Scientia Africana, Vol. 11 (No.1), June 2012. pp 14-24
 ISSN 1118 – 1931

SURVIVAL ANALYSIS OF MORTALITY DATA AMONG ELDERLY PATIENTS IN UNIVERSITY OF ILORIN TEACHING HOSPITAL ILORIN, NIGERIA.

A. A. Abiodun
Department of Statistics,
University of Ilorin, Nigeria.
E-mail: manfredwole@yahoo.com
GSM: 08068642680

Received: 02-02-12
Accepted: 21-04-12

ABSTRACT
A study on the mortality among old patients 60 years or more, admitted at University of Ilorin Teaching Hospital (UITH), Ilorin was carried out using survival analysis approach. Results revealed that the median survival time, which is the time beyond which half of the patients are expected to stay in hospital before death was higher for male patients than female patients. This was also found to be higher for the patients of age less than 70 years than those who are 70 years or more. It was found that interaction effects of age and gender of patients was significant. Older female patients were more likely to die earlier than their older male counterparts. Results of Akaike Information Criterion (AIC) revealed that models with interactions provided better fits than those without interaction. Models stratified on variable weekdays on which proportional hazards assumption was violated were found to have improved model fits than those that ignored stratification. Cox models were observed to outperform the Weibull models in all the models specified in the study.

***Key Words**: Survival analysis, Cox Model, Weibull model, interaction, stratified model.*

INTRODUCTION
Death is a definite and unique event, its records should be complete and accurate. However, in many countries in Africa particularly Nigeria, there is lack of statistics on birth and deaths due to unwillingness of the people to register this vital information while reliable in-hospital mortality data are scanty (Mandong and Madaki, 2002; Garko *et al*.,2003). Nevertheless, while many health cares and health system interventions are intended to save lives and improve quality of life, even with the best possible care, many deaths are not preventable. Many descriptive studies have been carried out on mortality mostly with more emphasis on the mortality rates. For example, Sanya *et al* (2011) reported the crude mortality rate of 22.4% in their analysis of data on death among old patients admitted at University of Ilorin Teaching Hospital (UITH) over 30 months period. Some international surveys have however reported lower mortality rates in various studies. For example, Lamont *et al* (1983) reported mortality rate of 20% from USA, Silva *et al (2009)* documented mortality rate of 16.4% in Brazil and Shoko *et al* (13) from Japan reported 17.7% morality rate amongst older patients. Analysis that focuses more attention on the length of hospitalization before death especially among elderly patients is also of great necessity which needs to be examined and this has motivated this study. The study therefore examines in-hospital mortality data among elderly patients using a Nigeria Teaching Hospital as a case study, with the hope to examine the time of hospitalization before

death in relation to some baseline characteristics of the patients as covered in the study.

Data on time to event (death in this study) is often analyzed using survival analysis methodology. One interesting aspect of survival analysis is investigating the relationship between the distribution of the response variable (time) and some related background characteristics or covariates that can possibly influence the survival experiences of subjects under investigation. For example in cancer study it may be of interest to investigate the relationship between the time to re-emergence of tumor after operation and a set of covariates such as age, gender and occupation of patients. In modeling survival time data, standard regression approach based on Ordinary Least Squares (OLS) is not often used because the data do not satisfy normality assumption required due to its skewed nature. One popular model in survival analysis is the Proportional Hazards (PH) model. For this model to be appropriate, it must satisfy the proportional hazards assumption which requires that the hazard ratio comparing any two specifications of predictors be constant over time. Proportional hazards assumption can be tested by plotting the graph of lo(-log(S(t))) against log(t) for the grouped predictors. The PH assumption is not met if the graphs cross for two or more categories of a predictor of interest. One way of handling such situation is to use stratified proportional hazard model.

This paper therefore analyses data collected on in-hospital patients aged 60 years and above using Parametric and Semiparametric Proportional Hazards (PH) models.

