression coefficients.

Assumptions of Cox proportional hazards model

In Cox proportional hazards model, one key assumption is that the survival curves for two or more strata (determined by the particular choices of values for the study of interest) must have hazard functions that are proportional over time (i.e., constant relative hazard).

Also, the proportional hazard is supported by a non-significant relationship between residuals and time and refuted by a significant relationship.

Statistical Model Significance Test*:* We used three tests to assess the significance of the coefficients in Cox Proportional Hazard. They are the partial likelihood ratio test, the Wald test and the Score test. We used (Hosmer&Lemeshow, 1999) and

Collett (2003) that recommended the procedure in variable selection that includes variables that are significant in the univariate analysis ($p<0.05$) and those considered clinically relevant to fit in the multivariate model.

Goodness of Fit Test: To assess the overall goodness of fit and assumptions of the Cox Proportional Hazard regression model, we used the Shoenfeld residuals. The Schoenfeld residual is defined as the covariate value for the individual that failed minus its expected value. (Yields residuals for each individual who died, for each covariate). Expected value of the covariate at time t_i= a weighted-average of the covariate, weighted by the likelihood of death for each individual in the risk set at t_i.

Residual = $x_{ik} - \sum_{i=1}^{j\in R(t_i)} x_{jk} P_j$

Schoenfeld (1982) proposed the first set of residuals for use with Cox regression. Instead of a single residual for each individual, there is a separate residual for each individual *for each covariate.*

Test for outliers: A regression outlier is an observation that has an unusual value of the dependent variable **Y,** conditional on its value of the independent variable**X.** DFBeta are a direct measure of the influence of an observation on regression parameter estimates. They examine how regression coefficients change if outliers are omitted from the model. DFBeta was used to detect outliers for this model.

Results and Discussions

Descriptive Survival Analysis: Table 1 exhibits that out of 413 TB patients, 361 patients were censored (87.41%) and 52 patients died (12.59%). The respective censored and deaths recorded for the covariates under study are shown below

Table 1: Characteristics of tuberculosis patient data under DOTS (Directly Observed Treatment Short-course) from three health centres in Makurdi Metropolis from December, 2018 to August, 2020

Patient characteristics		Total	Death	Percent death	Censored	Percent censored
Gender	Male	207	26	12.56%	181	87.44%
	Female	206	26	12.62%	180	87.38%
Age Category	0 – 24	142	11	7.75%	131	92.25%
	25 – 44	194	27	13.92%	167	86.08%
	≥45	77	14	18.18%	63	81.82%
TB Category	New	356	40	11.24%	316	88.76%
	Non New	57	12	21.05%	45	78.95%
Type of Tuberculosis	Pul. Positive	101	10	9.90%	91	90.10%
	Pul. Negative	146	20	13.70%	126	86.30%
	Extra Pulmonary	166	22	13.25%	144	86.75%
Smear result	Positive	101	10	9.90%	91	90.10%
	Negative	312	42	13.46%	270	86.54%
HIV Status	Positive	119	27	22.69%	92	77.31%
	Negative	294	25	8.84%	269	91.16%
Initial weight	< 35kg	31	6	19.35%	25	80.65%
	≥35kg	382	46	12.04%	336	87.96%

The table above presents the Tuberculosis patient's characteristics. From the results above, we can see that there is a similar infection rate of the disease among male and female. On age group mostly affected, the working class age is the mostly affected. It can also be seen from that new cases were more dominant than reoccurring cases of infections but the mortality rate is higher as long as an infected person still test positive to tuberculosis. Furthermore, extra pulmonary type of tuberculosis was found to be the most common among the study population followed by negative pulmonary type but having a higher mortality rate compared to others. The positive pulmonary tuberculosis type was the lowest among the three types of tuberculosis. The smear test result shows that patients with negative smear test result were more dominant than patients with positive smear test result. Patients with weight above 35kg before being infected with tuberculosis were far greater in number than patients below 35kg weight. Finally, from the survey, the number of tuberculosis patients who tested negative to HIV was more than the patients that tested positive to HIV. However, the mortality rate of HIV positive patient (22.69%) is higher than HIV negative tuberculosis patients (8.84%)

