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Cox Regression Model for HIV/AIDS Prevalence in Taraba State, Nigeria

A. N. Ahmadu[1, *] , **A. A. Akinrefon,** [2] **E. Torsen,** [3] **and S. Muhammad** [4]

[1,2,3,4]*Department of Statistics, Faculty of Physical Sciences, Modibbo Adama University, Yola, Nigeria*

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Abstract. This study examines the hazard trend of patients leaving with HIV/AIDS in Taraba State, Nigeria. The data for this study was extracted from the available standard national medical registers of the Federal Medical Centre Jalingo, Taraba State. The registers include the Pre ART register (register of patients at their first visit), the ART register (registration after ART initiation), and the follow-up patient form. Data were analyzed using simple frequency tables and the Cox proportional hazard model in Survival analysis. The goodness-of-fit test confirms a strong fit with p-value of 0.00391. From the Cox Proportional Hazard result, it was observed that four factors (Age group, CD4 Counts, Gender and Marital Status) considered which have adverse effect on $HIV\&AIDS$ prevalence in the study area it was found that $CD4$ Counts of infection (I, II, III and IV) and Marital Status were significant $(P - value < 0.000)$. in terms of the CD4 Counts, it was found that the probability of patients in stage IV experiencing the event (death) is 4 times those in the other stages of the infection. In terms of Marital Status, the finding revealed that the risk of patients who are single experiencing the event is twice that of married patients.

Keywords: ART, Cox Proportional hazard, HIV/AIDS, Survival function, Hazard ratio

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1. Introduction

HIV/AIDS continues to be a significant global health concern, affecting millions of individuals worldwide. The lifespan of HIV/AIDS patients can vary considerably, with several factors influencing disease progression and survival rates. Understanding these factors is crucial for healthcare professionals and policy-makers to develop effective strategies for managing and improving the quality of life for HIV/AIDS patients. This article aims to analyze the impact

*Corresponding author. Email: aa.norndigi@mau.edu.ng

of diagnosis date, gender, age, marital status and CD4 counts on the lifespan of HIV/AIDS patients, utilizing Cox regression and as well to model the CD4 counts data of patients from Federal Medical Centre, Jalingo Taraba State. Before now, many studies exist that have written much on the factors that affect the time to diagnosis of HIV/AIDS infection. For instance, the time of HIV/AIDS diagnosis plays a critical role in patient outcomes. Earlier diagnosis allows for early initiation of antiretroviral therapy (ART), leading to improved immune function and prolonged survival.

Marks *et al.* (2006) demonstrated that delayed diagnosis is associated with a higher risk of disease progression and mortality. Mugavero *et al.* (2013) in their studies showed that delayed diagnosis often leads to a delayed start of ART, resulting in lower CD4 counts and higher viral loads, both of which are strong predictors of disease progression. Therefore, interventions to promote early HIV testing and diagnosis are crucial for improving patient outcomes and prolonging lifespan. Gender as well has been recognized as a significant factor influencing the lifespan of HIV/AIDS patients. Numerous studies have reported differences in survival rates between men and women, with conflicting findings. Some studies have suggested that men have a higher risk of disease progression and mortality compared to women, May *et al.* (2011), while others have found no significant gender-based differences Oliva *et al.* (2010). However, they stated that factors such as access to healthcare, engagement in treatment, adherence to ART, and underlying biological differences may contribute to the observed gender disparities.

Palella *et al.* (2003) argued that age at the time of HIV/AIDS diagnosis has consistently shown to impact patient's survival. Young individuals tend to experience slower disease progression and longer lifespans compared to older adults. However, Pathai *et al.* (2014) in his studies discovered that old age is associated with a higher incidence of comorbidities, reduced immune response, and increased vulnerability to opportunistic infections, all of which contribute to poorer outcomes. Furthermore, age-related factors such as social support, socioeconomic status, and overall health status may influence disease progression and survival rates. Effective management strategies tailored to the unique needs of older HIV/AIDS patients are crucial for optimizing outcomes. Studies have also shown that CD4 counts are a key immunological marker used to assess the progression of HIV/AIDS and predict patient outcomes.

