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Research Article

COMPARISON OF COX'S AND WEIBULL REGRESSION MODELS IN ASSESSING THE PROGNOSTIC FACTORS FOR SURVIVAL OF ASTHMATIC PATIENTS

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ABSTRACT

Survival analysis is a branch of statistics for analyzing the expected duration of time until one or more events happen. This study aimed to compare the results of Cox Proportional hazards model and Weibull Regression model to determine the model that best fits for Asthma data and observe factors that affect asthma patient's length of stay in hospital. Kaplan-Meier (K-M) method was used to estimate the survival rates of patients and to plot the graph of survival curves using data obtained from Federal Medical Centre, Abeokuta, Nigeria on Asthma patients. In using the K-M method, it was observed that there was low survival rate from 14 days upward. Akaike Information Criterion (AIC) and Log likelihood methods were used to evaluate the two models. Weibull Regression Model had the least AIC value of 428.3163 with highest Log likelihood value of -205.2 which shows best performance in handling Asthma data as compared to Cox Regression Model with highest AIC value 485.2536 and least Log likelihood value of -235.63.The result of the study showed that the parametric Weibull Regression Model could better determine the factors associated with the Asthma disease than the semi-parametric Cox Proportional hazards model. Determinant factors such as sex, smoking, hereditary, obesity, environmental pollution and respiratory illness were found to be significant factors affecting the length of stay in hospital of Asthma patients.

INTRODUCTION

The word "asthma" originates from the Greek meaning short of breath. This means that any patient with breathlessness is asthmatic. Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or early morning. Asthma is one of the world's most common long-term conditions. The disease is estimated to affect as many as 300 million people worldwide and could increase by another 100 million by the year 2025 (Bateman, *et al.* 2008). The various causes of Asthma are: Genetic susceptibility, gene-environment interactions and environmental risk factors such as prenatal factors, indoor and outdoor allergens, smoking and other pollutants, race/ethnicity, socioeconomic status, obesity and respiratory illnesses. These factors are assessed for the survival of Asthmatic patients using survival models.

Survival analysis is a branch of statistics for analyzing the expected duration of time until one or more events happen, such as death in biological organism and failure in mechanical or electrical system. It measures the probability of how long it takes a given outcome to occur for a group of similar individuals known as failure times (Cox and Oates, 1984). The starting time from a defined point to the occurrence of a given event is called survival time (Berwick, 2004) and the analysis of such group data is called survival analysis (Altman, 1977). The methods were developed for studying the time from initiating events to some terminal events. These methods are mostly applied in medical and biosciences. However, the methods were successfully applied to many kinds of events across various disciplines.

Censoring is pervasive to survival analysis data. It is defined as the loss of observation on the life time variable of interest in the process of an investigation. In survival data, censoring frequently occurs for many reasons. According to Klienbaum and Klien(2005), there are generally three reasons why censoring may occur; when a person does not experience the event before the study ends; when a person is lost to follow-up during the study period; when a person withdraws from the study because of death (if death is not the event of interest) or some other reason.

Survival analysis has three aspect of modelling which are parametric, non-parametric and semi-parametric. In this paper, we will base our analysis on two models which are parametric (Weibull regression model) and semi-parametric (cox proportional hazard model). Firstly, we consider the factors affecting the survival of asthma patients in our community and then fit the model that is best for the analysis of asthma patients' data. The rest of the paper is organized as follows: section 2 presents relevant literature, section 3 gives the research methodology while section 4 presents the results and discussion and section 5 provides the conclusion.

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REVIEW OF LITERATURE

Asthma Chronic conditions are often the catalyst for physical, psychological, and financial burden. Individuals suffering from asthma often demonstrate difficulties in managing their condition as well as altering their lifestyle to include factors such as healthy exercise routines and appropriate environmental surroundings. Many authors have worked on survival of patients with different ailments and on comparison of parametric, semi-parametric and non-parametric survival models. Parametric models are only occasionally used in the analysis of clinical studies of survival although they may have advantages over Cox's model (Nardi and Schemper, 2003). Mohamad *et al.* (2007) gives instances that Researchers in medical sciences often tend to prefer Cox semi-parametric instead of parametric models for survival analysis because of fewer assumptions but under certain circumstances, parametric models give more precise estimates. Although Cox's semi-parametric model is the most frequently employed regression tool for survival data, fully parametric models may poses some advantages. Based on asymptotic results, Efron (1977) and Oakes (1977) showed that, under certain circumstances, parametric models lead to more efficient parameter estimates than Cox's model.

