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Application of Cox Proportional Hazard Model on Time to Recovery of Tuberculosis Patients in Selected Hospitals in Nasarawa State

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Abstract: *Tuberculosis (TB) is a continual infectious disorder that has a major health problem over the centuries, it has accounted for more human distress, suffering and loss of earning and failure of financial and social improvement than every other sickness. This study has investigated the average time to recovery of patients treated for Tuberculosis, risk factors of time to recovery of TB among patients and the hazard ratio of the predictive factors of time to recovery of TB among patients in the selected hospitals in Nasarawa state. The work used Cox proportional hazard model to model time to recovery of the disease. The average recovery time of TB patients attending the 3 selected hospitals in Nasarawa state over the study period was 7 months. The overall treatment success rate was 58.6%. Cox proportional hazard model was fitted and Chi-square test of model adequacy suggests that the model acceptably suits the data as ($p<0.05$). The effect of gender was significant and the odd of TB recovery for a male patient is 1.032 greater than female. The model shows that smear result (which is either positive or negative) has a negative effect on TB recovery. The model shows that smear positive patients have a 0.907 lower odd ratio compared to smear negative patients. This effect is not significant ($p=0.323>0.05$). Patient's age extensively influences the TB recovery time. Younger patients are 0.998 more likely to recover from TB than older patients. The healing factors of the sicknesses were tested and cox-proportional hazard model unveiled that tuberculosis type, gender and age of patients are the sizable predictors of recovery time of TB sicknesses inside the observed location. Pulmonary positive and pulmonary negative patients have greater chance of early healing than extra pulmonary TB patients. Males showed greater extraordinary of TB recovery than females and growing age became related to reduced strange of recovery. The outcomes of HIV status, smear result, patient's weight and patient's category (new or retuning) on TB recovery had been insignificant.*

Keywords: *Tuberculosis, Cox proportional hazard model, Recovery time, Risk factors*

Introduction

Tuberculosis (TB) is a chronic infection disease that has a major health problem over the centuries, it has accounted for more human misery suffering and loss of earning and failure of economic and social development than any other disease (USAID, 2009). In developing countries where population is dense and hygienic standards are poor, tuberculosis remains a major fatal disease; the high frequency of Mycobacterium tuberculosis in Sub-Sahara African countries as a result of poor nutrition, inadequate TB control measures, inadequate program for the disease and rapid growth of the population (Ponnuraja & Venkatesan, 2010).

TB is one of the most serious public health challenges worldwide. Globally, around 10.4 million people develop TB and 1.8 million people die from it (0.4 million of these also have HIV) (WHO, 2016). As in many high TB burden countries, passive case finding (PCF) is the default setup for TB case finding at health centers where people with TB symptoms seek care, and the providers can identify the conditions. Prolonged delays have been associated with further transmission of the infection in the community and thus posed a great challenge to TB elimination efforts globally. Therefore, understanding the specific determinants of delayed recovery can be used as a practical guide to enhance outreach programs, increase healthcare engagement, and to improve TB control strategies. Recent systematic reviews have reported empirical evidence associating socio-demographic, clinical, health system, and economic factors with treatment and recovery of TB.

There is a knowledge gap in the TB control and preventive measures. The few studies on TB do not track the survival history of patients and predictive factors of TB recovery. This study will examine the effect of age, gender, HIV status, smear result, and patient's initial weigh on the time to recovery of TB. The Proportional Hazards Model is used for multivariable analysis to identify factors associated with risk of event and the Cox proportional hazards model is the most widely used method of survival analysis. Hence, Cox proportional hazard model was used for the analysis and model building of recovery.