Lawn *et al.* (2001) has shown that lower CD4 counts reflect more advanced immunosuppression and are associated with an increased risk of opportunistic infections and mortality. Studies by Kuller *et al.* (2008) has proven that utilizing multiple linear regression have consistently identified CD4 counts as a strong predictor of survival in HIV/AIDS patients. Early initiation of ART and regular monitoring of CD4 counts are essential for maintaining immune function and extending the lifespan of patients with HIV/AIDS.

According to the study conducted by Nacher *et al.* (2018), the findings revealed that Human Immune Deficiency Virus (HIV) is an infection that attacks the body's immune system, specifically the white blood cells called CD4 cells. They're also called CD4 T lymphocytes or "helper T cells." That's because they help fight infection by triggering your immune system to destroy viruses, bacteria, and other germs that may make one sick. The loss of CD4 T-lymphocytes

will result in the inability to have a proper immune response HIV destroys these CD4 cells, weakening a person's immunity against opportunistic infections, such as tuberculosis and fungal infections, severe bacterial infections and some cancers. A CD4 count is a blood test that measures the number of CD4 cells in a sample of the blood. It is a type of white blood cell. If you have AIDS, your CD4 count is so low that you may develop serious infection from virus, bacteria or fungi that usually don't cause problems in healthy people. These are called "opportunistic infections," and they can become life-threatening and can lead to death.

There is no cure of AIDS but there is certain medicine which are used to slow down the virus for the HIV patient to stay healthier for a long time (Crandall, 1999). Udofia *et al.* (2021) conducted a study in South-South Nigeria to investigate and model the survival rates of patients undergoing Antiretroviral Therapy (ART), based on stages of immune suppression and opportunistic infections. The research utilized data from 170 Human Immune Deficiency Virus (HIV) patients treated at Federal Medical Centre Taraba State, Nigeria, spanning the period from January 1st 2015 to 31st December 2017.

However, Taraba State, according to the 1999 Sentinel Survey, is "hotspot" for HIV/AIDS in northeastern Nigeria. With increasingly mobile populations, the high prevalence of the disease within these hotspots will rapidly spread to other areas. Taraba State had a seven percent HIV prevalence rate in 1999, with the epidemic in a stage of exponential progression (FHI, 2009). The prevalence rate in the same period ranged from 7.0 to 5.2% (Tonwe-Gold *et al.,* 2007) and Taraba state HIV/AIDS Strategic Plan, 2007). Going by the 5.2% HIV/AIDS prevalence rate in Taraba state as at 2008, it could be estimated that about 127,167 people were living with the virus in the state. As at 2007, only 2,541 infected persons in the state were known to be placed on the antiretroviral therapy (ART) programme in the state.

A rapid assessment survey of HIV/AIDS prevalence carried out by the Family Health International (FHI, 2000) shows that the state has LGAs with high risk settings. Some of these LGAs include Zing LGA (Sabon Layi area), Gassol LGA (Mutum Biyu, Tella, Dan-anicha area), Jalingo (Sabon Layi, Gidin-Dorowa and the city center), Wukari and Sardauna (Gembu area). This is as a result of high sexual networking among the adolescents and young adults, extra-marital sex and concurrent sex partnerships, street hawking, polygyny; early marriage, divorce and frequent re-marriages/wife inheritance. Amongst the population, most women are vulnerable through sex because of poverty.

Recent review has shown that relatively few interventions to reduce AIDS stigma have been conducted, or at least rigorously evaluated and documented, in the State and the country in general. Much however, is not known about the hazard and survival trends of people living with HIV/AIDS under the auspices of these health center's as well as the factors/variables that contribute to these trends. The inadequacy in HIV/AIDS data presentation, forecasting and knowledge of hazard and survival trends of patients enrolled in our health Centre has thus necessitated this research.

A similar study was conducted using logistic regression model by Zaba *et al.* (2006) and thus, the model of health care delivery undertaken at that time was least effective for the sickest and poor patients. The research, however, did not

indicate the number of patients that survived or dead after the given period of study. Similarly, the researchers did not indicate the gender differences in survival and hazard functions since there could be gender differences in age, Marital Status and more particularly CD4+ T-cell. Hence it is the goal of this research to; describe the survival and hazard trends of males and females living with HIV/AIDS in Taraba State, determine the hazard rates in stages of infection, Age and Marital status.