Lui (2010) carries out a survival analysis for patients with breast cancer. The influence of clinical and pathologic features, as well as molecular markers on survival time are investigated. Special attention focuses on whether the molecular markers can provide additional information in helping predict clinical outcome and guide therapies for breast cancer patients. Hadiyat *et al.* (2017) conducts customer satisfaction surveys periodically to track their dynamics. One of the goals of this survey was to evaluate the service design by recognizing the trend of satisfaction score. Saheed and Seyyed (2017) described the comparison of Cox and parametric regression models regarding survival of children with acute leukemia in southern Iran. In a retrospective cohort study, information for 197 children with acute leukemia over 6 years was collected through observation and interviews. In order to identify factors affecting their survival, the Cox and parametric (exponential, Weibull, log-logistic, log-normal, Gompertz and generalized gamma) models were fitted to the data. Sadegh and Iraj (2017) evaluated the comparison of cox model and parametric models in the analysis of effective factors on event time of neuropathy in patients with type 2 diabetes. Hence this research hopes to convey an understanding in the analysis of parametric (Weibull Regression Model) and semi parametric (Cox Proportional Hazard Model) using data on asthmatic patients collected from the Federal Medical Center Abeokuta, fitting the model and making comparison using Akaike information criterion.

RESEARCH METHODOLOGY

Data Sources and Method of Collection

The data for this research originates from a secondary source. The data is from the Federal Medical Center, Abeokuta about patients registered for Asthma chronic diseases. The following factors were taken into consideration when collecting the data; ages, sex, heredity, smoking, obesity, environmental pollution, respiratory illness and patients length of stay in the hospital.

Model Analysis

Regression analysis is the art and science of fitting straight lines to patterns of data. In a linear regression model, the variable of interest (the so-called "dependent" variable) is predicted from k other variables (the so-called "independent" variables) using a linear equation. If Y denotes the dependent variable and $X_1, X_1, \ldots, X_p$ the independent variables, then the assumption is that the value of Y at time t (or row t) in the data sample is determined by the linear equation

$$Y_i = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p + \epsilon_i \tag{1}$$

where the $\beta_1, \beta_1, \ldots, \beta_p$ are the coefficients and the $X_1, X_1, \ldots, X_p$are independent and ϵ_i are $N(0, \sigma^2)$, β_0 is the so-called intercept of the model-the expected value of Y when all the X's are zero-and β_i is the coefficient of the variable X_i. The betas together with the mean and standard deviation of the epsilons are the parameters of the model. The corresponding equation for predictingY_t from the corresponding values of the X's is therefore

$$Y_i = \hat{\beta}_0 + \hat{\beta}_1 X_{i1} + \hat{\beta}_2 X_{i2} + \ldots + \hat{\beta}_p X_{ip} + \epsilon_i \tag{2}$$

where the β_i's are estimates of the Betas obtained by least-squares, i.e. minimizing the squared prediction error within the sample.

Weibull Regression Model

Weibull model plays the same role in the analysis of survival data as in the case of normal distribution in linear modeling. Weibull model is more general and flexible than exponential model and allow for hazard rates that are non-constant but monotonic. This model is characterized by positive parameters, the parameter $\lambda$is known as a scale parameter and p the shape parameter, because it determines whether the hazard is increasing, decreasing or constant over time$t$. In Weibull model, if the intercept and slope are roughly estimated as $\log(\lambda)$ and p and the lines are parallel, then the proportional hazard model is valid.
The survival function of the model is

