UNIVERSITY OF SOUTHAMPTON

Faculty of Social and Human Sciences

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Flexible Parametric Survival Models with Time-dependent Covariates for Right Censored Data

by

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Thesis for the degree of Doctor of Philosophy

February 2012

Abstract

In survival studies the values of some covariates may change over time. It is natural to incorporate such time-dependent covariates into the model to be used in the survival analysis. A standard approach is to use the semi-parametric extended Cox proportional hazard model. An alternative is to extend a standard parametric model, such as a Weibull regression model, to include time-dependent covariates. However, the use of such simple parametric models may be too restrictive. Therefore in this thesis we further extend the Weibull regression model with time-dependent covariates by using splines to give greater flexibility.

The use of Cox, simple parametric and Weibull spline models is illustrated with and without time-dependent covariates on two large survival data sets supplied by NHS Blood and Transplant. One data set involves times to graft failure of patients who have undergone a corneal transplant and contains many fixed covariates and one time-dependent covariate with at most one change point. The other data set concerns time to death of heart transplant patients and contains many fixed covariates and a time-dependent covariate with possibly many change points.

A simulation study is used to evaluate and compare likelihood-based methods of inference for the competing models. In the first stage attention is focused on selection of the number of knots in the Weibull spline model in the simple case with no covariates. Stage two examines the results of inferences from the Weibull splines model with fixed covariates. Stage three compares the results of inferences for parameters in the extended Cox model and two simple parametric models with time-dependent covariates. Finally, stage four examines the Weibull splines model with time-dependent covariates.

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Declaration Of Authorship

I, Hisham Abdel Hamid Elsayed, declare that the thesis entitled **Flexible Parametric Survival Model with Time-dependent Covariates for Right Censored Data** and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
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- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- none of this work has been published before submission.

Signed: ....

Date:..

Acknowledgements

I want to start by thanking my God who gave me this chance and blessing to complete this work. Also, I thank my parents to whom I am forever indebted and owe much than words can express.

I would like to express my sincere thank to my supervisor Dr.Alan Kimber for his valuable suggestions and support throughout my research.

I would like to express my gratitude to my dear wife for her tolerance, motivation and encouragement in every stage of my life.

I dedicated this thesis to my dear children Omar and Shady for their patience and sacrifices throughout my study.

This research was supported by a grant from the government of the Arab Republic of Egypt through my employer Ain Shams University.

Chapter 1

Introduction

Survival analysis is the class of statistical techniques for analysing survival data in the form of time from a start point to the occurrence of an event of interest. This analysis can be applied in different fields, such as: medicine, engineering, economics and biology. In engineering, survival analysis methods are applied to study life times of components and equipment. In economics, survival analysis methods are applied to, for example, duration of unemployment. In medical applications, the start may represent the time of recruitment of a patient to a clinical trial or the time of diagnosis of an illness. Note that the event of interest may be death or failure or a more positive outcome, such as cure or relief from symptoms, but in this thesis we shall use the term "survival time" generically.

The response variable T in survival analysis is the time from an origin to a defined end point, and is usually regarded as a non-negative continuous random variable. In practice the observed values of T may be rounded (for example, to the nearest minute). Some rounding may be ignored if the degree of rounding is small or may be accounted for via interval censoring. In some applications T itself is discrete (for example, T is the number of take off and landing cycles to failure of an aircraft system). However, in this thesis we shall always assume that T is continuous. In survival analysis we aim to model T, often as a function of explanatory variables, and to draw inferences about the parameters of the model.

1.1 Survival data

Standard Normal-based statistical procedures are not appropriate in survival data analysis. The first reason for that is the skewness of survival data. Generally, survival data are positively skewed. Consequently, alternative distributional models are introduced for studying survival data. Secondly, survival times are frequently censored, and then the standard statistical approaches can not be used. Censoring results where the exact time to the event of interest has not been observed. This may happen, for example, if a patient has been lost to follow-up or is still alive at the end of study. In other cases, the patient may die before the event of interest is observed or within an interval of time. The time from the start point until occurrence one of these cases is known as the "censoring time".