MATERIALS AND METHODS

Three mathematically equivalent functions are often used to characterise the non-negative continuous random variable T, denoting survival time which is the time *t*, that corresponds to the interval between a well-defined start-time t_0 and the time t_c of occurrence of some particular events. The first function is the density function f(*t*), which expresses the unconditional probability of a failure event occurring in interval (*t*, *t* +*Δt*) and it is given by

$$f(t) = \lim_{\Delta t \to 0} \Pr\left\{\frac{t \le T < t + \Delta t}{\Delta t}\right\}.$$

(1)

The second distribution is the survival function *S* (*t*), which is defined as the probability of surviving beyond some specified time *t* and is given by

$$S(t) = \Pr(T \ge t).$$

(2)

The third is the hazard function $\lambda(t)$, which is the conditional probability of experiencing the event in the small interval (*t*, *t* +*Δt*), given that such an event has not been experienced prior to *t* (i.e survived up to time t). This is expressed as

$$\lambda(t) = \lim_{\Delta t \to 0} \Pr\left\{\frac{t \le T < t + \Delta t | T \ge t}{\Delta t}\right\}.$$

(3)

The functions defined above are related to one another as

$$S(t) = \exp(-\int_0^t \lambda(u)du)$$

$$\lambda(t) = \frac{f(t)}{S(t)}$$

$$f(t) = \lambda(t)S(t)$$

Weibull distribution

The simplest distribution in survival studies is the exponential distribution (Lee et al, 2003). However it is less used in analysis because it is characterized by constant hazard whereas in real life situation, the baseline hazard is either increasing or decreasing over time in which case exponential distribution may not be appropriate. Weibull distribution is one distribution that is more commonly used instead. The density function *f*(*t*), survival function *S*(*t*) and the hazard function $\lambda(t)$ for Weibull distribution

Scientia Africana, Vol. 11 (No.1), June 2012. pp 14-24
© Faculty of Science, University of Port Harcourt, Printed in Nigeria ISSN 1118 – 1931

with shape parameter α and scale parameter λ are respectively given as

$$f(t) = \lambda\alpha(\lambda t)^{\alpha-1}\exp(-(\lambda t)^{\alpha}), \quad (4)$$

$$S(t) = \exp(-(\lambda t)^{\alpha})$$

and

$$\lambda(t) = \lambda\alpha(\lambda t)^{\alpha-1}$$

Proportional Hazards Model

The general form of Proportional hazards model for examining the relationship of survival distribution (hazard) with sets of covariates is given as

$$\lambda(t|Z_i) = \lambda_o(t)\exp(\gamma^{/} Z_i),$$

(5)

where $\lambda_o(t)$ is the baseline hazard, Z_i is a vector of covariates and γ is a vector of regression coefficients. When $\lambda_o(t)$ takes the form specified in (4) we have parametric proportional hazard model with Weibull baseline hazard. When no assumption is made about $\lambda_o(t)$ then the model in (5) will be called Cox proportional hazard model (Cox, 1972). It is a semiparametric model in the sense that though it makes no assumption about the baseline hazard $\lambda_o(t)$, it assumes parametric form for the effect of the covariates on the hazards.

Stratified Model

Simpson (1951) submitted that it is possible for the aggregated data to suggest that an effect of covariate is favorable when in fact, in every subgroup, it is highly unfavorable; and vice versa. It may therefore become necessary to stratify on such covariates. This is one method through which possible confounding covariates/interaction effect can be accounted for in the analysis. Stratification can provide us with stronger (or weaker) evidence, or more importantly, reverse the sign of the effect.

Suppose that there is a variable X_1 which has *M* levels (1,...,*M*), then (5) stratified by X_1 can be given by

$$\lambda(t|Z_i) = \lambda_{oj}(t)\exp(\gamma^{/} Z_i), j=1,\ldots,M \quad (6)$$

The model in (6) adjusts for X_1 without estimating its effects. Though the hazard functions for two different strata do not have to be proportional to one another in the combined data, proportional hazards are assumed to hold within a stratum.

Model Comparison

Often, there is tendency for two models to present similar parameter estimates whereas they may not be equally adequate for the data under study. In such a situation there is need for a statistical tool to compare such models. One such tool is Akaike Information Criterion (AIC) statistic which is expressed as