2. Materials and Method

Survival analysis is a branch of statistics for analyzing the expected duration of time until one or more events happen. The event can be death, occurrence of disease, marriage, divorce, etc. the survival time can be measured in days, weeks, months, years, etc. the response is often referred to as a failure time, survival time, or event time. The data was analyzed using R software.

2.1 *Kaplan-Meier Estimator*

The Kaplan-Meier estimator is a model used to estimate survival functions; it is a non-parametric estimator. The Kaplan-Meier estimator is also known as the Product Limit estimator. The Kaplan-Meier estimator is a powerful tool in the analysis of survival data because it takes into account censoring. The Kaplan-Meier survival curve is defined as the probability of surviving in a given length of time while considering time in many small intervals. The Kaplan-Meier method allows a table and a graph to be produced; these are used to estimate the survival time. The table to be generated is referred to as the life table and the graph is the survival curve (Oruonye, 2011).
Suppose that the survival times, including censored observations, of a homogenous group of n students are represented by $t_1, t_2, ..., t_n$. We assume that the survival times of the students are already ordered such that $t_1 \leq t_2 \leq ... \leq t_n$. For a given value t such that $t_i < t$, the probability $S(t)$ is then estimated by the Kaplan-Meier estimator given by:

$$\hat{S}(t) = \frac{r_1 - d_1}{r_1} \times \frac{r_2 - d_2}{r_2} \times ... \times \frac{r_i - d_i}{r_i} \tag{1}$$

Where r_k is the number of subjects alive just before time t_k (the k^{th} ordered survival time) and d_k denotes the number of subjects who experienced the event of interest at the time t_k (Cattleya, 2000).

2.2 *Hazard Function*

The hazard function is denoted by $\lambda(t)$ is the probability that an individual experience an event (for example death) within a small-time interval given that the individual has survived up to the beginning of the interval. It can, therefore, be interpreted as the risk of an HIV patients dying at time t. It is also said to be a function of the probability of an event in the time interval $[t, t + i]$, given that

the individual has survived up to time t. The density function is denoted as $f(t)$ and the survivor function is denoted as $S(t)$.
According to Janssen *et al.* (1998), the hazard function $\lambda(t)$ can be estimated using the following equation:

$$\begin{aligned}\lambda(t) &= \lim_{\Delta t \to 0} \frac{P(t \leq T \leq t + \Delta t | T \geq t)}{\Delta t P(T \geq t)} \\ &= \lim_{\Delta t \to 0} \frac{P(t \leq T \leq \Delta t)}{\Delta t P(1 - F(t))} \\ &= \frac{f(t)}{1 - F(t)} \\ \lambda(t) &= \frac{f(t)}{S(t)}\end{aligned} \tag{2}$$

2.3 *The Cox's Proportional Hazard*

The Cox Proportional Hazard model is a semi parametric model in which the hazard function of the survival time is given by

$$\begin{aligned}h(t, X) &= h_0(t) exp\Big[\sum_{i=1}^{p} \beta_i X_i\Big] \\ &= h_0(t) exp\big(\beta' X\big) \\ h(t, X) &= h_0(t) exp\big(\beta_1 X_1 + \beta_2 X_2 + ... + \beta_p X_p\big)\end{aligned} \tag{3}$$

where; $h_0(t)$ is called the baseline hazard function, which is the hazard function for an individual for whom all the variables included in the model are zero, $X = (x_1, x_2, \ldots, x_p)'$ are the values of vector of explanatory variables for a particular individual, and $\beta' = (\beta_1, \beta_2, ..., \beta_p)$ is a vector of regression coefficients. The corresponding survival functions are related as follows:

$$S(t, X) = s_0(t) exp\Big[\sum_{i=1}^{p} \beta_i X_i\Big] \tag{4}$$

This model, also known as the Cox regression model, makes no assumptions about the form of $h_0(t)$ (non-parametric part of model) but assumes parametric form for the effect of the predictors on the hazard (parametric part of model). Even though the baseline hazard is not specified, we can still get a good estimate for regression coefficients β hazard ratio, and adjusted hazard curves. The measure of effect is called hazard ratio. The hazard ratio of two individuals with

