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Survival Analysis on HIV/AIDS Patients Receiving Antiretroviral Treatment (A Case Study in University of Maiduguri Teaching Hospital)

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Abstract: *The study is aimed at estimating the mortality rate, identifying predictors that have significant impact on the survival status of patients and identify predictors of mortality in HIV-infected patients. Survival analysis with emphasis to Kaplan-Meier method and Cox proportional hazards was employed to achieve the objective. The data was retrospective study of 2021 patients collected from University Of Maiduguri Teaching Hospital between 2009 – 2014.The study shows that the overall mortality rate was 2.9 % and factor responsible for death include weight less than 45kg, low CD4 counts, WHO stage less than 4 and female gender were prone to death. It is recommended that early initiation of antiretroviral treatment was likely to have achieved better survival effects, provision of nutritional support and strengthening of the food by prescription initiative and counselling of patients for early presentation to treatment.*

Key words: *Antiretroviral therapy, HIV/AIDS, Survival*

INTRODUCTION

Worldwide, despite widespread efforts to control the disease, HIV/AIDS remains a serious public health challenges based on the USAID global estimation, by the end of 2016, there were 36.7million people living with HIV 1.0million death from AIDS –related causes and 1.8 million new HIV infections (WHO, 2010). Since the introduction of antiretroviral therapy (ART),AIDS-defining opportunistic infection and AIDS-related mortalities were decreased, and long-term survival in HIV positive population appears to be approaching that of the general population studies have shown declining rates of AIDS-related death. And describe a need for increasing focus on chronic disease management and health promotion. (Mageda et al. 2012) This effective treatment increases survival following HIV infection from 10 to12years to 25years and HIV infection can now be characterized as a manageable chronic condition. Reporting treatment outcomes of patients enrolled in ART program in important to demonstrate program effectiveness and justify continued funding that can help to identify opportunities for program improvement.

THE OBJECTIVES OF THE STUDY

The study is aimed at estimating the mortality rate and predictors that have impact on the survival of HIV positive view to

1. Estimating mortality rate of patients receiving antiretroviral treatment university of Maiduguri teaching Hospital.

2. Identify predictors that have significance impact on the survival status of patient who receive ART and care and

3. Identity predictors of mortality in HIV – infected patients such as gender, age group, weight and other variables.

LITERATURE REVIEW

The first two cases of HIV/AIDS in Nigeria were identified in 1985 and were reported at the International AIDS Conference in 1986 (Kanki and Adeyi , 2006).

- In 1991 the Federal Ministry of Health made their first attempt to assess the situation of HIV/AIDS in Nigeria (Kanki and Adeyi , 2006)
- Gender is identified as a factor of HIV/AIDS in Marzieh et al (2008), Martin et al (2004), Chaisson et al (1995), Chiesi et al (1995), Eyuel and Alemayehu (2011)
- Age as a predictor of HIV /AIDS is found in Isingo et al (2007), Chiesi et al. (1995), and Eyuel & Alemayehu (2011)
- Other factors are number of medication (Rabaud et al , 2000; Eyuel & Alemayehu 2011; Fransciso et al, 1998, Campos et al, 2002; Jerene et al, 2006); CD4 count (Chiesi et al., 1995, Eyuel and Alemayehu, 2011, Morgan et al., 1992 and Kitchen et al 2007); weight (Tang .et al 2003, Dickerson et al 1994)

METHODOLOGY

The data was collected for 2021 HIV/AIDS patients at (PEPFAR) or infectious Clinic of the University of Maiduguri Teaching Hospital.

- The response variable in this research is the "survival time" defined as the number of days from the date of enrollment of a patient in the HIV-care till one of the events "death", "lost to follow up", "dropped out", "stopped", "transferred out to other health centers or hospitals" occurred. This mean that the survival data studied here were "right-censored".
- The predictor variables are age (in full years), gender (male, female), marital status (single, married, Separated, divorced, widowed), weight (in kilograms), functional status (working, or not working), WHO clinical stages (stage 1, stage 2, stage 3, stage 4), number of medications taken (0,1, 2, 3, 4 etc), CD4 count (in mm^3), and antiretroviral therapy (ART) (yes, no).
- The Kaplan-Meier plot displays the survival probabilities, that is, cumulative probability of an individual remaining alive at any time after baseline. The survival probability is computed by

Probability of Survival on day i :

$$P_{(t_i)} = \frac{n_i - d_i}{n_i} \qquad (3.1)$$

where ni is the number alive the day before i and di is the number dying on day i.

The cumulative survival probability to day i, denoted S(ti), is the product of the survival probabilities up to day i. It is given by

$$S_{(t_i)} = \frac{n_i - d_i}{n_i} \times S_{(t_{i-1})} \quad = \frac{n_1 - d_1}{n_1} \times \frac{n_2 - d_2}{n_2} \ldots\ldots \frac{n_i - d_i}{n_i} \qquad (3.2)$$

The probabilities are only calculated for days when the event (e.g. death) occurs. When observations are censored, the probability of survival remains the same.