$$S(t) = \exp(-\lambda t)^p \tag{3}$$

The hazard function is

$$h(t) = \lambda P(\lambda t)^{p-1} \tag{4}$$

where $\lambda = (x_{i\,,}\, \beta)$
The probability density function is

$$f(t) = h(t)S(t) = \lambda P(\lambda t)^{p-1} \exp(-\lambda t)^p \tag{5}$$

The expected duration from Weibull model is

$$E(T) = \left(\frac{1}{\lambda}\right)^{\frac{1}{p}} \Gamma\left(1 + \frac{1}{p}\right) \tag{6}$$

whereΓ denotes gamma distribution.
The variance is

$$\mathrm{Var}(T) = \left(\frac{1}{\lambda}\right)^{\frac{2}{p}} \left\{\Gamma\left(1 + \frac{2}{p}\right) - \Gamma\left(1 + \frac{1}{p}\right)^2\right\} \tag{7}$$

Over the years, estimation of the shape and scale parameters for Weibull distribution function has been approached through Maximum Likelihood Method, which is considered to be the traditional method of estimation (Cohen and Whitten, 1982).

Let $t_1, t_1, \ldots, t_n$be a random sample from Weibull distribution with probability density function (pdf).

$$f(t/\lambda, p\ ) = \left(\frac{p}{\lambda}\right)\left(\frac{t}{\lambda}\right)^{p-1} \exp\left(\frac{-t}{\lambda}\right)^p \tag{8}$$

Taking the likelihood of the function

$$L(t/\lambda,p)=\prod_{i=1}^{n}\left(\frac{p}{\lambda}\right)\left(\frac{t_i}{\lambda}\right)^{p-1}\exp\left(\frac{-t_i}{\lambda}\right)^{p} \quad (9)$$

Where λ and $p$are the positive parameters to be estimated, and the natural logarithm of the likelihood function is

$$l_nL(t/\lambda,p)=nl_n(\lambda)-npl_n(\lambda)+(p-1)\sum_{i=1}^{n}l_n(t_i)-\sum_{i=1}^{n}\left(\frac{t_i}{\lambda}\right)^{p} \quad (10)$$

Differentiating with respect to p and λ in turn and equate the expression to zero

$$\frac{\partial}{\partial p}l_nL(t/\lambda,p)=\frac{n}{p}+\sum_{i=1}^{n}l_n(t_i)-\frac{1}{\lambda}\sum_{i=1}^{n}t_i{}^{p}\,l_np-0 \quad (11)$$

$$=\frac{-n}{p}+\frac{1}{\lambda^2}\sum_{i=1}^{n}t_i{}^{p}-0 \quad (12)$$

In eliminating the equations above, we simplify to get

$$\frac{\sum_{i=1}^{n}t_i{}^{p}l_nt_i}{\sum_{i=1}^{n}t_i{}^{p}}-\frac{1}{p}-\frac{1}{n}\sum_{i=1}^{n}l_nt_i=0 \quad (13)$$

This can be solved to get estimate of p using standard iterative procedure such as Newton Raphson method.

$$P=\left[\frac{\sum_{i=1}^{n}t_i{}^{p}l_nt_i}{\sum_{i=1}^{n}t_i{}^{p}}\frac{1}{n}\sum_{i=1}^{n}l_nt_i\right]^{-1} \quad (14)$$

Once$p$is determinedλ can be estimated using

$$\frac{-n}{p}+\frac{1}{\lambda^2}\sum_{i=1}^{n}t_i{}^{p}=0 \quad (15)$$

And

$$\lambda=\left[\frac{1}{n}\sum_{i=1}^{n}t_i{}^{k}\right]^{\frac{1}{p}} \quad (16)$$

Kaplan Meier Estimator

In medical trial, Kaplan-Meier (K-M) method is the recommended technique in Survival analysis. K-M is the most popular in developing survival function (Collectt, 2003). The method is used to measure the fraction of subjects living for a certain period of time after treatment. In analyzing the survival data, two functions that are dependent on time are of particular interest; the survival function and the hazard function. The survival function denoted by $S(t)$ is the probability of surviving at least to time t. The hazard function denoted by $h(t)$is the conditional probability of dying at time t having survived to that time. The graph of $S(t)$against t is called the survival curve. The Kaplan-Meier method can be used to estimate this curve from the observed survival times without the assumption of the underlying probability distribution. The method is based on the basic idea that the probability of surviving P or more periods from entering the study is the product of the P observed survival rates for each period i.e. the cumulative surviving; and is given by:

$$S(p)=(k_1)(k_2)(k_3)\ldots(k_p) \quad (17)$$

where k_1 = Proportion of surviving the first period and k_2 = Proportion of surviving beyond the second period conditional on having survived up to the second period and so on.