AIC = -2(log-likelihood) + $k \times p$,

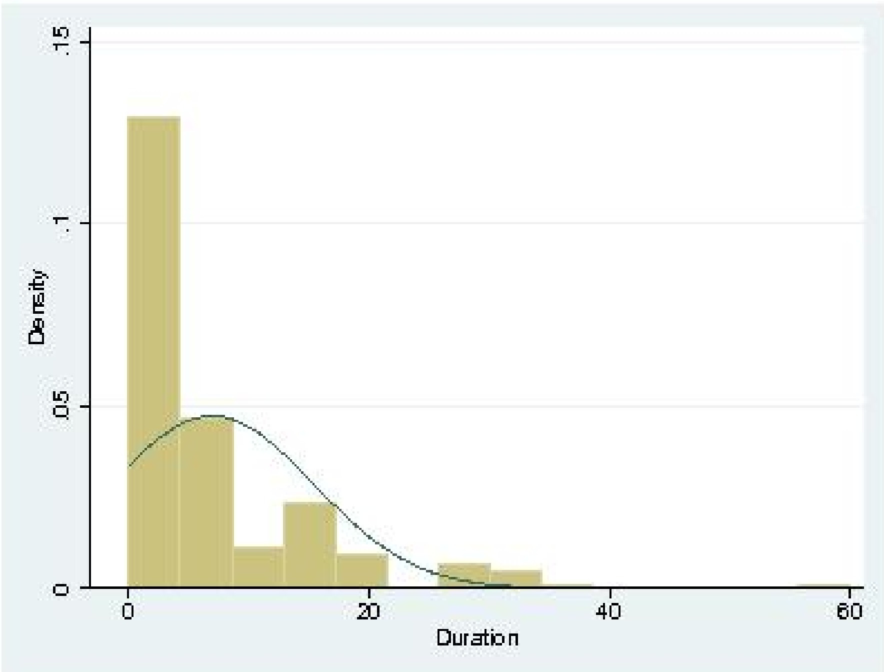
where k is the number of covariates in the specified model and p is the number of model-specific ancillary parameters. The value of p equals 2 for the three models used in this study (that is Weibull, Log-logistic and Log-normal). The smaller the value of AIC, the better the model.

The aim of this study is to investigate the relationship between duration of hospitalization before deaths and independent variables age and gender of patients. The specific interest is to examine such relationship under stratified and unstratified model frameworks and to investigate the comparative performances of Cox Proportional hazards (Semiparametric) and Weibull proportional hazards (parametric) survival models.

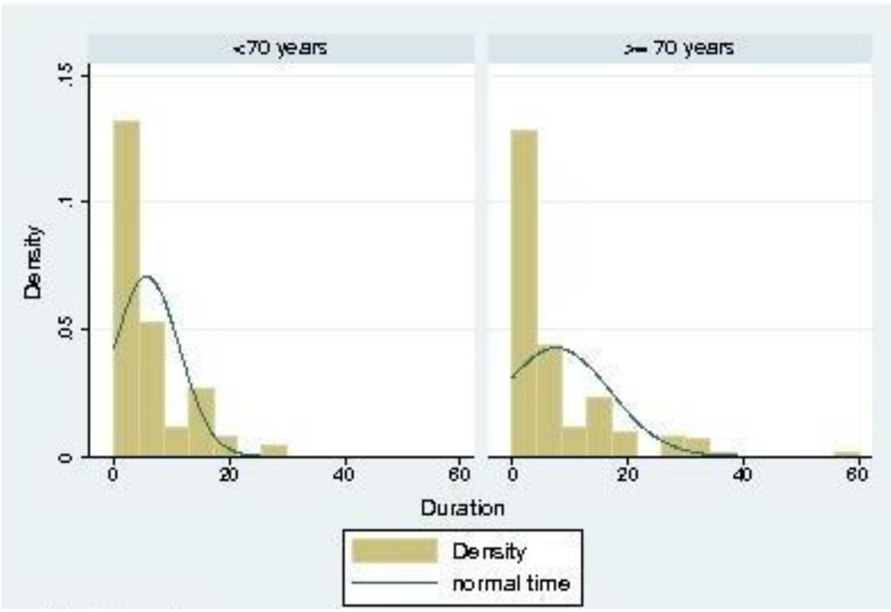
Data Analysis

This study involves elderly patients managed at University of Ilorin Teaching Hospital (UITH), Nigeria from January 2004 to July 2006. The data had earlier been analyzed by Sanya *et al* (2011). The study determines patterns and causes of mortality among patients 60 years and above. The current study utilizes duration of hospitalization before death as the response variable and explores this in relation to some factors that possibly influence mortality among these patients.