- The log rank test is used to tests the hypothesis that there is no difference in survival times between the groups studied at all time points in the study. The test statistic for comparing groups 1 and 2 is given by

$$\chi^2_{\log rank} = \frac{(o_1 - E_1)^2}{E_1} + \frac{(o_2 - E_2)^2}{E_2} \qquad (3.3)$$

Where O1 is the observed value in group 1 and E1is the expected value in group 1 computed by

$$E_1 = \sum_{i=1}^{k} \frac{din_{1i}}{ni} \qquad (3.4)$$

- Cox's regression compares the hazards (as ratios) of the two treatment groups and allows several variables to be taken into consideration. The Cox's regression model for hazard function is given by

$$\lambda_t(t) = \lambda_0(t) \exp(\beta_1 x_1 + \beta_2 x_2 + \ldots\ldots\ldots \beta_k x_k) \qquad (3.5)$$

where *lambda (ti)* is the hazard function at time point t for individual i, *lambda node (t)* is the base line hazard function, that is, hazard function when all explanatory variables are set to 0 and *exponent beta* is the hazard ratio interpreted as the predicted change in the hazard for a unit increase in the predictor.

RESULT

- Life Table is a descriptive procedure for examining the distribution of time-to-event variables. Here, the survival curves are presented since they are visual representation of life tables.

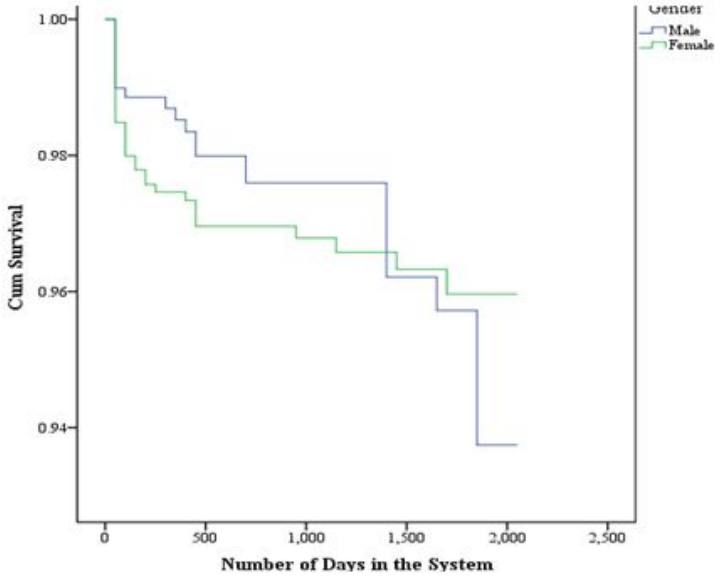

Figure 4.1 Survival Curve based on Gender

From Figure 4.1 above, it is observed that the greatest number of deaths took place in the first 1 year of admission with female HIV-position patients had short survival time to live compare to male, From the figure, it is also observed that the proportion of patients surviving is high (> 90%) and increases with time.

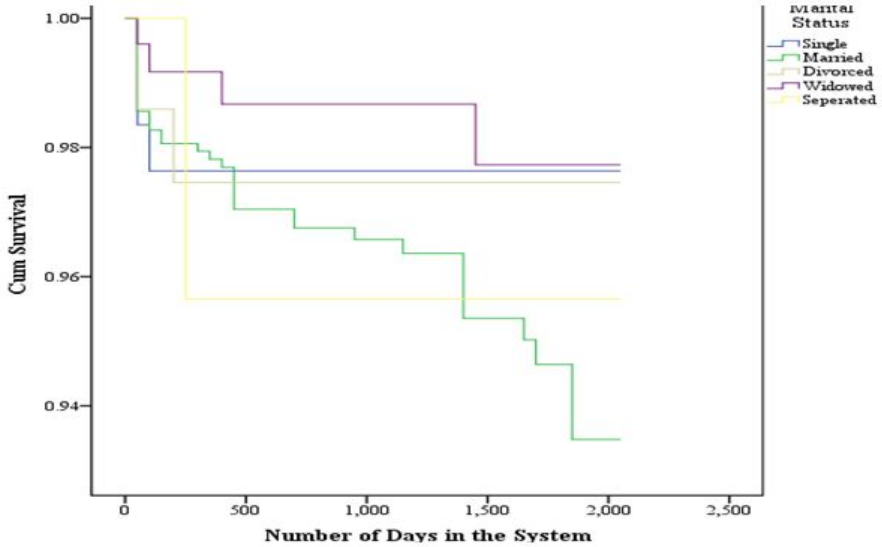

Figure 4.2 Survival Curve based on Marital Status

Figure 4.2 above shows that the greatest number of deaths occurred in the first one year. The majority of deaths occur among the married people. It is also observed from the figure that the proportion of patients surviving is high (> 90%) and increases with time, except for the married.