Censoring occurs by different mechanisms so that there are three major schemes of censoring (Gijbels, 2010). Type I censoring occurs when a set of subjects enter to the study at a certain time and the study is stopped at a predetermined time. In this case, the subjects that have not failed when the study ends, are considered as a type I censored observations. In type II censoring, the study starts with a certain number of subjects and continues until failure of a predetermined number of those subjects. For example, in a reliability examination of a group of n components, the study is stopped after a predetermined number of r units have failed. If failure times are recorded as $T_1 \leq T_2 < \ldots < T_r$, the remaining $n-r$ units have a failure time, larger than T_r, and then they are considered as type II censored observations with censoring time measured to T_r. In type I censoring, the time is fixed while the number of observations is random. In contrast, in type II censoring, the time to failure is random whereas the number of observations is predetermined.

In random censoring, the study starts at a certain time and continues until a predetermined time. Subjects enter the study and are followed up until the event of interest is observed or loss to follow-up occurs during the study period. It is assumed that each individual i has his own survival time T_i and censoring time C_i. There are three types of random censoring: left, right and interval censoring. The observation is encountered as left censored when the event occurs before the observation time. For example, assume a group of patients are recruited for some time after an organ transplantation. One month after the surgery, the patients are monitored to determine if the organ has failed. The patients whose organ fails before the end of the month are considered as a left censored observations. Interval censoring occurs when the event is experienced within an interval of time. Suppose that a patient is examined every 6 months and the event is observed in the second follow-up time but the event time is not known exactly. Then, the actual survival time is between 6 and 12 months, and this patient gives an interval censored observation.

In this thesis, I will be concerned with right censoring which is the most frequent type in survival analysis. Thus, from now on the term "censoring" will mean "right censoring". To illustrate this type of censoring, suppose a patient is recruited to study at time t_0 and still alive until time $t_0 + t_c$, the time t_c may be unknown for different reasons such as

- The patient is still alive at the end of the study, and so death is not observed.
- The patient cannot be tracked so he or she has been lost to follow-up.
- The patient drops out from the study of some reason.

In such situations, the individual is known to be alive until time $t_0 + t_c$, and t_c is known as right censoring survival time. Generally, for subject i where $i = 1, 2, \ldots, n$, assume that the observed survival time is t_i and censoring time is t_{c_i}, and then the recorded survival times and status for n subjects are

$$(Z_1, \delta_1), (Z_2, \delta_2), \ldots\ldots, (Z_n, \delta_n) \tag{1.1}$$

where $z_i = min(t_i, c_i)$ and δ_i is an indicator variable that takes the value 1 if the event is observed and 0 otherwise (Gijbels, 2010).

To illustrate right random censoring, assume that a group of patients were recruited at different times while their examination was performed over a certain period until death or the end of the study. Some of these patients may be lost to follow-up or still alive to the end of the study (Collett, 2003). Figure 1.1 illustrates these cases, the patients who died are denoted by "D", and the patients who were lost to follow-up are represented by "L" while the letter "A" refers to the patient who was still alive at the end of the study. The figure shows that patients $1, 2, 5$ and 7 died before the end of the study so they are uncensored observations and their survival times are the times from recruitment to the death time. Patients 3 and 4 were lost to follow-up while patient 6 was alive at the end of the study. Consequently, patients $3, 4$ and 6 are considered as right censored observations.

In right random censorship, it is assumed that the censoring process is random and non-informative. Firstly, randomness assumption means that the actual survival time for any individual is independent from the mechanism that may cause that individual to be censored. Then an individual whose survival time is censored at a certain time must be representative for all the other individuals with the same prognostic factors who have survived to the same time (Collett, 2003). Secondly, assumption of non-informative censorship means that there no individuals will be withdrawn as a result of, for example, any changes in their physical conditions.

In survival analysis techniques, the censored observations are encountered and involved in the analysis. Ignoring those observations may lead to bias in the inferences. Consequently, special statistical procedures and models are adopted to treat survival data that includes right random non-informative censored observations.