(a) Overall duration of hospitalization



(b) Duration of hospitalization by age



Scientia Africana, Vol. 11 (No.1), June 2012. pp 14-24
© Faculty of Science, University of Port Harcourt, Printed in Nigeria *ISSN 1118 – 1931*

(c) Duration of hospitalization by gender

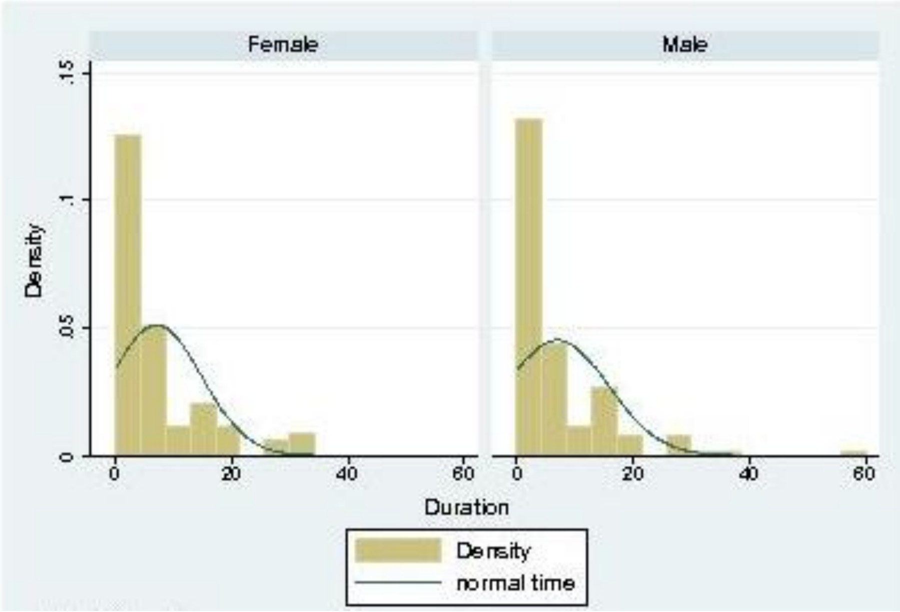
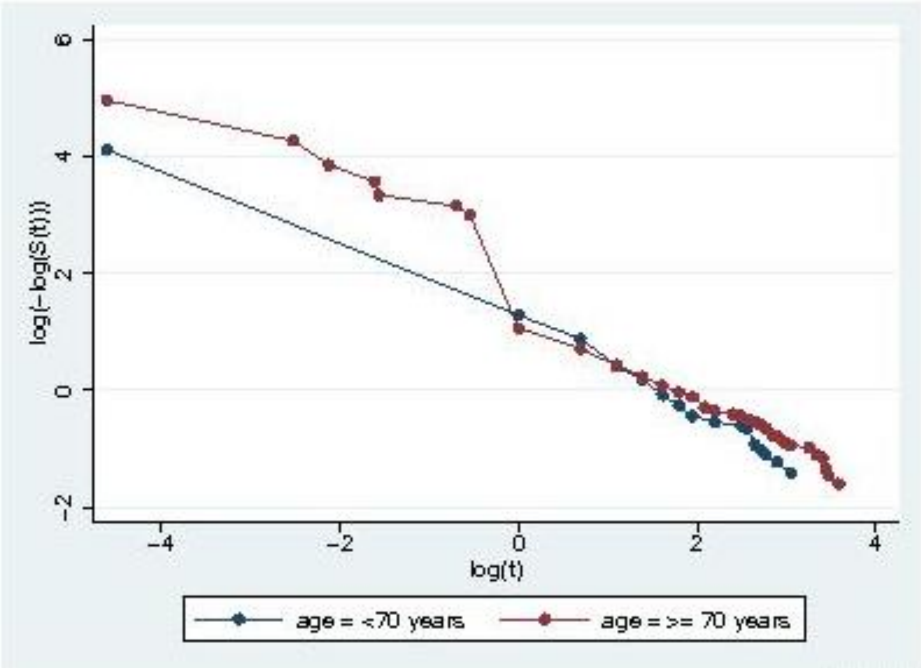