Survival Analysis for Tuberculosis Patients: The table below shows the estimates of the survival time probability and the number at risk of death due to tuberculosis within a successive time range of 30 days. The 95% shows the lower and upper confidence interval of probability of patients at risk of death within the period of interval (30 days)

Table 2: Survival Probability of Tuberculosis Patients

Time	n.risk	n.event	Survival	std.err	lower 95% CI	upper 95% CI
1	413	0	1.0000	0.00000	1.0000	1.0000
30	405	8	0.9806	0.00678	0.9674	0.9940
60	338	58	0.8370	0.01836	0.8018	0.8738
90	330	8	0.8172	0.01921	0.7804	0.8557
180	296	27	0.7503	0.02153	0.7092	0.7937
270	199	81	0.5337	0.02543	0.4861	0.5860
360	99	91	0.2836	0.02350	0.2411	0.3336
450	25	83	0.0251	0.00873	0.0127	0.0496

From the table above, it can be deduced there is a higher risk to death as a patient continue to suffer from the disease. That is, the risk of death is very low during infection at the earlier time, but as the disease is prolonged in patients 'body immune system, the probability or chances of survival depreciates.

Kaplan Meier estimates and plots for covariates

For individual covariates, the Kaplan Meier analysis is done to plot the estimates of the survival probabilities for patients using the covariates under study

Sex: The figure below shows the Kaplan Meier curve for sex of Tuberculosis patient

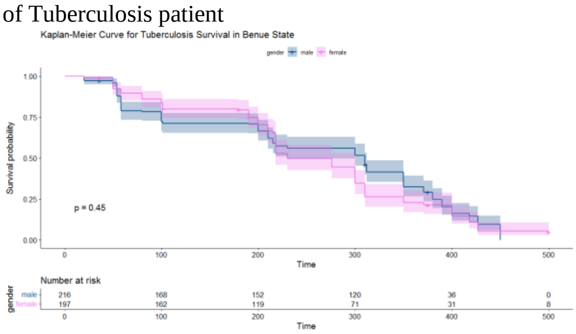

Figure 1: The Kaplan Meier curve for sex of Tuberculosis Patients

From the figure above, it can be deduced that on a short run bases (first day to 200 days) after testing positive to tuberculosis, the female have more chances of survival than her male counterpart. However, after about 200 days from being infected with the disease, the male have a relatively higher survival experience than the female patients. The p-value which is 0.45 shows that it is significant.

Smear Test: The figure below shows the estimate of the number of survivals for tuberculosis patients associated with positive or negative smear test

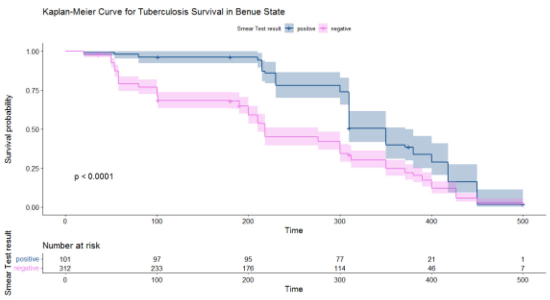

Figure 2: Kaplan Meier Curve on Smear Test Result of Tuberculosis Patients

The figure above shows that the positive smear test patients risk to death is smaller than the Tuberculosis patients that have tested negative to smear test result.

Type of Tuberculosis: The figure below shows the risk of survival of patients from the three types of tuberculosis

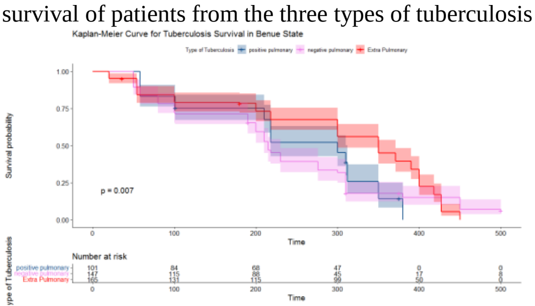

Figure 3: Kaplan Meier Curve on type of Tuberculosis

From the Kaplan Meier plot above, it shows that Tuberculosis patients with Extra pulmonary have a better survival probability followed by Tuberculosis patients with positive pulmonary. The patients with negative pulmonary tuberculosis type are more at risk of death among the three tuberculosis types.