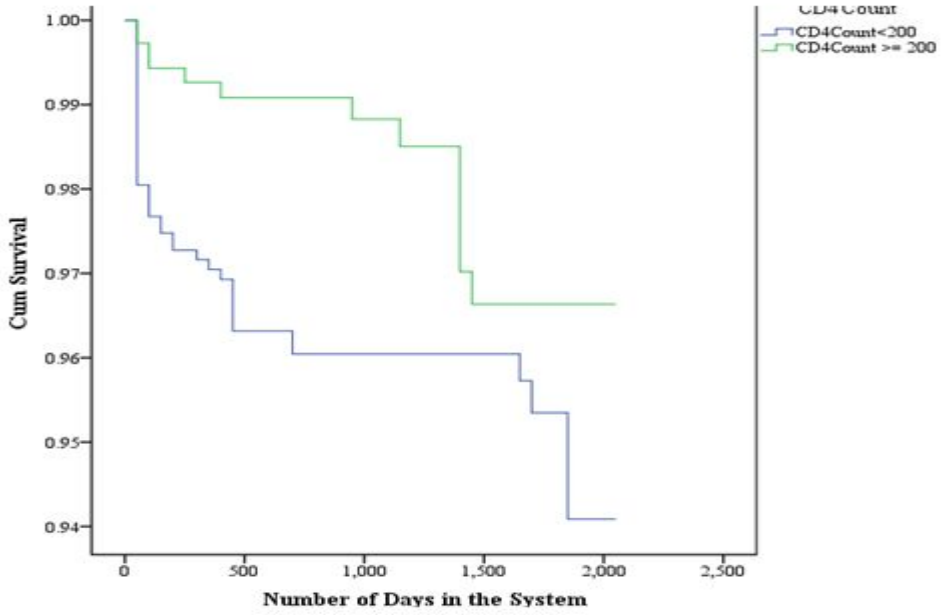

Figure 4.3 Survival Curve based on CD 4 Count

Figure 4.3 also shows the greatest number of deaths occurring in the first 1 year, with more deaths among those with CD4 count less than 200. The proportion of patients surviving is high (> 90%) and increases with time.

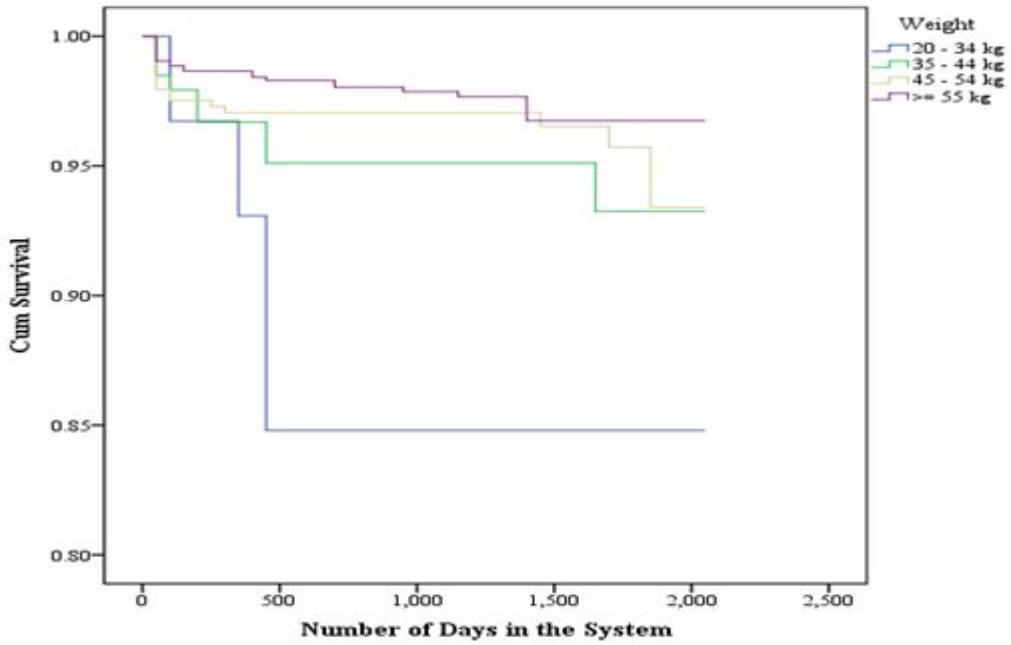

Figure 4.4 Survival Curve based on Weight of Patients

- In Figure 4.4, it is observed that patients died more in the first year of admission/follow up. More deaths are observed among patients of less than 45 kg weight. Patients of weight greater than 45 kg have higher probability of survival.

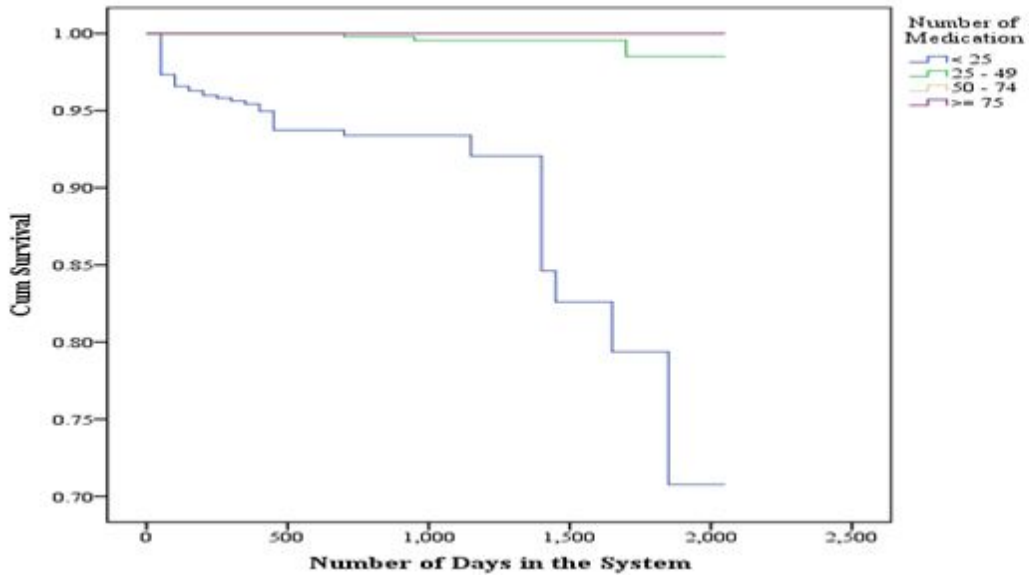

Figure 4.5 Survival Curve based on Number of Medication

- In Figure 4.5, it is also observed that deaths occur mostly in the first year of admission/follow up. Patients that have taken less than 25 medications have recorded more deaths. On the other hand, no death has been recorded among patients who have taken more than 50 medications, and have higher probability of survival.