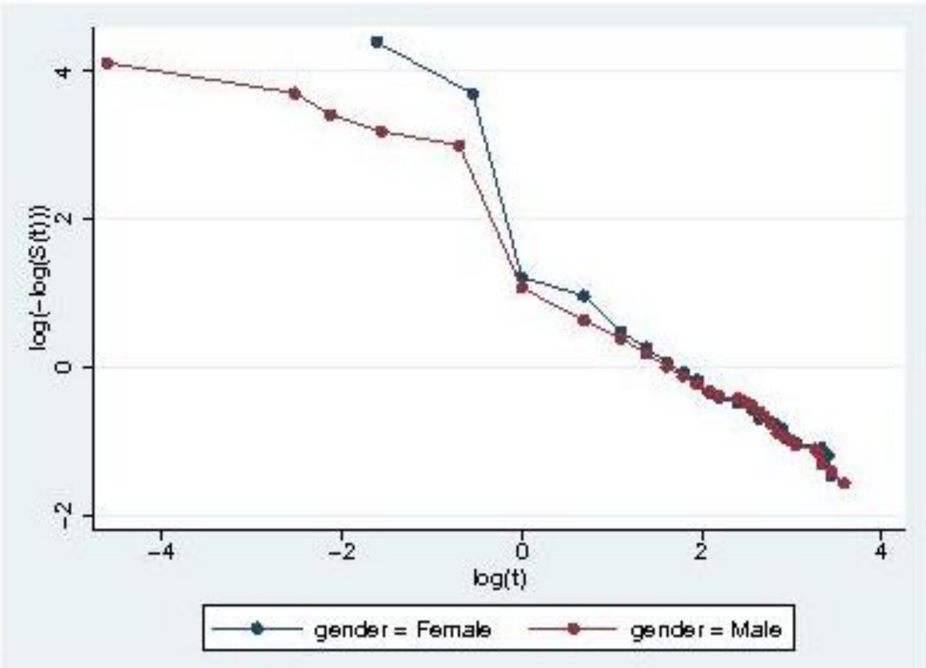
Figure 1: Duration of hospitalization in days (a) overall, (b) by age (c) by gender

Information was collected on patient's duration of hospitalization before death. None of the patients involved in this study was censored (that is all the patients experienced event of death) during the period under investigation. Explanatory information were also collected on patients age and gender and other covariates including week day, diagnosis, and some laboratory results which were thought to be capable of influencing the mortality of patients as covered by this study. All brought-in-deaths were excluded in the study. After thorough data screening, 206 subjects were included in the analysis. The explanatory included in the study are age, gender and weekday. To meet the objectives of the study, the seven days of the week has been re-categorized in two forms, first it is categorized into "week" and "weekend" and called week-dichotomized. Secondly, it is categorized into three: "early week", "midweek" and "weekend" and called week-categorical. Age is dichotomized at the median value into "less than 70 years" and "70 years and above".

(a) PH test for age

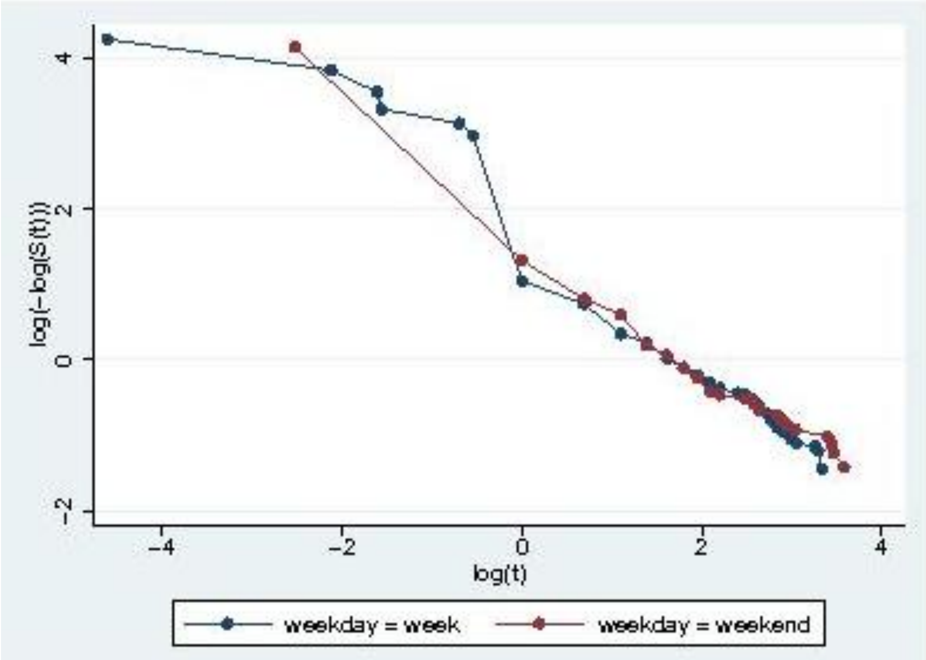


(b) PH test for gender



Scientia Africana, Vol. 11 (No.1), June 2012. pp 14-24
© Faculty of Science, University of Port Harcourt, Printed in Nigeria *ISSN 1118 – 1931*