different covariates x and x^* is given by:

$$\begin{aligned} HR &= \frac{\hat{h}(t, X^*)}{\hat{h}(t, X)} \\ &= \frac{\hat{h}_0(t) exp\Big[\sum_{i=1}^{p} \hat{\beta}_i X_i^*\Big]}{\hat{h}(t) exp\Big[\sum_{i=1}^{p} \hat{\beta}_i X_i\Big]} \\ HR &= exp\Big[\sum_{i=1}^{p} \hat{\beta}_i (X_i^* - X_i)\Big] \end{aligned} \tag{5}$$

This hazard ratio is time-independent, which is why this is called the proportional hazards model. Taking survival time as the dependent variable and Age, Sex, CD4+ T-cell count ($HIV/AIDS$ stage) and Marital status as the independent prognostic factors, and based on the fact that the ratio of the hazards for any two individuals i and j is constant over time the expected model will assume the form

$$S(t, X) = s_0(t) exp\big(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4\big) \tag{6}$$

Where are estimated coefficients of the regression model such that, $\beta_0 = \ln(s_0)$, is the baseline constant for the regression model (Cox, 1972).
$\beta =$ Relative risks
$X_1 =$ Age of the patients during first sero-conversion
$X_2 =$ CD4 counts (WHO defined status since sero-conversion)
$X_3 =$ Gender, and
$X_4 =$ Marital status.

These variables in R environment are represented by using dummy variables (1 or 0) except the age of the patients and survival time which are continuous. The required model for the research is however, dependent on the significance of each of these factors at 5% level of significance.

3. Results and Discussion

Of the 170 patients recorded for the period under study, it was observed that 37.1% were male while the remaining 62.9% were female. According to World Health Organization (WHO) defined stages I, II, III, and IV with CD4 +T-cell count below 400copies/µl, 300copies/µl, 200copies/µl, and 100copies/µl respectively it was observed that 50.6% of the patients were in stage I, 21.2% in stage II, 18.8% in stage III while the remaining 9.4% were found in stage IV of the infection. 50% of the patients were married. After the study period of 36 months, 53 patients experienced the event (death) which take a proportion of 31.2% of the total patients considered while the remaining 68.8% were censored (does not experienced the event) or lost to follow up.

Table 1: Distribution of the Patients Based on Age Group, Stages of Infection and status

					Status		
	WHO Stages				Deaths	Censored	
Age group	**I**	**II**	**III**	**IV**	**(Events)**	**LTF**	**Alive**
10-21	6	2	6	1	7	3	5
22-45	74	32	23	13	41	46	55
46+	6	2	3	2	5	2	6
Total	**86**	**36**	**32**	**16**	**53**	**51**	**66**

Source: Federal Medical Centre Jalingo, Taraba State 2018.

Table 1 shows the distribution of the patients based on Age group, WHO Stages and Status. Based on the distribution, it was observed that patients within the working age group of 22-45 years are the most likely victim of the disease. Finding reveals that there are so many factors that attributed to this number which predisposes them to behavioral attitudes that enhance the spread of HIV/AIDS. There is no indication of gender difference in survival. Patients in the age group 22-45 years have higher percentages of HIV infection taking a portion of 83.53% of the total patient enrolled in the study. Out of this total 54.17% of the patients belongs to stage I of the HIV infection. A test of homogeneity of the survival curves (KM-plots) for Gender, Marital Status and WHO stages of the infection was also carried out and presented as follows.