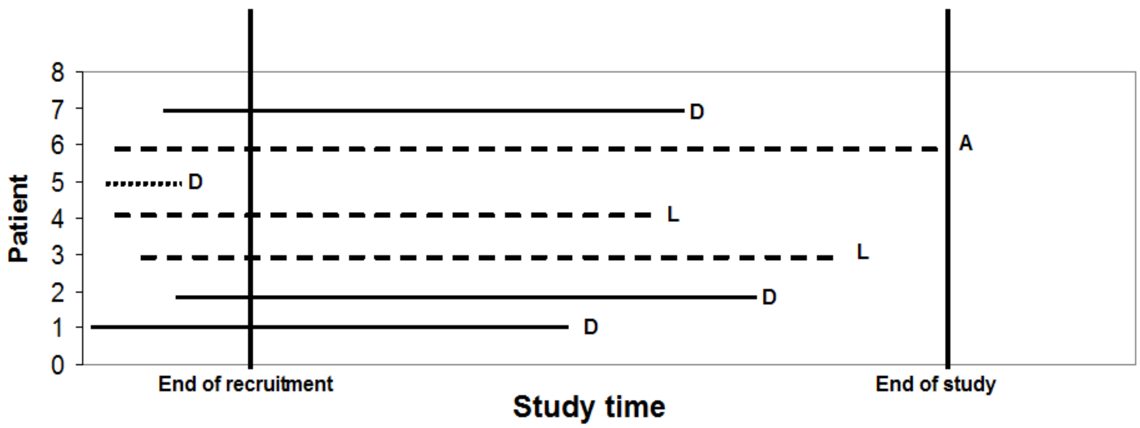

Figure 1.1: Study time for seven patients with different status

1.2 Basic functions of survival analysis

Survivor and hazard functions play a basic role in summarising survival data. To define these functions as in Collett (2003), let T be a non-negative random variable that represents the survival time of an individual. Let T have continuous probability density function $f(t)$. The distribution function of T is given by

$$F(t) = P(T < t) = \int_0^t f(u)du, \tag{1.2}$$

The survivor function, $S(t)$, is the probability that the survival time is greater than or equal t:

$$S(t) = P(T \geq t) = 1 - F(t). \tag{1.3}$$

The hazard function $h(t)$ is defined by

$$h(t) = \lim_{\Delta t \to 0} \left\{ \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t} \right\}. \tag{1.4}$$

Thus, $h(t)$ can be regarded as the instantaneous failure rate of an individual who has survived to time t. The conditional probability in (1.4) can be written as

$$P(t \le T < t+\Delta t | T \ge t) \quad = \quad \frac{P(t \le T < t+\Delta t)}{P(T \ge t)},$$

which is equivalent to

$$\frac{F(t+\Delta t) - F(t)}{S(t)},$$

and then the hazard function can be written as

$$h(t) = \lim_{\Delta t \to 0} \left\{ \frac{F(t+\Delta t) - F(t)}{\Delta t} \right\} \frac{1}{S(t)}$$

$$= \frac{f(t)}{S(t)}. \tag{1.5}$$

The survivor function is $S(t) = 1 - F(t)$, so that the hazard function is

$$h(t) = -\frac{d}{dt} \{\log S(t)\}.$$

Hence,

$$S(t) = \exp\{-H(t)\}, \tag{1.6}$$

where

$$H(t) = \int_0^t h(u)du. \tag{1.7}$$

The function, $H(t)$, is known as the cumulative hazard function.