Methodology

The data for the analysis were obtained from records of three (3) selected hospitals in Nasarawa state, namely; Dalhatu Araf Specialist Hospital Lafia, General Hospital, Obi and Model Hospital Akwanga. Nasarawa state, Nigeria. The method of data analysis that was utilized in the study is survival analysis using Cox Proportional Hazard Model referred as Cox-Regression

Cox's regression model is a method of survival analysis that allows several variables to be taken into account and tests the independent effects of these variables on the hazard of the event. Hazard is the risk of reaching the event at time point *t*, given that the individual has not reached it up to that time point, *t*. A lower hazard rate implies a higher survival rate. If the outcome is death the hazard rate can be interpreted as the mortality rate (Ellen, nd). Cox's regression model is given by:

$$\lambda_i(t) = \lambda_0(t)\exp(\beta_1 x_1 + \beta_2 x_2 + \ldots . + \beta_k x_k) \tag{1}$$

Where:

$\lambda_i(t)$ = the hazard function at time points t for individual i

$\lambda_0(t)$ = the baseline hazard function (hazard function when all explanatory variables are set to 0).

β_i = the coefficient of explanatory variable i

$x_1, x_2, \ldots x_k$, Are explanatory variables

Results

Table 1: Descriptive statistics of categorical variables

Variables	Frequency	Percentage (%)
Gender		
Male	357	50.3
Female	353	49.7
Patient Category		
New	394	55.5
Non-new	316	44.5
Tuberculosis Type		
Pulmonary positive	321	45.3
Pulmonary negative	255	36.0
Extra pulmonary	133	18.7
Smear Result		
Positive	384	54.1
Negative	326	45.9
Initial Weight		
<35kg	377	53.1
>=35kg	333	46.9
HIV Status		
Positive	376	53.0
Negative	334	47.0
TB Recovery		
Recovered	416	58.6
Not recovered	294	41.4

Source: Dalhatu Araf Specialist Hospital, Lafia; General hospital, Obi; Model Hospital Akwanga.

The descriptive statistics for categorical variables from three hospitals (Dalhatu Araf Specialist Hospital, Lafia; General Hospital, Obi; and Model Hospital, Akwanga) revealed that, the sample is nearly evenly split between males (50.3%) and females (49.7%). A little over half of the patients are new (55.5%), and the majority have pulmonary tuberculosis, with 45.3% being pulmonary positive, 36.0% pulmonary negative, and 18.7% extra pulmonary. More than half (54.1%) tested positive for tuberculosis through smear tests, and 53.1% have an initial weight of less than 35 kg. Also, 53.0% of the patients are HIV positive, indicating a significant co-occurrence of HIV and tuberculosis. Regarding recovery, 58.6% of the patients have recovered from tuberculosis, while 41.4% have not yet recovered.

Table 2: Descriptive statistics of continues variables

Variable	N	Min.	Max.	Mean	Std. Dev.
Age (years)	710	10	84	39.0859	17.53947
Recovery time (months)	710	0	19	7.3845	2.88961
Valid N (total)	710				

Table 2 presents the descriptive statistics of age (in years) and recovery time (in months) of TB patients attending Dalhatu Araf Specialist Hospital, Lafia, General Hospital, Obi and Model Hospital Akwanga over the study period. The average age of TB patients was 39 years and average recovery time was 7 months.

Table 3: Omnibus Tests of Model Coefficients

-2 Log Likelihood	Overall (score)			Change From Previous Step		
	Chi-square	df	p-value	Chi-square	df	p-value
4746.727	3.013	8	0.006	3.014	8	0.006

a. Beginning Block Number 1. Method = Enter

From Table 3, the omnibus test are measures of how well the model performs. The chi-square change from previous step is the difference between the –2 log-likelihood of the model at the previous step and the current step. The Chi-square statistics are a goodness of fit for the Cox-regression model. The Overall (score) Chi-square test the Null Hypothesis that the constant and all other parameters are zero (i.e., H_0: β_i=0, for i= 0, 1, 2…. k; for k explanatory variables). The Chi-square statistic indicates a good fit if the p-value is less than 0.05. Here, the P-value value is 0.006 implying that the model acceptably fits the data.