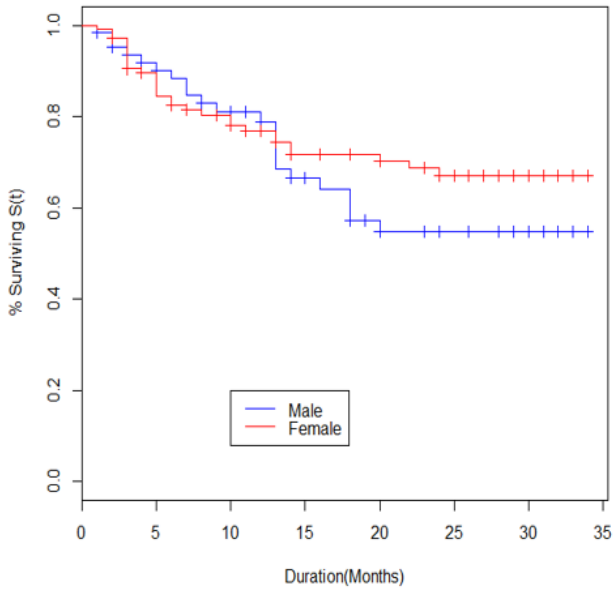

Figure 1: HIV/AIDS Patients Survival Plots by Gender.

Despite the little differences in mean survival time of the male cohort over that of the female cohort, the P-Values of the Likelihood ratio (0.331) test statistic indicates that, the difference between the two survival curves is statistically insignificant. This therefore implies that, there is no significant gender survival difference in HIV patients in the study area. Meanwhile, patient's Marital Status as well as the patient's CD4+T-cell count as he/she moves from one stage of HIV infection to another are determinants of the survival trends of patients and as shown in Figures 2 and 3 below .

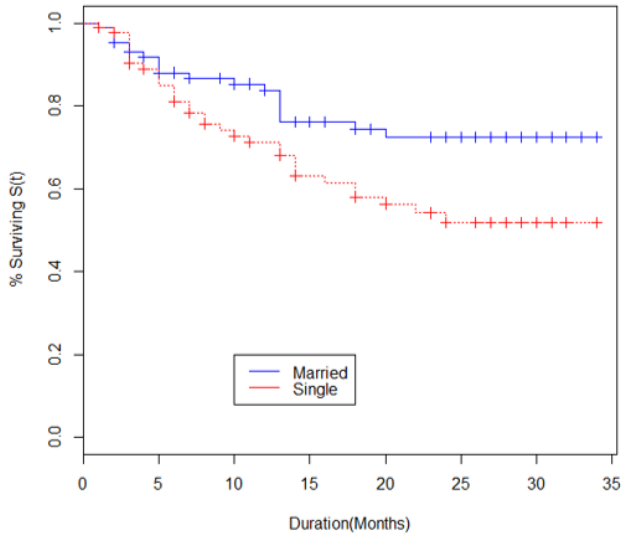

Figure 2: HIV/AIDS Patients Survival Plots by Marital Status

Despite the wide differences in marital status of the HIV patients, the P-Value of the Likelihood ratio (0.0235) test statistic indicates that, the difference between the two survival curves is statistically significant. Meaning single cohort patience experiences the event more than the married cohort looking at the time differences in commencement of the event (6 months) and end differences of (10 months).

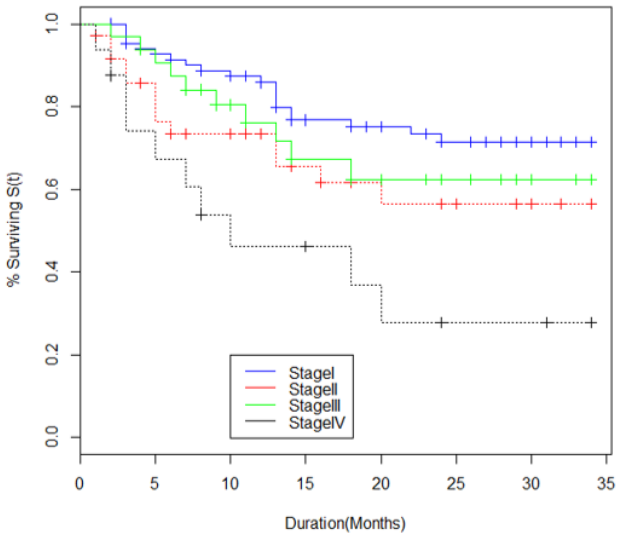

Figure 3: HIV/AIDS Patients Survival Plots by Stage

That is, patient's status as he/she moves from one HIV stage of infection to another experience about significant percentage decrease in his/her chances of survival at sero-conversion this follows that patience in stage IV have four times chance of experiencing the event than those in stage I, a patient's chance of survival is hindered as his/her CD4+T-cell count reduces from 500 copies/µl. A patient's age and sex does not help in explaining the survival trend of the patient. In general, despite the wide differences in stages of infection, the P-Value of the Likelihood ratio (0.00391) test statistic indicates that, the difference between the four survival curves is statistically significant. This therefore implies that, there is significant survival difference in stages of infection amongst the HIV/AIDS patients in the region.