1.3 Non-parametric analysis

A basic tool in survival analysis for a homogeneous sample of possibly censored survival data is the Kaplan-Meier estimator. Suppose that a number of r survival times $t_1, t_2 \ldots, t_r$ in which $t_1 < t_2 < \ldots < t_r$ with some censoring times which lies within these observed times. The Kaplan-Meier estimate of the survivor function is calculated at each survival time t_j and defined by (Collett, 2003)

$$\hat{S}(t_j) = \prod_{j=1}^{k} \left(\frac{n_j - d_j}{n_j} \right), \tag{1.8}$$

where $t_k \le t < t_{k+1}$, $k = 1, \ldots, r$, n_j is the number of observations under risk and d_j is the number of deaths at time t_j. Similarly, the Kaplan-Meier estimate of the hazard function at the survival time t_j is defined by

$$\hat{h}(t_j) = \frac{d_j}{n_j \tau_j}, \tag{1.9}$$

where $\tau_j = t_j - t_{j-1}$ and $j = 1, 2, \ldots, m$. The cumulative hazard function has an important role in the analysis of survival data. The hazard function is the derivative of the cumulative hazard function, and then the slope of the cumulative hazard function can be used to explore the shape of the hazard function. From (1.6)

$$H(t) \quad = \quad -\log\{S(t)\}.$$

Then the Kaplan-Meier estimate of the cumulative hazard function at time t_j is

$$\hat{H}(t_j) = -\sum_{j=1}^{k} \log\left(\frac{n_j - d_j}{n_j}\right), \tag{1.10}$$

where $k = 1, 2, \ldots, r$. An important aim of the non-parametric analysis is to compare different treatment groups. The initial procedure is performed graphically based on comparing plots of the estimated survivor functions for each group. This step is followed by applying one of statistical tests that used to compare survival times for different groups. The most frequently used methods are the log rank test and the Wilcoxon test which can be extended for comparing more than two groups. Stratified tests may be employed when the individuals of each group have their own covariates that must be included in the comparison of such groups (Allison, 1995).

1.4 Semi-parametric modelling

Frequently it is of interest to relate the survival distribution to covariates. In some cases, the distribution of the sampled population is unknown or cannot accurately be fitted by one of the available distributions. Consequently, parametric models are not applicable and alternative approach is the semi-parametric modelling through the model introduced by Cox (1972) (Selvin, 2008). This model is called the Cox proportional hazards model, which is a flexible tool for fitting the relationships between censored survival times and multiple explanatory variables (Dietz *et al.*, 2004). In the Cox model, the hazard function for the *ith* individual is

$$h_i(t) \quad = \quad \psi(x_i)h_0(t),$$

where $\psi(x_i)$ is the relative hazard function and $h_0(t)$ is the baseline hazard function that represents the hazard function when the explanatory values are equal to 0 (Collett, 2003). Let $\psi(x_i)$ be a function that includes p explanatory variables and defined as

$$\psi(x_i) \quad = \quad \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi}),$$

and then the hazard function for the *ith* individual is commonly used as

$$h_i(t) = \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi})h_0(t), \tag{1.11}$$

where $i = 1, 2, \ldots, n$.

The β parameters may be estimated using the partial likelihood function based on the β coefficients in the proportional hazard function without specifying the baseline hazard function $h_0(t)$ (Allison, 1995). For k observed failure times $t_1 < t_2 < \ldots, t_k$, the partial likelihood function is considered as the joint probability of these failure times according to their order. The probability of an individual i who failed at time t_i is given by

$$\frac{h_0(t_i)\exp(x_i^T\beta)}{\sum_{\iota \in R(t_i)} h_0(t_i)\exp(x_\iota^T\beta)} \quad = \quad \frac{\exp(x_i^T\beta)}{\sum_{\iota \in R(t_i)} \exp(x_\iota^T\beta)},$$

where $R(t_i)$ is the risk set at time t_i. Thus, the partial likelihood function is defined as

$$L = \prod_{i=1}^{n} \left\{ \frac{\exp(x_i^T\beta)}{\sum_{\iota \in R(t_i)} \exp(x_\iota^T\beta)} \right\}^{\delta_i}, \tag{1.12}$$

where δ_i takes the value 1 for uncensored observation and 0 otherwise. This partial likelihood function is valid only when there are no tied observations. In the presence of ties, modifications to (1.12) were introduced by Cox (1972), Breslow (1974) and Efron (1977). The Cox proportional hazards model may be more robust than the alternative parametric proportional hazards model that might involve misspecification of the baseline hazard function $h_0(t)$ (Dietz *et al.*, 2004).