c) PH test for week-dichotomized



(d) PH test for week-categorical

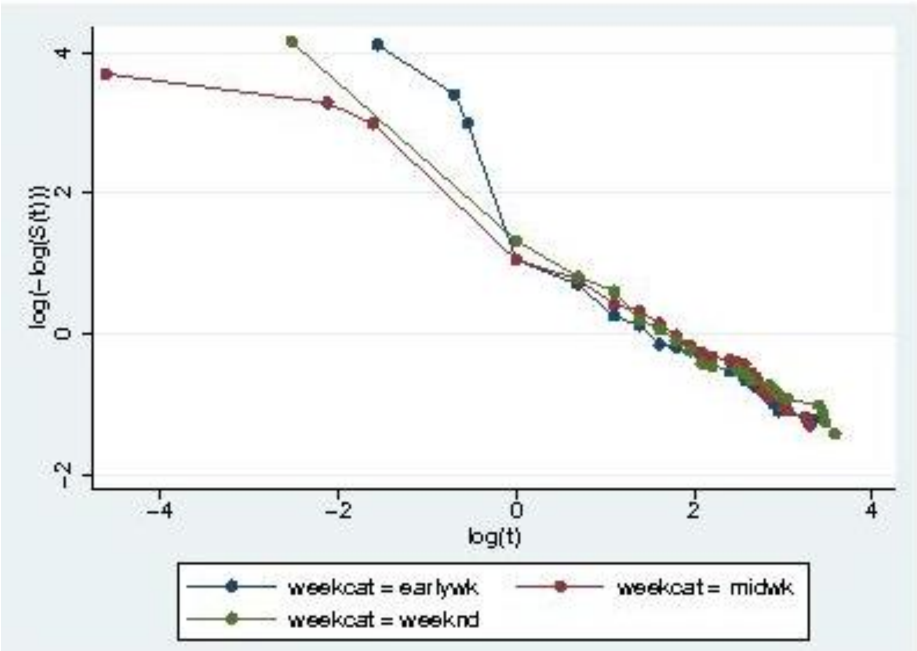


Figure 2: Graphical test of Proportional Hazards (PH) assumption

The density plots of the duration of hospitalization before death, interpolated on the histogram are shown in Figure 1 (a-c), for overall data and also by age and gender of the patients. It is observed that in all the plots, the higher proportion of patients stay for shorter time in the hospital before experiencing the event of death, and this reduces with increasing length of stay in the hospital before death. However all the plots show right skewness, which is an indication that analyses based on normality assumption will be inappropriate for the data.

Figure 2(a-e) show the plots of lo(-log(S(t))) against log(t) to check the PH assumption for the categorical variables and it is observed that the assumption is violated for week-dichotomized and week-categorical as the lines of the graphs are seen to cross one another. We have therefore stratified on these variables.

The median survival time which is a better measure of central tendency for skewed data than arithmetic mean has been computed at the exploratory stage for the combined data and also by age and gender. The estimated median survival time is the value of $t(50)$ at which $\hat{S}(t(50)) = 0.5$ and this gives the time beyond which 50% of the individuals under study are expected to survive or equivalently, the time within which 50% of the patients are expected to die. The parametric (Weibull) proportion hazards model and the Semiparametric (Cox) proportional models are also fitted to investigate the relationship between duration of hospitalization and predictors age and gender with and without interactions and under stratified and unstratified model frameworks. Due to the violation of proportional hazards assumptions by certain covariate (week day), models were stratified on such covariate based on two stratification schemes, that is week dichotomized and week categorical. Incorporation of these two schemes separately was to adjust for variations due to the period of the weeks with respect to the mortality of patients. It can ordinarily be conjectured that patients die more on weekends when only skeletal services are rendered by medical personnel as against during the week when full services are usually rendered.

RESULTS

The overall median survival time for the combined data shows that 50% of the patients survived beyond 5.0±2.8 days. For female patients, the median survival time is 4.9±1.2 days while it is 5.2±3.1 for the male patients. 50% of patients less than age 70 years died within 5.6±2.3 days while for those who are 70 years and above, 50% of them died within 4.7±3.4 days.