Table 4: Variables in the Cox Regression Model

Variables	Coefficients (β)	SE	Wald Statistic	df	p-value	Exp(β)
Gender	0.031	0.099	0.1	1	0.031	1.032
Age	-0.002	0.003	0.43	1	0.012	0.998
init_weight	0.042	0.099	0.181	1	0.67	1.043
patient_cat	-0.107	0.099	1.156	1	0.282	0.899
TB_type (1)	0.108	0.136	0.629	1	0.028	1.114
TB_type (2)	0.115	0.141	0.664	1	0.015	1.122
smear_result	-0.098	0.099	0.977	1	0.323	0.907
HIV_stat	-0.127	0.099	1.656	1	0.198	0.88

Table 4 present the effect of the explanatory variables on the dependent variable (time to recovery from TB disease). To understand the effects of each explanatory variable, we look at Exp(β), which is the hazard ratio (also called odd ratio) and can be interpreted as the predicted change in the hazard for a unit increase in the explanatory variable.

The model cox-regression model can be expressed as:

$$\lambda_i(t) = \lambda_0(t)\exp(.031x_1 - .002x_2 + .042x_3 - .107x_4 + .108x_5 - .098x_6 - .127x_7) \quad (2)$$

Using the log transformation, the eqn. (3.16) would be written as:

$$log(\lambda(t)|X) = log(\lambda_0(t)) + (.031x_1 - .002x_2 + .042x_3 - .107x_4 + .108x_5 - .098x_6 - .127x_7) \quad (3)$$

Gender of patients:

For gender, female was considered as the reference category (recall from the categorical variable coding that female = 1 for the regression) and the effect of gender was positive (β =.031). The value of $Exp(\beta)$ = 1.032 for gender means that the odd of TB recovery for a male patient is 1.032 times that of a female patient. The p-value indicates the significance of gender in TB recovery (p=0.031<0.05).

Age of Patients:

Patient's age showed a significant negative effect in the cox-regression model which indicates a decreased chance of TB recovery as age increases ($\beta = -0.002, \text{p} = 0.012 < 0.05$). The $Exp(\beta)$ = .998 means that older patients are .998 less likely to recover from TB than younger patients. Conversely, it means that younger patients are .998 more likely to recover from TB than older patients.

Patient's Initial Weight:

The effect of patients' weight before treatment on the odd of Tb recovery was also examined in the cox regression model. The weight was classified into two (2) groups; below 35kg (<35kg) and 35kg or above (>=35kg). The reference category was older patients (>=35kg). The results showed that the initial weight of patient has a positive non-significant effect ($\beta = 0.042, \mathrm{p} = 0.670 > 0.05$). The $Exp(\beta) = 1.043$ showed that patients below 35kg (<35kg) have a 1.043 increased odd of TB recovery than patients of 35kg or above (>=35kg).

Patient Category:

In this study, the sampled patients were classified in to two categories (new and non-new patient). The reference category are non-new patients. The model coefficient showed non-significant negative effect of patient category($\beta = -0.107, \mathrm{p} = 0.282 > 0.05$). The $Exp(\beta) = 0.899$ shows that new patients are 0.899 more likely to recover from TB than returning patients. This may be due to the fact that returning patients may have miss their dose(s) during first treatment or are drug resistant. Although, the p-value indicated that this effect is non-significant and may be due to chance.

Type of TB Diseases:

There are three (3) type of tuberculosis diseases observed among the sampled patients in this study. These are pulmonary positive (TB type 1), pulmonary negative (TB type 2) and extra pulmonary (TB type 3). The reference category is extra pulmonary (TB type 3). Both TB types 1 and 2 showed significant positive effect in our cox regression model.

For pulmonary positive (TB type 1), $\beta = 0.108, \mathrm{p} = 0.028$ and $Exp(\beta) = 1.114$ which indicates that pulmonary positive TB patients has a 1.4114 greater odd of TB recovery compared to extra pulmonary TB patients. For pulmonary negative (TB type 2), $\beta = 0.115, \mathrm{p} = 0.015$ and $Exp(\beta) = 1.122$ which indicates that pulmonary negative TB patients has a 1.122 greater of recovery that the extra pulmonary TB patients (considered as the reference category in this study).

Smear Result:

The cox regression model shows that smear result (which is either positive or negative) has a negative effect on TB recovery. The reference category are patients whose smear result is negative. The model estimates are $\beta = -0.098, \mathrm{p} = 0.323$, $Exp(\beta) = 0.907$ which shows that smear positive patients have a 0.907 lower odd ratio compared to smear negative patients. This effect is not significant as$\mathrm{p} = 0.323 > 0.05$.