The proportional surviving period i having survived up to period i is given by

$$k_i=\frac{r_i-d_i}{r_i} \quad (18)$$

wherer_i is the number alive at the beginning of the period and $d_i$is the number of deaths within the period.

Cox Proportional Hazard model

Cox Proportional Hazard Model or Cox regression model abbreviated as Cox (PH) is a well-recognized statistical technique for exploring the relationship between the survival of a patient and the several explanatory variables or covariates. The principle of Cox Proportional hazard model is to link the survival time of an individual to covariates. A positive regression coefficient for an explanatory variable means that the hazard for patient having a high positive value on that particular variable is high. On the other hand, a negative regression coefficient implies a better prognostic for patients with higher value of that variable. Cox method does not assume any particular distribution for survival times, rather it assumes that the effect of different explanatory variables on survival are constant over time and are additive in a particular way. The model assumes that the hazard for two individuals x_1 and x_2 is proportional. In other words, the hazard of an individual is proportional to the hazard of any other individual. The hazard function is the probability that an individual will experience an event within a small time interval, given the individual has survived up to the beginning of the interval. It can be interpreted as the risk of dying at time t.
The hazard is modelled as:

$$h(t/x)=h_0(t)exp(\beta_1x_1+\beta_2x_2+\ldots+\beta_px_p) \quad (19)$$

where$x_1,x_2,\ \ldots,x_p$are explanatory variables.
$h_t$is the baseline hazard time t representing the hazard for a person with value 0 for all explanatory variables. $\beta_1,\beta_2,\ \ldots,\beta_p$Regression coefficients describing the importance of the covariates, which is estimated by the partial likelihood estimation procedure.

Parameter estimates in Cox model are obtained by maximizing the partial likelihood function for the observed data simultaneously with respect to $h_0(t)$andβ. A popular approach is proposed by Cox, (1975), he proposed that the partial likelihood does not depend on$h_0(t)$ which is obtained for β. Partial likelihood is a procedure developed to take inferences about the regression parameters in the presence of nuisance parameters i.e. $h_0(t)$in Cox model.

To estimate the model, let $t_1,t_2,\ \ldots,t_n$ be the observed survival time for n individuals, let the ordered time r individual be $t_1<t_2<\ldots<t_r$and letR_{t_j} be the risk set just beforet_j and $r_j$for its size, so that $R_{t_j}$is the group individuals alive and uncensored at time just prior tot_j.

The conditional probability that individual dies at t_j given that one individual from the risk set R_{t_j}dies at $t_j$is given by

$$Prob\left(\text{individual } i \text{ and } t_j \,/\, \text{one death from the risk set } R_{t_j} \text{and} t_j\right)$$

$$=Prob(\text{individual } i \text{ dies at } t_j)\,/\,Prob\,(\text{one death at} t_j)$$

= Prob(individual i dies att_j) / $\sum_{k=R_{t_j}} Prob$(individual k dies att_j)

$$= \frac{\exp\left(\beta^1 X_i(t_j)\right)}{\sum_{k=R_{t_j}} \exp\left(\beta^1 X_i(t_j)\right)} \quad (20)$$

Now the partial likelihood function of cox model is given as

$$L(\beta) = \prod_{j=1}^{r} \frac{\exp\left(\beta^1 X_i(t_j)\right)}{\sum_{k=R_{t_j}} \exp\left(\beta^1 X_i(t_j)\right)} \quad (21)$$

in which $x_i t_j$ is the vector covariate value for individual i who dies at t_j.