Tuberculosis Category: The tuberculosis is categorized as new and non-new or follow up cases. The figure below shows the survival experience of new registered cases of tuberculosis patients and follow up cases of Tuberculosis

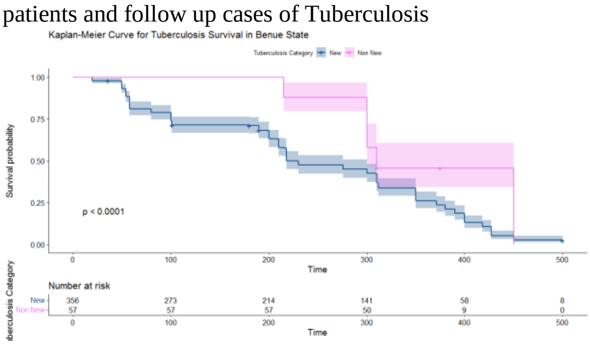

Figure 4: Kaplan Meier Curve on Tuberculosis Category

From the figure displayed, we see that non – new cases have a higher probability of survival than newly discovered tuberculosis cases.

Initial Weight: This shows the weight of a patient tested positive to Tuberculosis. The figure below shows the initial weight of patients categorized into two; patients greater than 35 kg and patients less than 35 kg.

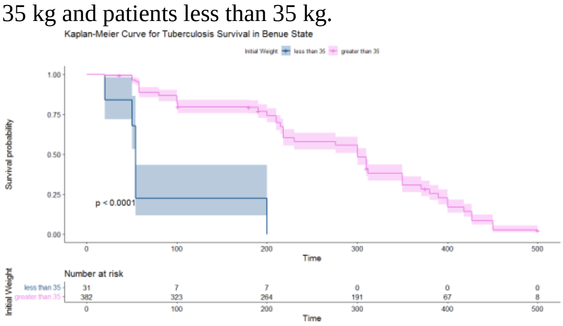

Figure 5: Kaplan Meier Curve showing the survival probability and number at risk

From the figure above, it can be clearly seen that patients with weight greater than 35kg has a greater survival probability than patients with weight below 35kg

HIV Status: This variable shows the HIV status of Tuberculosis patients

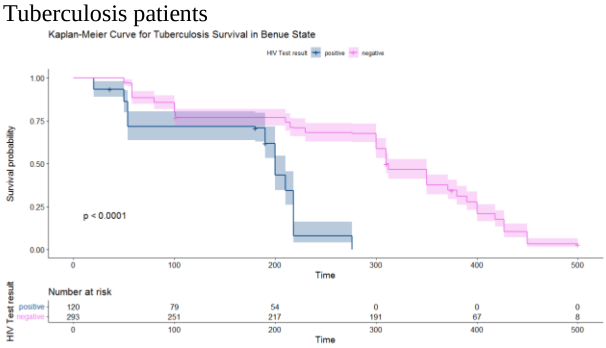

Figure 6: Kaplan Meier Curve showing the survival probability and number at risk for HIV Status Covariate

From the figure above, it can be deduced that Tuberculosis patients who are positive to HIV test result have a lower chances of survival than their HIV negative counterparts.

Cox Proportional Hazard Model Parameter Estimates: We consider a multivariable model that contains all variables which were included in the study. That is age, gender, TB category, type of TB, Smear test, HIV test and initial weight. The table below show the output of the results obtained from the estimate of the model parameters in R

Table 3: Estimates of Model Parameters
The table below shows the estimates of the Cox Proportional Regression Analysis

	Coef	exp(coef)	se(coef)	Z	Pr(>|z|)	exp(coef)	exp(-coef)	Lower .95	Upper .95
Age	-0.009	0.9904	0.004956	-1.927	0.0439	0.9905	1.0096	0.9809	1.0002
Gender	-0.039	0.9619	0.121923	-0.318	0.7503	0.9619	1.0396	0.7575	1.2216
TB Category	-0.341	0.7112	0.216459	-1.574	0.1155	0.7113	1.4059	0.4654	1.0871
Type of TB	-0.384	0.6810	0.076249	-5.039	4.69e-07	0.6810	1.4684	0.5865	0.7908
Smear Test	0.162	1.1763	0.153516	1.058	0.2901	1.1763	0.8501	0.8707	1.5893
HIV Status	-1.336	0.2629	0.202158	-6.608	3.89e-11	0.2629	3.8033	0.1769	0.3908
Initial Weight	-1.545	0.2132	0.319499	-4.838	1.31e-06	0.2132	4.6915	0.1140	0.3987