HIV Status:

The effect of HIV status of TB patients was also examined by the cox-regression model. The reference category were negative patients. The results shows that HIV status has a negative insignificant effect on TB recovery; $= -0.127, \mathrm{p} = 0.198$ $Exp(\beta) = 0.880$. The odd ratio indicates that HIV positive patients has 0.880 less likely to recover from TB. Although this effect is not significant ($\mathrm{p} = 0.198 > 0.05$).

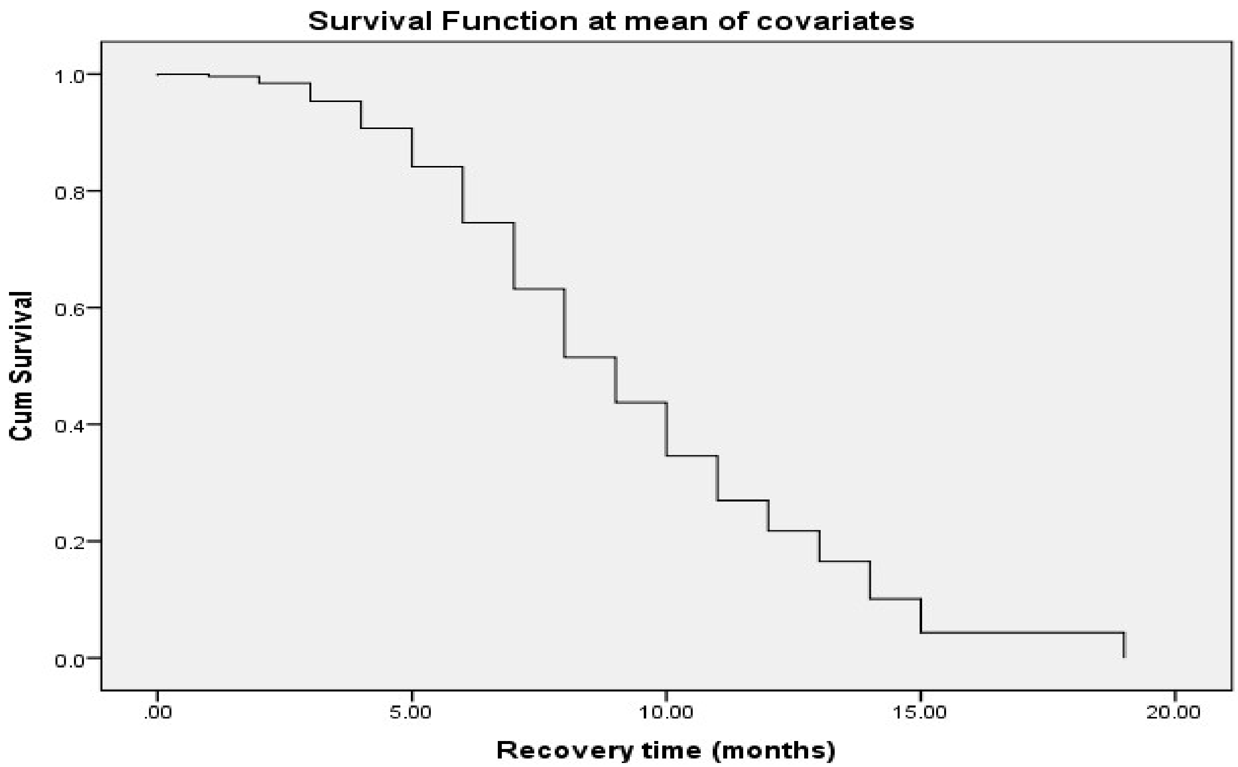

Figure 1: Basic survival curve

The basic survival curve (Figure 4.1) is a visual display of the model-predicted time to recovery (survival) for the "average" patient. The horizontal axis shows the time to event. The vertical axis shows the probability of survival (TB recovery). Thus, any point on the survival curve shows the probability that an average patient will remain unrecovered past that time. Past 15 months, the survival curve becomes smooth which shows that there are fewer patients who have been on TB treatment in the selected hospitals for that long, so there is less information available, and thus the curve is flatty.