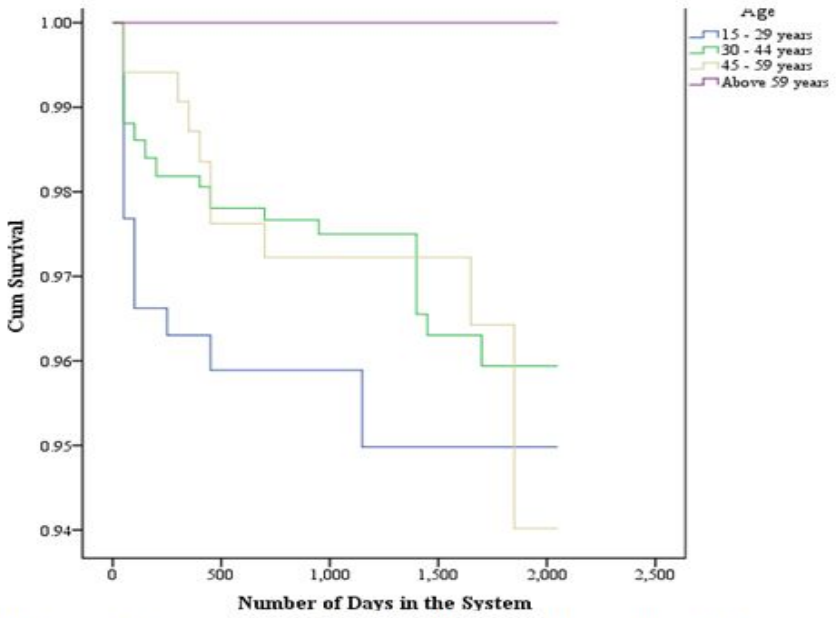

Figure 4.6 Survival Curve based on Age

In Figure 4.6, it is observed that patients in the sexually active age (15 – 44 years) have recorded more deaths, with most deaths occurring in the first one year

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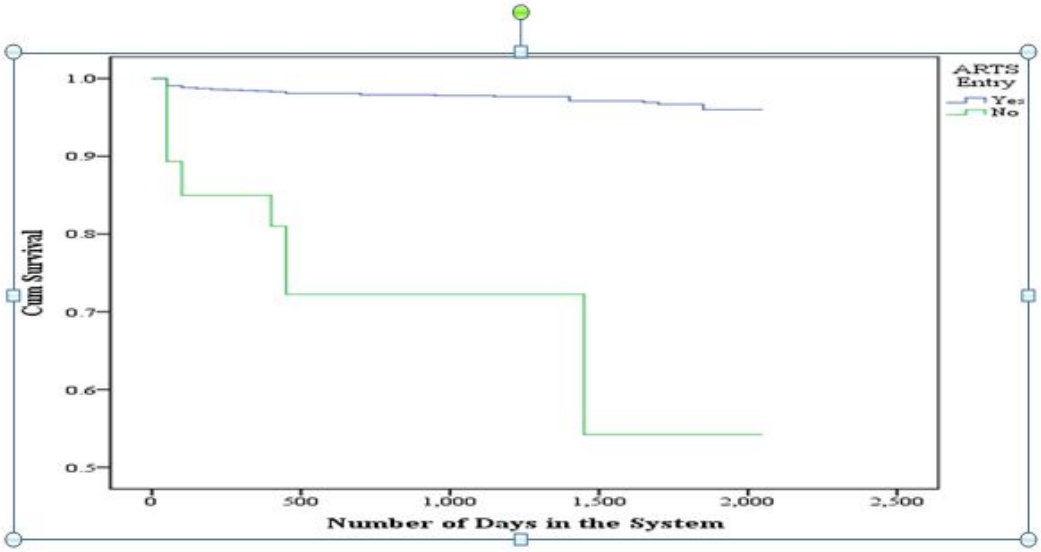

Figure 4.7 Survival Curve based on ARTS Entry

- Figure 4.7 show those patients taking ART have higher survival probability. The figure shows that most deaths occur in the first years of admission /follow up.

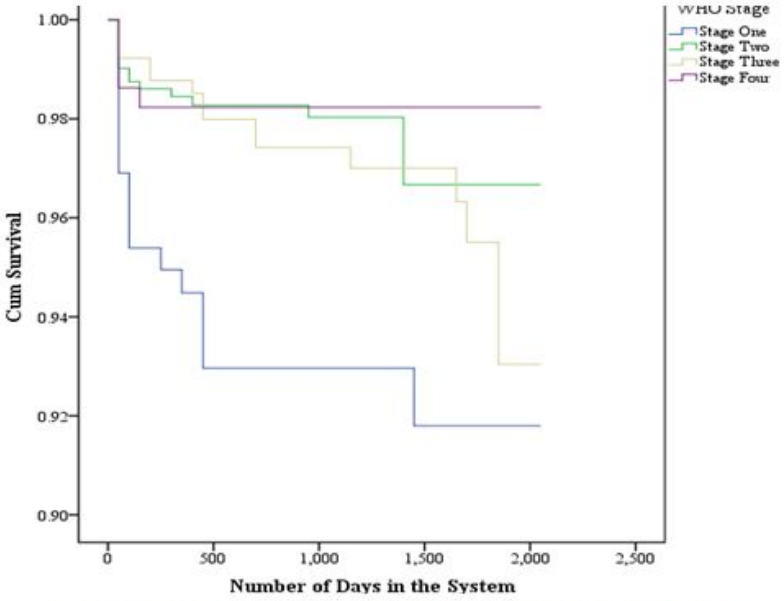

Figure 4.8 Survival Curve based on WHO Stage

Figure 4.8 shows that patients in WHO (World Health Organization) stage one recorded more deaths. The curves clearly show that most deaths occur in the first year. Patients in WHO stage four have higher probability of survival.