Signif.codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
Concordance = 0.701 (se = 0.013)
Likelihood ratio test = 176.9 on 7 df, p=<2e-16
Wald test = 201.8 on 7 df, p=<2e-16
Score (logrank) test = 293.8 on 7 df, p=<2e-16

Statistical Significance
The Wald test values (marked Z) corresponds to the ratio of each regression coefficient to its standard error. The Wald statistic evaluates whether the beta coefficient is statistically significant. From the output, we can conclude that the variable Smear Test has a higher statistical significant coefficient than other covariates.
The Regression Coefficient: the regression coefficient from the result (marked “coef”) shows that Tuberculosis patients with positive smear test has the highest risk of death while Initial weight of Tuberculosis patients has the lowest risk of death.
Hazard Ratio: the exponential coefficients (marked as “exp(coef)”) gives the effects size of covariates (hazard ratio). This result shows an insignificant effect of other covariates to affect the risk of death of a particular variable. For the case of Smear test which has the highest hazard ratio (HR = 1.17) with a confidence interval 0.8707 to 1.5893 indicates that smear test makes a smaller contribution to the difference in the Hazard Ratio after adjusting other covariates that is holding the other covariates constant, an additional positive smear test of a patient induce daily hazard of death by 1.17% which is not a significant contribution.
Confidence Intervals: The summary output gives the upper and lower 95% confidence intervals for the hazard ratio (exp(coef))
Global Statistical Significance of the Model: The output gives three alternative test for overall significance of the model. The Likelihood-ratio test, Wald test and the Score-logrank statistics are all statistically significant indicating that the model is significant.
Test for Proportional Hazard Assumptions: The Schoenfeld residuals were used to test for assumptions of proportional hazards model. The plot of Schoenfeld residuals against time for all covariates is as shown below

