1. Introduction
Survival analysis is concerned with studying the time between entry to a study and a subsequent event and becomes one of the most important fields in statistics. The techniques developed in survival analysis are now applied in many fields, such as biology (survival time), engineering (failure time), medicine (treatment effect of drugs), quality control (lifetime of components), credit risk modeling in finance (default time of a firm).

The Cox proportional hazard model is now the most widely used for the analysis of survival data in the presence of covariates or prognostic factors. This is the most popular model for survival analysis because of its simplicity, and not being based on any assumptions about the survival distribution. The model assumes that the underlying hazard rate is a function of the independent covariates, but no assumptions are made about the nature or shape of the hazard function. In the last several years, the theoretical basis for the model has been solidified by connecting it to the study of counting processes and martingale theory, which was discussed in the books of Fleming and Harrington (1991) and of Andersen et al. (1993). These developments have led to the introduction of several new extensions of the original model. However, the Cox proportional hazard model may not be appropriate in many situations and other modifications such as stratified Cox model (Kleinbaum, 1996) or Cox model with time dependent variables (Collett, 2003) can be used for the analysis of survival data.

A frailty model is a random effects model for time variables, where the random effect (the frailty) has a multiplicative effect on the hazard. It can be used for univariate (independent) failure times, i.e., to describe the influence of unobserved covariates in a proportional hazards model. The aim of this paper is to compare the performance of Cox proportional hazard model, Cox time dependent model and Frailty model using Heart attack data. The result shows that Cox time dependent model is better than other models.

2. Non-linear Regression Models

2.1 Cox Proportional Hazard Model
It is a mathematical modeling approach for estimating survival curve when considering several explanatory variables simultaneously. It is also called semi parametric model. The proportional hazard model describes the relationship between the hazard function of the risk of an event and a set of covariates. The Cox proportional hazard model is usually written in terms of the hazard model. It is given below as described by Cox (1972)

\[ h(t,X) = h_0(t) \exp(\sum_{i=1}^{k} \beta_i x_{i}) \]  

where \( h(t,X) \) is baseline hazard and \( \beta_i \) is parameter vector and are independent variables. The above equation (1) reveals that the hazard at time \( t \) is the product of two quantities. The first of the above, i.e., it is called the baseline hazard function. The second quantity is the exponential expression. This model gives an expression for the hazard at time \( t \) for an individual with a
given specification of a set of explanatory variables denoted by \( \beta \). An important feature of equation (1), which concerns the proportional hazard assumption, is that the baseline hazard is a function of \( t \), but doesn’t involve the \( \beta \). The baseline hazard function is left unspecified so that the time to event random variable is not assumed to follow any particular distribution and this is one of the essential properties of proportional hazard model (Lee, 1992).

### 2.2 Cox Time Dependent Covariate Model

Time dependent covariates have been studied a number of authors (Crowley & Hu, 1977; Cox & Oakes, 1984; Andersen, 1986; Fisher & Lin 1999). A baseline Cox analysis ignores the change of updated covariate values usually yields smaller effect estimates than a time dependent analysis using all temporal information available (Aydemir et al., 1999). Also Altman and De Starola (1994) called this the time decay of the effects of entry values. One of the earliest applications of the use of time varying covariates in a biomedical setting may be found in Crowley (1977).

Let denote the value of the covariate measured at time \( t \). Let denote the value of the covariate for subject \( i \) at time \( t_i \):

\[
X_i(t_i) = [X_{i1}(t_i), X_{i2}(t_i), X_{i3}(t_i), \ldots, X_{ip}(t_i)]
\]

The notation in the above equation is completely general in the sense that, if a particular covariate, is fixed then this has lead to use the time dependent notation in equation (1) exclusively. The generalization of the proportional hazard regression function to include possibly multiple time varying covariates is

\[
h(t, X(t), \beta) = h_0(t).e^{\beta X(t)}
\]

and the generalization of the partial likelihood function

\[
l_p(\beta) = \prod_{i=1}^{n} \left[ \frac{s_i^{X_i(t_i)} \prod_{j=1}^{p} \frac{e^{\beta X_{ij}(t_i)}}{1-e^{\beta X_{ij}(t_i)}}} {\prod_{j=1}^{p} e^{\beta X_{ij}(t_i)}} \right]
\]

### 2.3 Frailty Models

Frailty is an unobserved random factor that modifies multiplicatively the hazard function of an individual or group or cluster of individuals. Vaupel et al. (1979) introduced univariate frailty model (with a gamma distribution) into survival analysis to account for unobserved heterogeneity or missing covariates in the study population. The idea is to suppose that different patients possess different frailties and patients more frail or prone tend to have the event earlier that those who are less frail. The model is represented by the following hazard given the frailty:

\[
h(t | Z, X) = Z h(t | X)
\]

can be equal to the baseline hazard function in (Cox regression model). The baseline hazard function can be chosen non-parametrically, or parametrically. An important point is that the frailty \( Z \) is an unobservable random variable varying over the sample which increases the individual risk if or decreases if \( t \). The model can also be represented by its conditional survivor function

\[
S(t | X) = \exp \left( - \int_0^t h(u | X) \, du \right) = \exp \left( -Z \Lambda(t | X) \right), \quad (6)
\]

where \( \Lambda(t | X) = \int_0^t h(u | X) \, du \)