- **Means for Survival Times**

The estimated time until death for the subjects at the factor categories in this study are summarized in Table 4.1 below

Table 4.1 Means, Standard Errors and 95% Confidence Intervals for Survival Time (days) at various Factor Categories

Factor	Level	Mean			
		Estimate	Std Error	95% Confidence Interval	
				Lower	Upper
Gender	Male	2106.433	13.664	2079.651	2133.215
	Female	2343.700	14.473	2315.332	2372.067
Marital Status	Single	2108.510	18.872	2071.521	2145.500
	Married	2104.937	13.021	2079.416	2130.457
	Divorced	2370.846	26.202	2319.491	2422.201
	Widowed	2128.611	25.425	2078.778	2178.443
	Separated	1993.609	78.624	1839.505	2147.712
WHO Stage	Stage 1	2022.477	33.641	1956.540	2088.415
	Stage 2	2371.708	13.607	2345.037	2398.378
	Stage 3	2104.381	16.819	2071.415	2137.346
	Stage 4	2148.913	16.904	2115.782	2182.045
ARTS Entry	Yes	2363.341	10.003	2343.735	2382.947
	No	1435.119	166.045	1109.670	1760.568
CD 4 Count	≥ 200	2327.787	15.155	2298.083	2357.490
	< 200	2147.354	11.270	2125.266	2169.443
Weight	20 - 34 kg	1785.116	119.894	1550.124	2020.109
	35 - 44 kg	2054.702	36.732	1982.708	2126.696
	45 - 54 kg	2104.509	17.657	2069.901	2139.118
	≥ 55 kg	2371.254	11.401	2348.909	2393.600

From Table 4.1, it is observed that the mean time to death is higher in female (2343.7 days) than in males (2106.4 days) for the factor gender. For the factor marital status, the mean time to death is

higher (2370.8 days) for the divorced and lower (1993.6 days) for the separated. For World Health Organization Stages, those in stage 2 have higher mean time to death (2371.7 days) while those in stage 1 has the lowest mean time to death (2022.5 days). Those who are under ART have higher mean time to death of 2363.3 days while those that are not under ART have lower mean time to death of 1435.1 days. Patients with CD4 count ≥ 200 have higher mean time to death (2327.8 days) while those with CD4 Count < 200 have lower mean time to death (2147.4 days). Patients in the weight category of 50 – 74 kg have higher mean time to death (2357.9 days), while those in the weight category of 25 – 49 kg have lower mean time to death. In the age category and number of medication category, the mean times to death were not computed because no event (death) was observed in the above 59 years and 50 – 74 and ≥ 75 categories, respectively. The probab ility of survival in these categories is 1.

- **Log-Rank Test**

The Log Rank test was employed to tests the hypothesis that there is no significant difference in survival times between the factor categories at all time points in the study. The test results for all factor categories in this study are summarized in Table 4.2 below.

Table 4.2 Log Rank (Mantel-Cox) Test of Difference in Survival Times

Factor	Chi-Square value	Degrees of Freedom	p-value (sig.)	Remark
Gender	.119	1	.730	DNR
Marital Status	3.626	4	.459	DNR
WHO Stage	18.790	3	.000	Reject
ARTs Entry	128.151	1	.000	Reject
CD4 Count	6.061	1	.014	Reject
Weight	16.592	3	.001	Reject
Number of Medication	103.526	3	.000	Reject
Age	5.019	3	.170	DNR

1. From Table 4.2, it could be seen that significant differences do not exist among the categories of the factors gender, marital status and age since their p-values (0.730, 0.459 and 0.245, respectively) are greater than the standard level of significance of 0.05. On the other hand, significant differences are seen to exist among the categories of factors WHO Stage, ARTs entry, CD4 Count, weight and number of medication with p-values 0.000 (< 0.001), 0.000 (< 0.001), 0.014, 0.001 and 0.000 (< 0.001), respectively.
2. **Hazard Functions**

   One feature of the Kaplan-Meier procedure is the hazard function. The hazard plot presents the risk of reaching the endpoint (death). In this study, hazard plots are presented for the various factor categories considered.

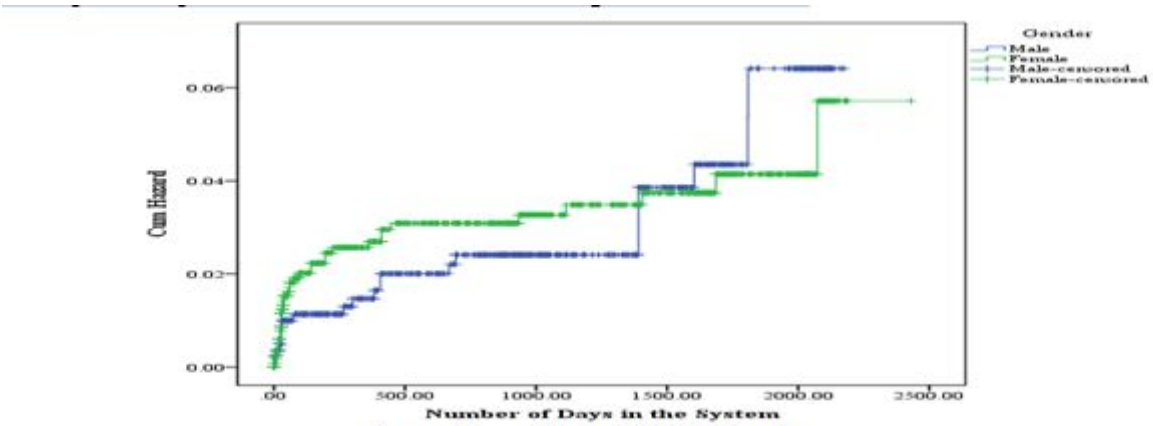

Figure 4.9 Hazard Plot for Gender

- From Figure 4.9, it can be observed that the risk of dying does not differ with gender. The risk is higher in males than in females in the first year but reduces in both sexes as time increases.