Table 2: Testing Global Null Hypothesis ($\beta = 0$)

	Chi-Square	DF	P-Value
Likelihood Ratio	21.82	7	0.00273
Wald test	22.39	7	0.00218
Score (logrank)	24.67	7	0.00087

All the three statistics, Likelihood ratio, Wald, and Score (logrank) with 6 degrees of freedom has very small P-Values (0.00273, 0.00218, and 0.00087 respectively) less than the given level of significance of 0.05. All the three statistics are thus significant indicating that, at least, one of the coefficients of the model is not zero and can thus be used to explain the model explicitly.

Table 3: Maximum Likelihood Estimates

	Coeff	Std.Error	Z	HRexp	P-Value	95%(Lower	Upper)CI
Age 2	-0.1850	0.4552	-1.790	0.0734	0.4426	0.1814	1.080
Age 3	-0.1377	0.6816	-0.202	0.8399	0.8713	0.2291	3.314
Stage 2	0.7842	0.3635	2.158	0.0310^{*}	2.1907	1.0744	4.467
Stage 3	0.2945	0.4012	0.734	0.4630	1.3425	0.6115	2.947
Stage 4	1.3573	0.4029	3.369	0.0008^{**}	3.8858	1.7640	8.560
Gender F	0.3719	0.3007	1.237	0.2162	1.4505	0.8045	2.615
Marital Status S	0.7279	0.3303	2.204	0.0275^{*}	2.0708	1.0840	3.956

Coeff =$Parameter\ \ Estimates$, **Std.Error =**$Standard\ \ Error\ \ of\ \ Estimates$, **HRexp =**$Hazard\ Ratio\ (exponent\ of\ estimates)$.

The signs of the coefficients of the parameter estimates, indicates the direction of relationship of the variables and survival time. For this model, we observed that most of the sign of the regression coefficient are positive. The negative coefficient for age group two and three indicates that patients in this category have less survival time than those in the reference category (group one). This is illustrated more clearly using the hazard ratio. This further demonstrates the fact that, older patients have a higher risk of dying as compare with younger ones. Specifically, each additional year at the time of sero-conversion is associated with a 2.0% increase in the hazard of death though this covariate is statistically insignificance in explaining the model effect.

A patient's status as he/she moves from one HIV stage of infection to another say from stage one to stage two, stage three and to stage four experiences a serious decrease in his/her chances of survival. This mean that patients in stage one has longer survival time than patients in the remaining stages follows by those in stage three then stage one and lastly those in stage four. The hazard ratio as indicated in the table above clearly explain that patients in stage four of the HIV/AIDS infection are three times faster than those in stage one in experiencing the event (death). This result coincides with the findings of Allison (2010) that the hazard rate of patients in stage four of the HIV/AIDS infection is at least four times than hazard rate of those in the other category.
Patient's marital status is another significant factor that explains patient's survival and hazard trend. Married couple has longer survival time than single patients. The hazard ratio of unmarried couple is twice that of married couple. This means that single patients are two times faster in experiencing the event than married patients.

4. Conclusion

This study thus uses survival analysis to compare the gender survival trends of HIV patients, Marital Status and the risk of survival of the patients in the various stages of the infection in the region. Based on findings, it was found that Gender, Marital Status and CD4 Counts have significant effects on the survival and hazard time of HIV/AIDS patients leaving with the virus in Taraba State. I recommend that the Government, voluntary organizations and nongovernmental organizations should intensify effort in the campaign on HIV/AIDS so as to increase the level of awareness. This could be achieved through organizing public lectures, preaching in Mosque and Churches, posting of handbill and jingles in media houses. For future study, I recommend that a comparative analysis should be done on some of the competing parametric models in survival analysis such as Weibull, log-logistic and lognormal models.

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