1.5 Parametric modelling

In survival data analysis, when the assumption of a specific probability distribution for the data is tenable, parametric survival models are employed. In this case, more precise inferences are obtained, the estimates of relative hazards, and survival time quantiles will often have smaller standard errors (Collett, 2003). There are two main types of parametric survival models. Firstly, when a proportional hazard assumption is valid, a parametric proportional hazards model using an exponential, Weibull or Gompertz distribution can be used. For example, in the Weibull proportional hazard model, the baseline hazard function is given by

$$h_0(t) \;=\; \lambda\gamma t^{\gamma-1},$$

where λ and γ are the Weibull scale and shape parameters respectively, so that the hazard function of individual i is

$$h_i(t) \;=\; \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi})\lambda\gamma t^{\gamma-1}.$$

Secondly, an accelerated failure time model may be more appropriate when proportional hazards assumption is not tenable. In this case, a parametric model is applied based on different distributions, such as: Weibull, log-logistic, log-normal, gamma and inverse Gaussian. In this model, the baseline time axis is rescaled by the explanatory variables. The hazard function in the Weibull accelerated failure time model is defined as

$$h_i(t) \;=\; \exp(-\eta_i)h_0\left[t/\exp(\eta_i)\right],$$

where $h_0(t)$ is the baseline hazard function and

$$\eta_i \;=\; \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi}.$$

Figure 1.2 was inspired by a figure in Collett (2003). This figure illustrates the hazard function in the proportional hazards model comparing to the accelerated failure time model.

To estimate parametric survival model, the general form of the likelihood function may be written as

$$L = \prod_{i=1}^{n} \{h_i(t_i)\}^{\delta_i} \{\exp\left[-H_i(t_i)\right]\}, \tag{1.13}$$

where $h_i(t_i)$ is the hazard function, $H_i(t_i)$ is the cumulative hazard function for the desired model and δ_i is the censoring indicator for the ith individual.

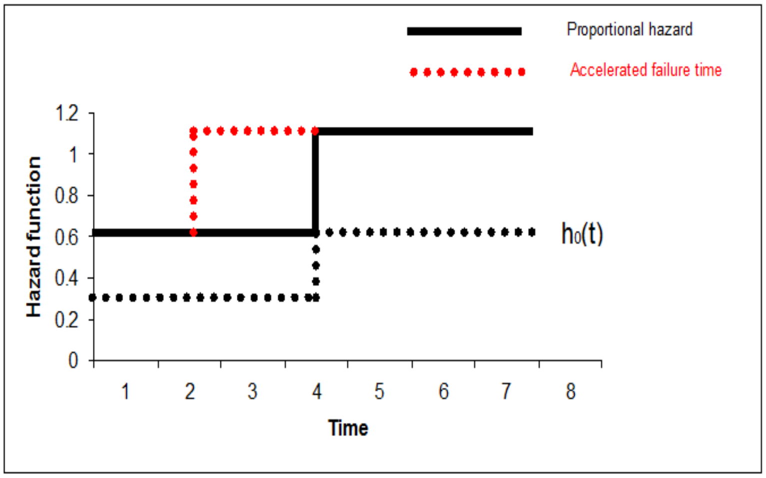

Figure 1.2: The baseline hazard function for individuals in group 1, $h_0(t)$, and the hazard function in group 2 under a proportional hazards model (black solid) and accelerated failure time model (red dots)

1.6 Time-dependent covariates

In many survival analysis studies, patients might be observed frequently during the study period until censoring or failure. Throughout this duration, the measurements of some predictor covariates may be taken at certain follow-up times. For example, in prostatic cancer studies, the size of tumour and other covariates may change over time. These changes are recorded at regular times. When the values of these covariates are updated, the survival model should be adapted to incorporate these updated values. The more recent values of the covariate may have better predictive power than baseline values recorded at the start of the study. Covariates that change through time are called time-varying covariates or time-dependent covariates (Collett, 2003).