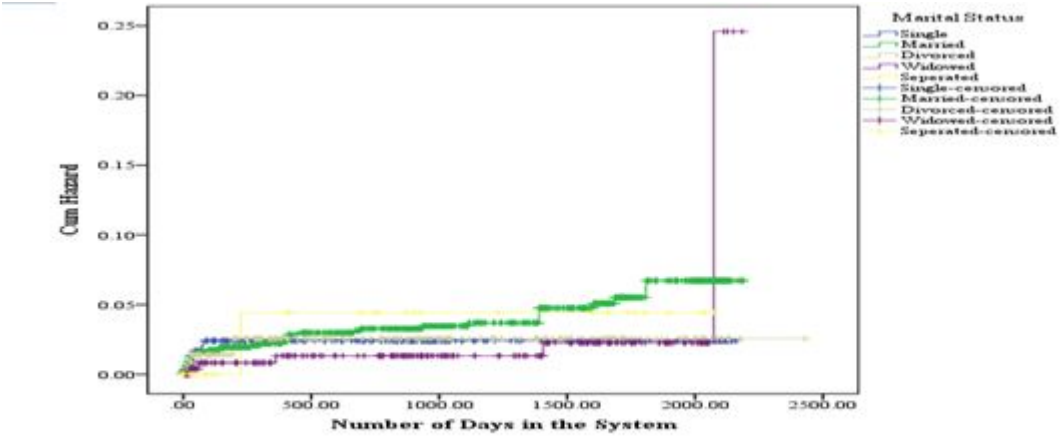

Figure 4.10 Hazard Plot for Marital Status

- In Figure 4.10, it is observed that the risk of dying increases with time for all categories of the marital status, though it is higher among the married.

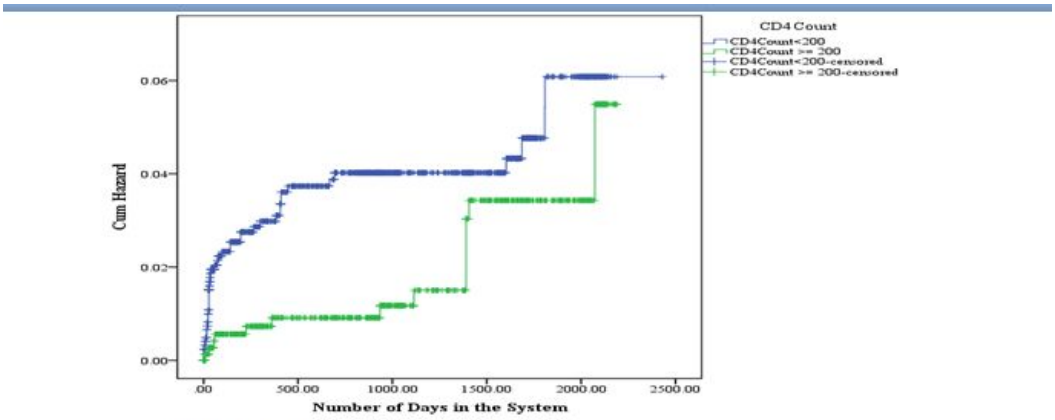

Figure 4.11 Hazard Plot for CD4 Count

- In Figure 4.11, the risk of dying is high for patients with CD4 count < 200.

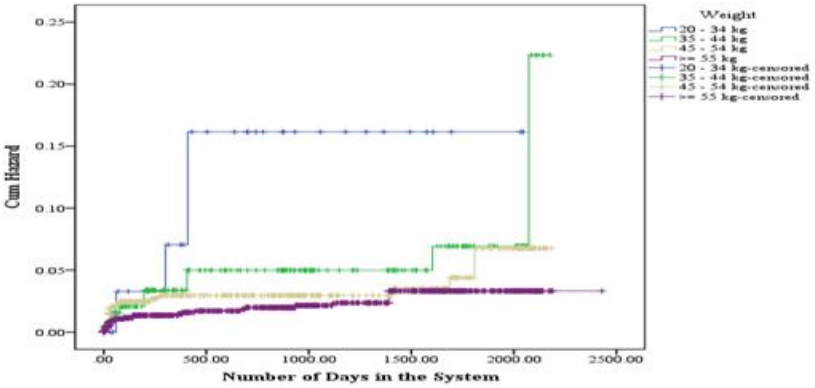

Figure 4.12 Hazard Plot for Weight

- In Figure 4.12, the risk of dying is higher for patients of weight less than 34 kg, followed by patients of weight 35 – 44 kg.