The log partial likelihood is given as:

$$\log L(\beta) = \sum \left\{ \beta x_i - \log\left(\sum_{j=R_{t_j}} \exp(\beta^1 X_i) \right) \right\} \quad (22)$$

The partial likelihood is valid when there are no ties in the data set, but often ties occur in continuous survival data that are collected in days, weeks and months. If there are only few ties Breslow, (1974) gave approximation as:

$$L(\beta) = \prod_{j=1}^{r} \left\{ \frac{\prod_{j=D_{tj}} exp(\beta^1 X_i)}{\left[\sum_{j=R_{tj}} \exp(\beta^1 X_i)\right]^{di}} \right\} \quad (23)$$

whereD_{tj} =Set of individual failing at t_j

di = Number of failure occurring at t_j

Akaike Information Criterion (AIC)

In statistical modeling, one of the main challenges is to select a suitable model from a candidate family to characterize the underlying data. Model selection criteria provide a useful tool in this regard. Akaike information criterion is a measure of the relative quality of statistical models for a given set of data. It estimates the quality of model, relative to each of the other models. It deals with the tradeoff between the goodness of fit of the model and the complexity of the model. It is defined as:

$$AIC = -2(l/T) + 2K/T \quad (24)$$

where l = log likelihood value, K = number of parameters and T = Total number of observations

The aim is to find the model with the lowest value of selected information criterion. The $-2(l/T)$ term appearing in the formula is an estimate of the deviance of the model fit.

RESULTS AND DISCUSSION

Results

Table 1 Kaplan-Meier (K-M) Survival Function

Length of stay	No.Risk	No.Event	Survival	Std.Error	Lower 95% CI	Upper 95% CI
1	73	2	0.9726	0.0191	0.9359	1.000
7	25	60	0.1507	0.0419	0.0874	0.260
14	11	5	0.0822	0.0321	0.0382	0.177
21	6	1	0.0685	0.0296	0.0294	0.160
42	3	0	0.0685	0.0296	0.0294	0.160
63	1	0	0.0685	0.0296	0.0294	0.160
84	1	0	0.0685	0.0296	0.0294	0.160
105	1	0	0.0685	0.0296	0.0294	0.160

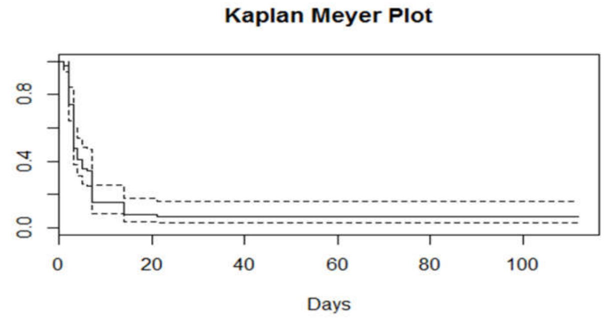

Figure 1 Kaplan Meier's curve

From fig 1, it indicates that there is low survival rate at days from 14 upward. Also there is high survival rate within 7 days below, that is the survival function starts dropping from 14 days.

Table 2 Results from Analysis on Cox Proportional Hazard Model

Covariates	Hazard Ratio	Std.Error	P-values	Lower 95% CI	Upper 95% CI
Age	1.0122	0.01304	0.3518	0.98667	1.038
Sex	0.8079	0.27012	0.4296	0.47578	1.372
Smoking	0.2260	0.90143	0.0996	0.03872	1.326
Hereditary	0.3530	0.75229	0.1663	0.08079	1.524
Obesity	0.5330	0.92543	0.4966	0.08690	3.269
Resp.Illness	0.2670	0.75489	0.0802	0.06080	1.172
Env.Poll	0.3612	0.80627	0.2065	0.07437	1.754

Log likelihood = -235.63 AIC =485.2536

Cox proportional hazard model indicates that age, sex, obesity, smoking, hereditary, respiratory illness and environmental pollution are major factors affects the length of stay of patients and contributes more to the risk of deaths among patients having Asthma.

Table 3 Result from Analysis on Weibull Regression Model

Covariates	Hazard Ratio	Std.Error	Z	P-values
Age	-0.0251	0.0126	-2.000	0.0455
Sex	0.2555	0.2838	0.900	0.3680
Smoking	1.4066	0.9005	1.562	0.1183
Hereditary	0.8679	0.7858	1.105	0.2694
Obesity	0.3363	0.9644	0.349	0.7273
Resp.Illness	1.3185	0.7879	1.673	0.0943
Env.pollution	0.7679	0.8299	0.925	0.3548

Log likelihood= -205.2AIC = 428.3163

The resultfrom the analyses show that sex, hereditary, obesity, environmental pollution, smoking and respiratory illness are the significant factors affecting survival of patients in Weibull regression model.