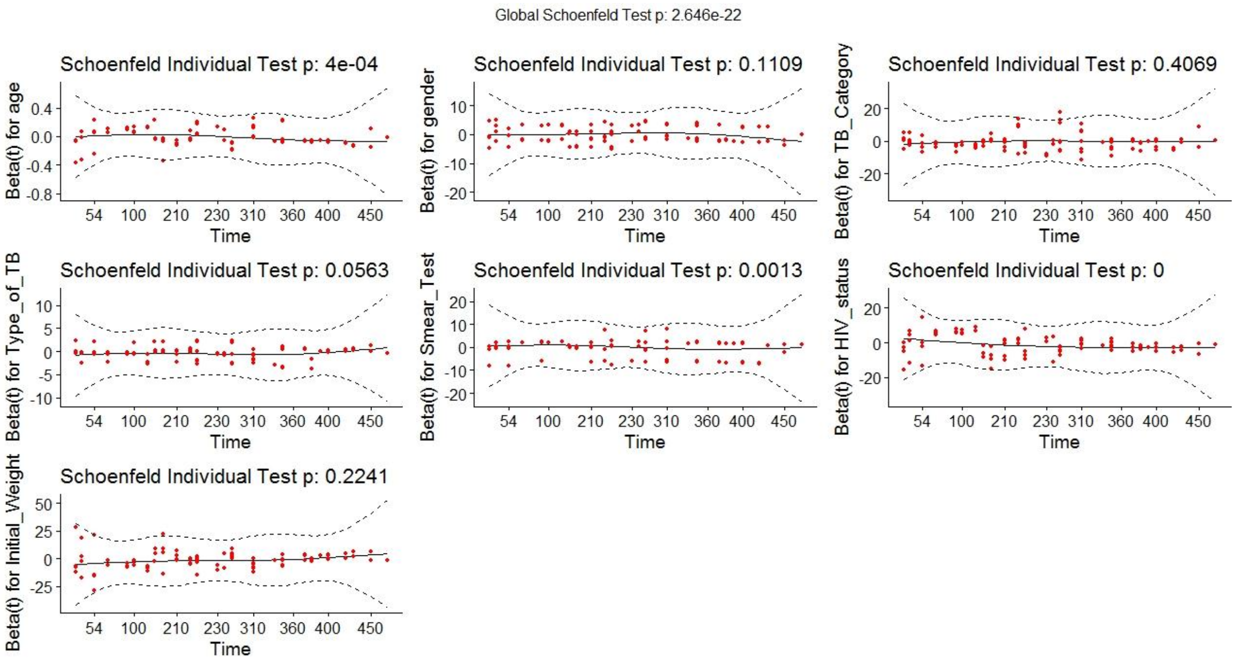

Figure 7: Schoenfeld residual plot for covariates

From the Schoenfeld residual plots displayed above, it can be shown that there is a random pattern against time. that is, the plot shows no particular pattern with respect to time. This shows that the covariates are independent of time and hence satisfies the assumptions of a fitted proportional Hazard model.

4.6 **Test for Outliers using dfbeta values**: the method used to detect outliers for the proportional Hazard Model was the inspection of the dfbeta values plot. The figure below shows the test result for outlier detection on the covariates under study.

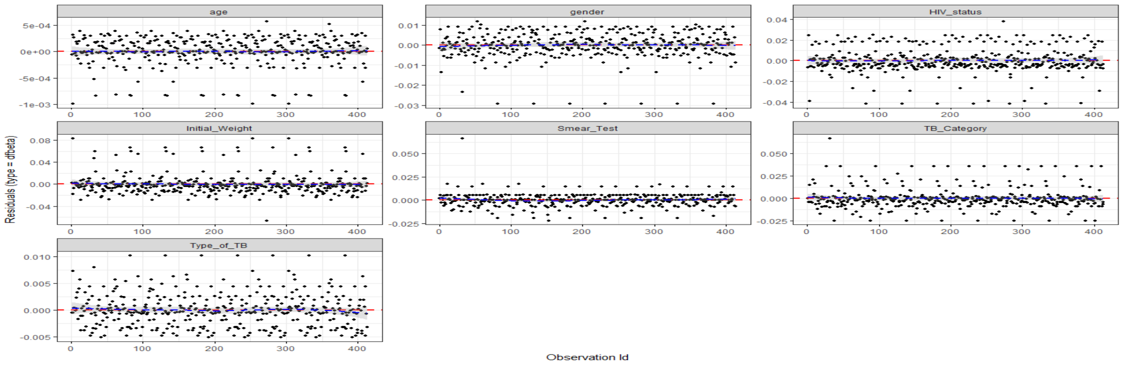

Figure 8: Index plot of DFBeta for the Cox Regression of time to death on Tuberculosis covariates.

The figure above examines the influential observations in the model. It plots the estimated changes in the regression coefficient. The plot shows that comparing the magnitudes of the largest dfbeta to the regression coefficient suggests that none of the observations is terribly influential individually, even though very few of the DFBeta values for smear test and TB category are large compared to the others.

Conclusion: This study deals with covariates that are categorical in nature, it is an attempt to identify the affect of covariates on the survival of patients tested positive to tuberculosis, and we found from the Kaplan Meier survival estimates that there is a significant difference in survival by HIV status, Type of Tuberculosis and Initial weight. However, there is no significance difference in the survival experience of gender, Tuberculosis category and smear test. The gender is the highest insignificant covariate from the study while the most significant covariate is the HIV status of patients. This implies that a HIV positive tuberculosis patient has a risk for death higher than a tuberculosis patient without HIV infection. From the findings, it was concluded that in other to reduce the morbidity rate of tuberculosis patient with co-infection, special attention be given to the patients characteristics most especially Tuberculosis patients that are HIV positive, pulmonary negative tuberculosis type and weight below 35kg.
The limitations of the study are as follows: The study conducted based on secondary data which might have incomplete information. Also information might have been missed in case of many censored observations. In many tuberculosis patients, multiple causes of death may not be determined accurately.

Competing Interest: The authors declare that they have no competing interest

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