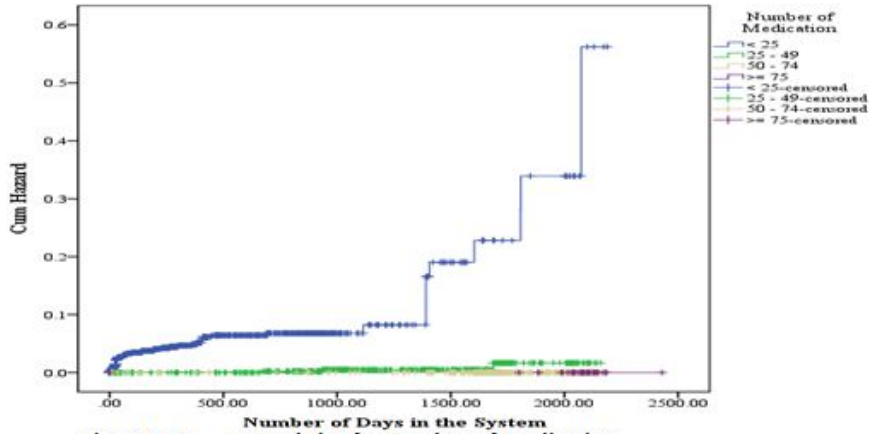

Figure4.13 Hazard Plot for Number of Medication

1. In Figure4. 13, the risk of dying is higher for patients who have taken less than 25 times the number of medications. No risk is observed for patients who have taken 50 or more number of medications.

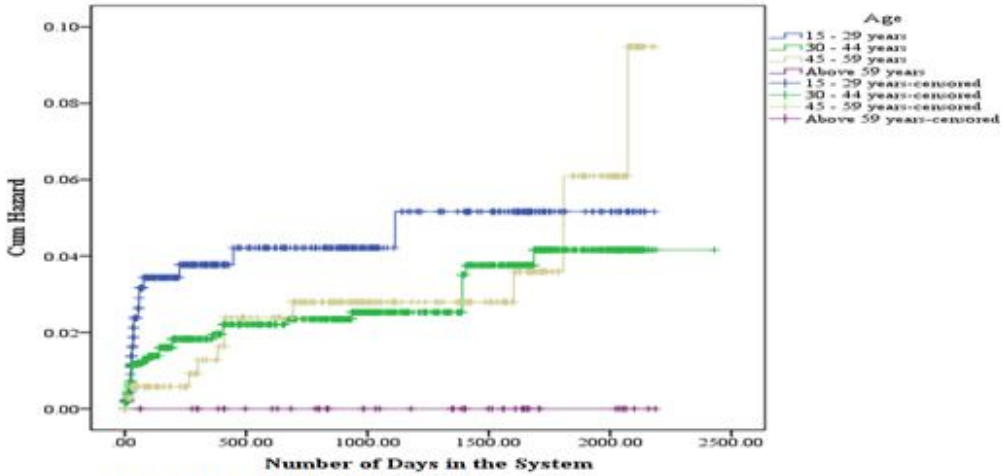

Figure 4.14 Hazard Plot for Age

2. It is clear from the plot that the risk of dying is higher in the age category of 15 – 29 years and 30 – 44 years in the early years in the study. The risk in the age interval 45 – 59 years becomes higher after four and half years. However, no risk is observed in the age 60 years and above.