Table 4 Comparisons of Cox and Weibull Models Using Aic Criterion and Log Likelihood Test

Covariates	Cox Proportional Hazard Model		Weibull Regression Model	
	HR	Standard Error	HR	Standard Error
Age	1.01	0.01304	-0.03	0.0126
Sex	0.81	0.27012	0.26	0.2838
Smoking	0.23	0.90143	1.41	0.9005
Hereditary	0.35	0.75229	0.87	0.7858
Obesity	0.53	0.92543	0.34	0.9644
Resp. illness	0.27	0.75489	1.32	0.7879
Env.Pollution	0.36	0.80627	0.77	0.8299
Log likelihood	-235.63		-205.2	
AIC	485.2536		428.3163	

This analysis compares estimation methods using Weibull and Cox models under proportional hazards framework of survival data. Cox proportional hazard model AIC and log likelihood are 485.2536 and -235.63 respectively while the AIC and log likelihood are 428.3163 and -205.2 respectively

DISCUSSION

This paper compares cox proportional hazard and Weibull regression survival modelsusing data on Asthma disease considering seven different factors: age, sex, smoking, hereditary, obesity, respiratory illness and environmental pollution collected from the Federal Medical Centre, Abeokuta, Ogun state, Nigeria. With Kaplan-Meier survival analysis procedure, the study examined the distribution of length of stay of asthma patients. The overall median survival time was 39 days with survival function of 10%,indicating that less than 10% of the asthma patients stayed less than 39 days and the other 90% stayed longer than the diagnosed time.

The Cox model estimates revealed that the hazard ratio computed for age is 1.01. Hazard ratio for results of sex is 0.81. The hazard ratio for smoking is 0.23. The hazard ratio for hereditary is 0.35. Also for obesity is 0.53 and respiratory illness is 0.27, and lastly environmental pollution is 0.36. Therefore the factors significant to this model areage, smoking, hereditary, obesity, respiratory illness and environmental pollution.

For Weibull model estimates, the hazard ratio for age is -0.03. The hazard ratio for sex is 0.26. Similarly, hazard ratio for smoking is 1.41. The hazard ratio for hereditary is 0.87. The hazard ratio for obesity, respiratory illness and environmental pollution are 0.34, 1.32 and 0.77 respectively. Therefore, the factors significant to this model are smoking, hereditary, obesity, respiratory illness and environmental pollution.

Overall model comparison was done using Akaike Information Criterion (AIC) and log likelihood. As observed, from Table 4.4 Weibull regression model had the least AIC value and the highest value for the log likelihood which shows best performance in handling Asthma data, Cox regression model with highest AIC value and least log likelihood value performed less. In other words, in the present study, the Weibull model provided a better fit to the study data than Cox proportional hazard model with respect to the fitted AIC where the criterion value for Weibull is lower than that of Cox.

CONCLUSION

This study compares Cox's and Weibull Regression Models in assessing the predictive factors for survival of asthmatic patients.Kaplan Meier procedure estimates a better survival curve for the data by indicating the risk of survival for the patients. It was found that 10% of the patients survive beyond the median survival rate. Cox proportional hazard model indicates that all the factors considered are significant to the survival of patients having asthma while the Weibull regression model indicates all other factors as being significant except age. Also, the result of AIC and Log likelihood show that Weibull regression model fit the asthma patients' data more than Cox Proportional hazard model. This show that the parametric Weibull regression model could better determine the factors associated with the Asthma disease than the semi-parametric Cox proportional hazard model. Therefore, it would be better for researchers of the health care unit to consider this model in their researches concerning Asthma disease. Our results agreed with the results obtained by Hui, *et al.* (2011) where they compared Cox and Weibull models using gastric cancer data. They concluded that their data supported Weibull model as an alternative to Cox model based on AIC.

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