The marginal survivor function can be calculated by

\[
S(t | X) = \int S(t | Z, X) g(z) \, dz = E[S(t | Z, X)] = L(\Lambda(t | X))
\]

Eilers and Rødstrøm (1992) proved that frailty model with mean is identifiable with univariate data, when covariates are included in the model. Many distributions can be chosen for the frailty, but the most common frailty distribution with gamma distribution. The Gamma distribution has been widely applied as a mixture distribution (Clayton, 1978; Hougaard, 2000; Oakes, 1982; Vaupel et al., 1979; Yashin et al., 1995). Other distributions which are sometimes applied for the frailty distribution are the well known normal, the log normal (McGilchrist and Aisbett, 1991), the three parameter distribution (PVF) (Hougaard, 1986), and inverse Gaussian distribution. The effect of different frailty distribution is investigated by Congdon (1995). If the value of the frailty is assumed to be constant within groups, the models are called shared frailty models.

### 3. Application to Heart attack data

The data obtained from the John Wiley & Sons website, ftp://ftp.wiley.com/public/scitech_med/survival. It may also be obtained from the website for statistical services at the University of Massachusetts at Amherst by going to the data sets link and then the section on survival data http://www.umass.edu/statdata/statdata. The data from the Worcester Heart Attack Study (WHAS) have been provided by Goldberg (2005) of the Department of Cardiology at the University of Massachusetts Medical School. Data have been collected during 13 one-year periods (1975-1988), on all myocardial infarction (MI) patients admitted to hospital in the Worcester, Massachusetts Standard Metropolitan Statistical Area. Event is coded as 1 and censoring is coded as 0. Table 1. describes the subsets of covariates used, with their codes and values.

**Table 1. Description of the covariates obtained from WHAS**

| COVARIATES | DESCRIPTION | CODES/UNITS |
|------------|-------------|-------------|
| AGE        | Age         | years       |
| SEX        | Gender      | 0 = Male, 1 = Female |
| CPK        | Peak Cardiac Enzyme | Int. units |
| SHO        | Cardiogenic shock complications | 0 = No, 1 = Yes |
| CHF        | Left Heart Failure Complications | 0 = No, 1 = Yes |
| MIORD      | MI Order    | 0 = First, 1 = Recurrent |
| YRGRP      | Grouped Cohort Year | 1 = 1975 & 1978, 2 = 1981 & 1984, 3 = 1986 & 1988 |

### 4. Model Results

**Table 2. Parameter Estimates under different Models**

| COVARIATES | MODELS | S.E. | S.E. | S.E. | S.E. |
|------------|--------|------|------|------|------|
| AGE        | .035*  | .006 | .033* | .006 | .032* | .006 |
| SEX        | .045   | .134 | .008 | .133 | -.013 | .133 |
| SHO        | 1.860* | .217 | 1.906* | .215 | 1.822* | .207 |
| CHF        | 5.63*  | .143 | 5.64* | .144 | .585* | .143 |
| MIORD      | 2.69*  | .132 | 2.11  | .132 | .226  | .132 |
5. Results
The non-linear regression models were fitted using STATA 12 and the results are presented in Table 2. From the table we see that the three covariates namely AGE, SHO, CHF are significantly associated with the survival time under all the model. Among the models, Time dependent Cox model has the lowest level of deviance compared to all other models. It is further noted that all other models have significantly higher deviance compared to Time dependent Cox model.

6. Discussion and Conclusion
From the Table 2, it is found that the, SEX is not significant to the survivorship. Controlling for other covariates the risk of death increases by 3.6 % as a patient's age increases by 1 year. Controlling for other covariates, the risk of death of patients with recurrent heart attack is 1.3 times the risk of patients with first heart attack. Using Cox PH model for all covariates the result showed significant p-values except the covariate SEX. When Extended Cox PH model was used for the time dependent covariate, Peak Cardiac Enzyme (CPK). The result is based on CPK as a time dependent covariates, after adjusting all the covariates. We observed that the result of time dependent covariates is better than the results of Cox PH Model. The application of frailty model to the same data assuming individual heterogeneity is also considered. For Frailty model, we see that all the covariates are statistically significant except SEX and MIORD. This leads to the conclusion that the individual heterogeneity in SEX and MIORD differs significantly between the patients. Among the models, Time dependent Cox model has the lowest level of deviance compared to all other models.