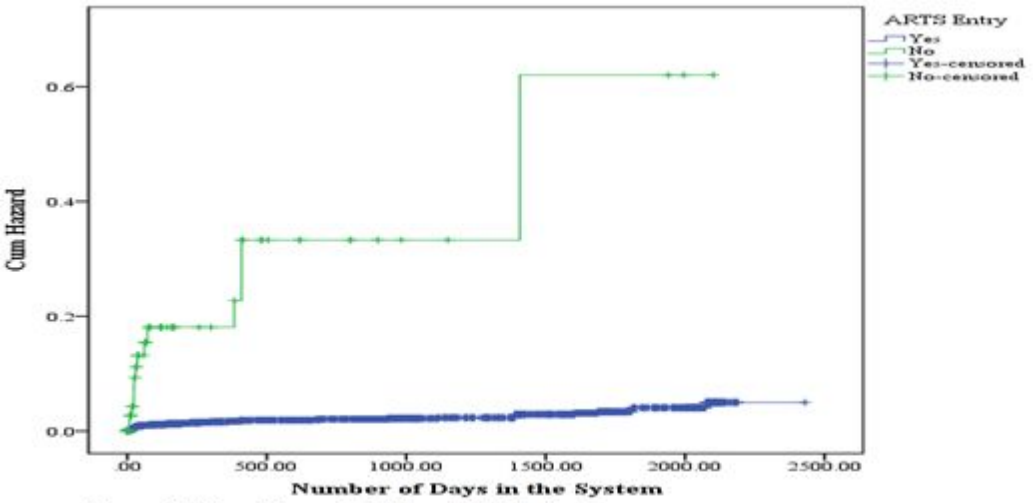

Figure 4.15 Hazard Plot for ARTS Entry

3. It is clear from Figure 4.15 that the risk of dying is higher among patients who do not take ART.

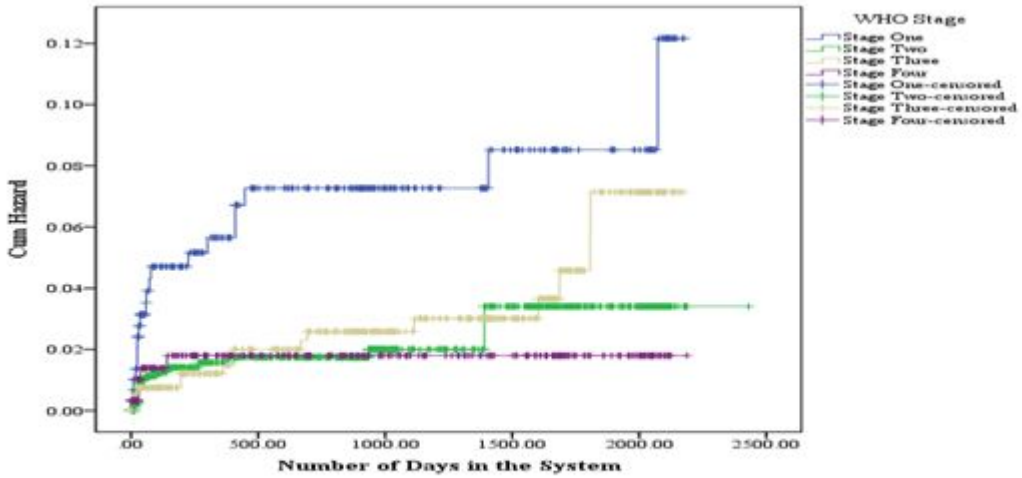

Figure 4.16 Hazard Plot for ARTS Entry

- In Figure 4.16, it is clear that those in the WHO Stage 1 have higher risk of dying, followed by those in stage 3, then those in stage 2. Those in stage 4 have lower risk of dying.
- **Cox's Regression**
- The Cox's Regression procedure is useful for modelling the time to a specified event, based upon the values of given covariates. The central statistical output is the hazard ratio. In this study, the covariates that are useful in predicting the event are gender, marital status, WHO Stage, ARTS Entry, CD4 Count, Weight, Number of Medication and Age. The results are given in Table 4.3 below

Table 4.3 Estimates of Variables in Cox's Regression

	B	SE	Wald	Df	p-value	Exp(β)	95% CI for Exp(β)	
							Lower	Upper
Gender	.026	.298	.007	1	.931	1.026	.572	1.840
M Status (1)	-.579	1.089	.283	1	.595	.560	.066	4.739
M Status (2)	.106	1.029	.011	1	.918	1.112	.148	8.350
M Status (3)	-.341	1.117	.093	1	.760	.711	.080	6.345
M Status(4)	-.339	1.111	.093	1	.761	.713	.081	6.289
WHO Stage (1)	.773	.538	2.065	1	.151	2.167	.755	6.221
WHO Stage (2)	.232	.515	.203	1	.653	1.261	.460	3.460
WHO Stage (3)	.491	.521	.886	1	.346	1.633	.588	4.537
ARTS Entry	-1.887	.367	26.368	1	.000	.152	.074	.311
CD4 Count	1.051	.331	10.058	1	.002	2.861	1.494	5.479
Num Med (1)	11.148	65.105	.029	1	.864	69396.828	.000	1.814E+060
Num Med (2)	7.986	65.107	.015	1	.902	2938.794	.000	7.710E+058
Num Med (3)	1.434	66.086	.000	1	.983	4.197	.000	7.512E+056
Age (1)	7.459	20.736	.129	1	.719	1735.596	.000	776937.000
Age (2)	7.157	20.735	.119	1	.730	1282.807	.000	572668.000
Age (3)	7.174	20.736	.120	1	.729	1304.758	.000	583202.000
Weight (1)	.550	.605	.826	1	.363	1.734	529	5.679
Weight (2)	.484	.382	1.606	1	.205	1.622	.768	3.427
Weight (3)	.301	.314	.920	1	.337	1.351	.731	2.497

- Using Cox' regression to test hypothesis that H_0 = There is no evidence of a greater risk of death between variables at different levels and the reference category and H_i = There is evidence of a greater risk of death between variables at different level and the reference category. Comparing the result with standard significance level of 0.05, the study revealed that for gender, marital, WHO clinical stages, number of medication, age and weight at different level have p-values greater than the standard level of significance of 0.05. This means that we accept Ho and conclude that there is no evidence of a greater risk of death between variables at different level and the reference category. While for CD4 count and

ARTs their p-values is less than the standard level of significance of 0.05, therefore we rejects H_0 and conclude that there is evidence of a significant difference between the different level of response or accept H_i. The Exp(β) value is 2.861 which means that the risk of death in patients with CD4 count less than 200 is 2.861 times those patients with CD4 count greater than 200 and the Exp(β) value is 0.152 which means that the risk of patients on ARTs is 0.152 times those not on ARTs respectively.

SUMMARY

- A total of 2021 patients were included for this study, comprising 1186 females (58.7%) and 835 males (41.3%). Total of 59 (2.9%) patients were reported dead within the period of study while 1962 (97.1%) were censored. The study revealed that the greatest number of deaths took place in the first 1 year of admission/follow up of patients and after initiation of ART treatments, it was also observed that the proportion of patients surviving is high (> 90%) and was increases with time. From among the variable included in the study, female HIV-positive patients had short survival time to live compare to male with majority of deaths occurs among the married people most especial those with CD4 count less than 200, weight less than 45 kg, taken less than 25 medications, sexually active age between 15-44years and WHO clinical stage one.

RECOMMENDATIONS

- Free antiretroviral treatment will significantly improve the survival of HIV/AIDS patients. A lower level of mortality was detected among the patients on antiretroviral treatment in UMTH.
- Earlier initiation of antiretroviral treatment is likely to have achieved better survival effects.

- Provision of nutritional support and strengthening of the food by prescription initiative and counselling of patients for early presentation to treatment is recommended.

Contribution to the Knowledge

- The study revealed a higher mortality in WHO stage one contrary to other studies that reveal higher mortality in among other stages; this could be due to concomitant diseases or side effects of initiation of the drugs, depressive illnesses of knowing they are HIV positive or due to non adherence to medication.

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