Table 1 shows the values of Hazard Ratios along with the P-values for the covariates age and gender as reported by the Weibull PH model and Cox PH model. Variables are identified as significant using 0.05 significances level. In both models, age of the patients show a statistically significant association with duration of hospitalization before death. As it is observed under the Weibull PH model, controlling for gender, the hazard ratio is 0.815 (P=0.042) for patients aged less than 70 years compared to patients who are 70 years or more. This means that the risk of death.

Scientia Africana, Vol. 11 (No.1), June 2012. pp 14-24
© Faculty of Science, University of Port Harcourt, Printed in Nigeria *ISSN 1118 – 1931*

Table 1: Hazard Ratio (HR) and P-values for Weibull PH model and Cox PH Model with and without interaction term

Model Specification	Variable	Weibull Proportional Hazards Model HR (P-value)	Cox Proportional Hazards Model HR(P-value)
Unstratified and no interaction	**Age**		
	< 70 years	0.815 (0.042)	0.810 (0.037)
	> 70 years	1	1
	Gender		
	Male	0.969(0.094)	0.962(0.110)
	Female	1	1
Unstratified plus interaction	**Age**		
	< 70 years	0.834 (0.037)	0.828(0.021)
	> 70 years	1	1
	Gender		
	Male	0.711 (0.046)	0.698(0.051)
	Female	1	1
	Age _Gender	0.675 (0.048)	0.658(0.054)
Week-dichotomized plus interaction	**Age**		
	< 70 years	0.820 (0.039)	0.787 (0.024)
	> 70 years	1	1
	Gender		
	Male	0.724 (0.040)	0.702 (0.035)
	Female	1	1
	Age_Gender	0.820 (0.006)	0.786 (0.002)
Week-categorical plus interaction	**Age**		
	< 70years	1	1
	> years	0.827(0.045)	0.801 (0.031)
	Gender		
	Male	0.749 (0.046)	0.822 (0.040)
	Female	1	1
	Age_Gender	0.862 (0.019)	0.791(0.007)

For patients below 70 years of age is about 18 % less than for patients 70 years or more. The results is similar under Cox PH model, the hazard ratio is 0.810 (P=0.037) for patients below 70 years (21% less) compared to those 70 years or more. The difference is statistically significant under both models. There is no evidence of significant difference between the risk of death between males and females when age is held constant. As observed, the hazard ratio for male patients is 0.969 (0.094) and 0.962(0.110) under Weibull PH model and Cox PH model respectively, when compared to their female counterparts.

After including interaction term of age and gender in the unstratified models, both the main effects as well as the interaction effects of age and gender become significant. As seen, the hazard ratio is 0.675 (0.048) for age–gender interaction under Weibull PH model, indicating that there is a higher risk of death for female patients aged 70 and above than for the men in the same age group. This finding is similar under Cox PH model with hazard ratio of 0.658 (0.054). It is observed that the main effect of gender which is not significant when there is no interaction term included, becomes significant under this setting. Interaction effect of age gender is found to be highly significant when models are stratified. As observed, when stratified by week dichotomized, Weibull PH model and Cox PH model have P-values 0.006 and 0.002 respectively, and these are 0.019 and 0.007 respectively, when stratified by week categorical. However these do not have proportionate effects on the main effects of age and gender in the models with interaction term. For example, the hazard ratios of main effects of age and gender are not too different from the unstratified models under both Weibull and Cox models. Form of stratification (whether week dichotomized or week categorical) does not appear to have different influence on the risk of death on the patients. Table 2 shows the results of AIC to compare the various models reported above. It is generally observed that Cox (Semiparametric) models generally presents lower AIC than Weibull (Parametric) models across all the model specifications. Also the values of AIC for all models that include interaction of age and gender are less than those without the inclusion of interaction under both Weibull and Cox models.

Table 2: Akaike Information Criterion (AIC) for the models

Model Specification	AIC	
	Weibull PH Model	Cox PH Model
No interaction and unstratified	690.1	685.8
Interaction and unstratified	677.4	673.7
Interaction and stratified by week_dichotomised	669.5	666.3
Interaction and stratified by week_categorical	668.9	665.8

For example when the model is not stratified, AIC for model with interaction term under Weibull model is 677.7 compared with 690.1 when interaction term is not included whereas these values are 673.7 and 685.8 respectively under Cox model. Comparing model with interaction under stratified and unstratified setting, it is observed that the stratified models (by week dichotomized and week categorical) each performs better than unstratified model. However, no obvious difference between the values of AIC between models with the two stratification schemes week dichotomized and week categorical.