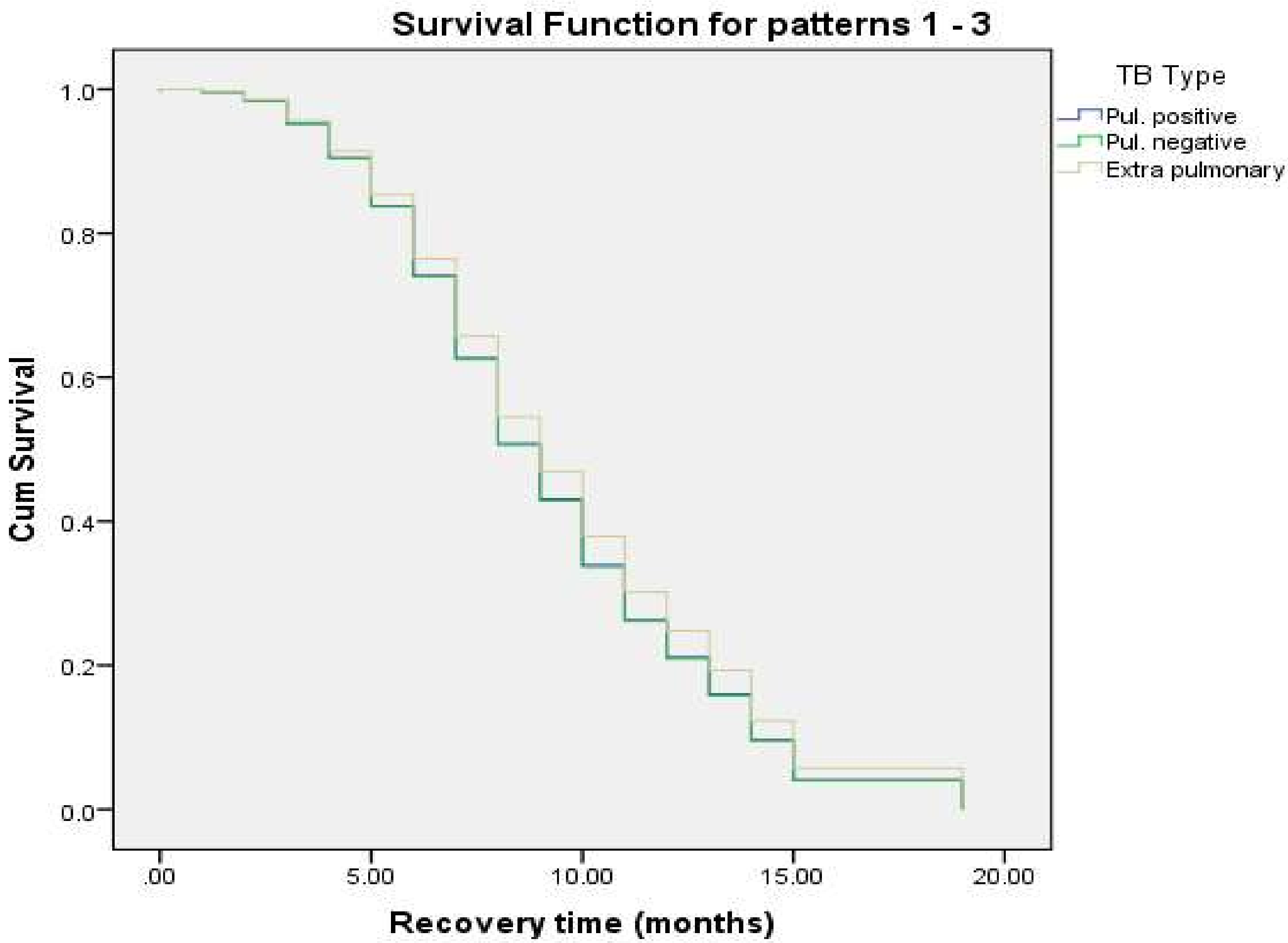

Figure 2: Survival (Hazard) Plot for TB type

Figure 2 shows the survival plot of patients based on type of TB disease. The horizontal axis shows the time to event. The vertical axis shows the cumulative hazard, equal to the negative log of the survival probability. It is clear from the plot that the probability of TB recovery decreases with time for both pulmonary positive, pulmonary negative and extra pulmonary tuberculosis diseases.

Discussion of Findings

The average recovery time of TB patients attending Dalhatu Araf Specialist Hospital, Lafia, General Hospital, Obi and Model Hospital Akwanga, Nasarawa state, Nigeria over the study period was 7 months. The overall treatment success rate was 58.6% as against the findings of Sariem *et al.*, (2020) in Jos-North and Mangu Local Government Areas of Plateau State who observed a 67.4% recovery rate. Cox proportional hazard model was fitted and Chi-square test of model adequacy indicates that the model acceptably fits the data ($p<0.05$). The effect of gender was significant and the odd of TB recovery for a male patient is 1.032 greater than female. This agreed with the results of Oga-Omenka *et al.*, (2020) that males were shown to have a 1.34 [95% CI 1.0–1.7] times greater chance of completing treatment after TB diagnosis. This agrees with the findings of Ponnuraja (2010) that males seem to have significantly larger response time than females. Sariem *et al.*, (2020) also observed that gender is a significant factor associated with TB treatment success.

Patient's age significantly affects the TB recovery time. Younger patients are 0.998 more likely to recover from TB than older patients. This agrees with the findings of Sariem et al. (2020) that age is a significant factor associated with TB treatment success. The effect of patients' weight was positive and non-significant. Patients below 35kg (<35kg) has a 1.043 increased odd of TB recovery than patients of 35kg or above (>=35kg). Derek et al., (2014) who compared Cox model and the Accelerated Failure Time model using HIV/TB Coinfection data also observed that weight is a significant determinant of the patient's survival from TB at 5% significance level.

New diagnosed patients have greater chance of recovery ($\mathrm{Exp}(\beta) = 0.899$) than returning patients. This may be due to the fact that returning patients may have treatment default, missing dose or are drug resistant. Although, the p-value indicated that this effect is non-significant and may be due to chance. The effect of TB type on recovery was observed to be significant. Extra pulmonary TB was considered as the reference category pulmonary positive TB patients has greater odd of TB recovery than extra pulmonary TB patients ($OR = 1.4114, \mathrm{p} = 0.028$). Pulmonary negative patients also have greater of recovery that the extra pulmonary TB patients ($OR = 1.122, \mathrm{p} = 0.015$). The probability of TB recovery decreases with time for both pulmonary positive, pulmonary negative and extra pulmonary tuberculosis diseases (Figure 2).

The cox regression model shows that smear result (which is either positive or negative) has a negative effect on TB recovery. The model shows that smear positive patients have a 0.907 lower odd ratio compared to smear negative patients. This effect is not significant ($\mathrm{p} = 0.323 > 0.05$).

HIV positive patients has less chance of TB recovery ($OR = 0.880$), although this effect was not significant ($p = 0.198 > 0.05$). These results disagreed with the findings of Sariem et al. (2020) that HIV status is associated with TB treatment success.

As observed from the Cumulative survival plot (Figure 4.1) after 15th month, the survival curve shows that there are fewer patients who have been on TB treatment in Dalhatu Araf Specialist

Hospital, Lafia, General Hospital, Obi and Model Hospital Akwanga, Nasarawa state, Nigeria for that long, so there is less information available, and thus the curve is flatty.

Conclusion

Tuberculosis is a chronic infectious disease that need serious medical concern. The recovery factors of the diseases were examined and cox-proportional hazard model unveiled that tuberculosis type, gender and age of patients are the significant predictors of recovery time of TB diseases in the study area. Pulmonary positive and pulmonary negative patients have greater chance of early recovery than extra pulmonary TB patients. Males showed greater add of TB recovery than females and increasing age was associated with decreased odd of recovery. The effects of HIV status, smear result, patient's weight and patient category (new or retuning) on TB recovery were insignificant.

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