DISCUSSION

This study was carried out on the mortality among old patients, who are 60 years or more, admitted at University of Ilorin Teaching Hospital (UITH). Survival analysis approach was employed where duration of hospitalization before death was the response variable. The data did not contain censored observation since all patients covered by the study were dead. Median survival time was used to describe the average survival experiences for the combined patients and also by some baseline characteristics of the patients including age and gender. Weibull and Cox models, within the Proportional hazards framework were used to investigate the relationship between duration of hospitalization before death and certain variables thought to be influential factors. It was found that the median survival time (the time beyond which half of the patients are expected to survive) was higher for male patients than female patients. It was also found to be higher for the patients less than 70 years than those who are 70 years or more. Inclusion of interaction of age and gender was observed to have significant effects on the duration of hospitalization before death. It was found that older female patients were more likely to die earlier than their older male counterparts. It was

Scientia Africana, Vol. 11 (No.1), June 2012. pp 14-24
© Faculty of Science, University of Port Harcourt, Printed in Nigeria *ISSN 1118 – 1931*

also observed from model diagnostic using Akaike Information Criterion (AIC) that models with interactions actually provided better fits than those without interaction terms. Stratifying models using week dichotomized and week categorical stratification schemes was found to improve the models. However, form of stratification did not appear to affect the models differently. One interest of this study was to investigate the comparative performance of Cox (Semiparametric) and Weibull (parametric) survival models with respect to the hospital data under study. Currently, parametric models are not often used in the analysis of medical survival data studies. Applied statisticians seem to be concerned about the required assumptions on the baseline distribution and the assumed efforts in arriving at appropriate models. Cox model has been known to be more efficient than the parametric model analysis in such situations (Harrel, 2001). In this study, Cox models were observed to outperform the Weibull models in all the specifications which are in line with Harrel's submission.

REFERENCES

Alessandra N, A. Schemper, M. (2003). Comparing Cox and Parametric Models in Clinical Studies. S*tatistics in Medicine* **22**, 3597-3610. Published in John Wiley & Sons, Ltd.

Cox D.R (1972). Regression models and Life-tables (with discussion). *J. Roy. Statist. Soc. Ser. B. 34, 187-220.*

Garko, S.B., Ekweani, C.Nand Anyiam, C.A (2003). Duration of hospital stay and mortality in the medical wards in Ahmadu Bello University teaching hospital, Kaduna. Ann Afr Med. 2:68-71.

Harrel, E.H(2001). Regression Modelling strategies (With Applications to Linear Models, Logistic Regression and Survival Analysis). *Springer-Verlag New York*, Inc.

Lamont, C.T., Sampson, S., Matthias, R. and Kane, R. (1983). The outcome of mortality of hospitalization for acute illness in the elderly. *J. Am. Geriatr. Soc.* 31:282-8.

Lee, E.T. and Wang, J.W. (2003). Statistical Methods for survival Survival Data Analysis.
3rd Edition, John Wiley & Sons, Inc., Hoboken, New Jersey.

Mandong, B.M and Madaki, A.J(2002). Mortality in a Nigerian teaching hospital: Experience at Jos University Teaching Hospital (JUTH) 1995-1999. Highland Med. Res. J. 1:16-8.

Organisation for Economic Co-operation and Development, *Health at a Glance, OECD Indicators 2005* (Paris: OECD Publishing, 2005).

Sanya, E.O., Abiodun, A. A., Kolo, P., Olanrewaju, T. O. and Adekeye, K. (2011). Profile and causes of mortality among elderly patients seen in a tertiary care hospital in Nigeria. *Annals of African Medicine Vol. 10, No. 4; 2011.* **ISSN 1596-3519,***DOI:* 10.4103/1596-3519.87043.

Shoko, T., Shiraishi, A., Kaji, M. and Otomo, Y. (2010). Effects of preexisting medical conditions on in hospital mortality: Analysis of 20,257 trauma patients in Japan. *J. Am. Coll Surg.* 211:338-46.

Silva, T.J., Jerussalmy, C.S., Farfel, M.J., Curiati, J. and Jacob-Filho W. (2009). Predictors of in-hospital mortality among older patients. *Clinics (Sao Paulo)*. 64:613-8.

Simpson, E.H. (1951). The interpretation of interaction in contingency tables. *J.R.Statist. Soc.*, B, 13, 238 - 241.