Time-dependent covariates may be internal or external covariates. An internal time-dependent covariate relates directly to the patient. Examples of internal variables in medical applications are measures of kidney function, red cell count, blood pressure and serum cholesterol level (Collett, 2003). In contrast, external variables are not related to the body conditions or status. Recording the values of these variables does not require the survival of the patient. In many cases, these measurements can be known before, at the start point of the study and at any future time. For example, the predetermined dosage of a medicine which may be altered during the study, or prearranged changes of the type of immunosuppressant that are used after transplant operations. Additionally, some external variables are completely independent of any patient characteristics, such as the value of atmospheric sulphur dioxide or air temperature. For some diseases, the survival times of patients are significantly affected by these values (Collett, 2003).

Time-dependent covariates may take various forms. For example, a time-dependent covariate may be binary with at most one change, depending on a certain condition during the study time (Allison, 1995); or it may be continuous and updated regularly; or it may be constructed as an interaction between a fixed covariate and a function of survival time. Extending a model to include a time-dependent covariate requires some difficulties in handling this covariate to be resolved.

- The covariate may be recorded at follow-up times with units, say months, that do not match up the survival time units, say days, (Allison, 1995). The solution to this problem is to change the monthly follow-up time units to be counted in days.

- The covariate will usually only be measured at a certain number of occasions. Therefore, it may be necessary to approximate its value at intermediate points (Collett, 2003).

- Prediction in survival models with time-dependent covariates represents another difficulty, because the changing nature of the covariate with time means that its value at different future times will be unknown.

- The survival curves cannot be estimated, because of estimating the curve requests recording the value of the time-dependent covariate for the subject. In this case, knowing this value means that this subject has not been observed or still alive or in the risk set and then survival time for this subject cannot be used to estimate the survivor function (Fisher and Lin, 1999).

For the last problem, a non-parametric method for estimating survival curves for each level of the categorical time-dependent covariate can be employed, this method is tenable for the continuous covariates after they are categorized. In Schultz *et al.* (2002) a method proposed by Simon and Makuch (1984), which depends on the number of the individuals who are still alive at each death time for each time-dependent covariate level, can be applied. The idea here is the same as in the Kaplan-Meier method, in calculating the survival probabilities at each death time. However, this technique calculates the number of individuals at risk for each covariate level, instead of using the same number in the risk set for all covariates. A different simple way to estimate survival curves in the presence of a time-dependent covariate was suggested by Collett (2003). This way is executed for any individual with a certain value for the time-dependent covariate. For example, in a study of heart transplant survival data with age group as a fixed covariate and creatinine level as a time-dependent covariate, the survival curves for different age groups can be estimated using specific creatinine level values.

In the presence of time-dependent covariates, modified survival models must be adopted. One of these models is the Cox regression model that is adjusted to involve both fixed and time-dependent covariates. The partial likelihood function in (1.12) is extended when the survival data contains covariates that change over time. However, parametric modelling may be a better approach for this type of covariate when a specific distributional assumption is appropriate for the data.

1.7 Heart and cornea transplant data

Heart failure occurs in an individual when the heart has difficulty in pumping enough blood arround the body. This happens for many reasons, such as heart attack, hypertension, valve problems, infections, alcohol, smoking and drug use. The usual symptoms of heart dysfunction are breath shortness, cough, low exercise tolerance and fluid retention (Jurt *et al.*, 2008). When these symptoms cannot be treated by usual heart surgery or other medications, heart transplantation may be performed. Many factors may affect the survival time after the transplant operation. The most common factors are donor age and the following factors for the recipient: age, sex, diabetes status, smoking, alcohol consumption, urgency of transplant needs, and use of medications before and after the operation. These factors were treated as fixed covariates through several studies using semi-parametric and parametric proportional hazards models (see section 2.5). In heart transplant studies, kidney function was studied as a predictor in the Cox proportional hazards model in Bidbins-Domingo *et al.* (2004) and

Sarnak *et al.* (2003). In the heart transplant data set supplied by NHS Blood and Transplant, which will be used in this thesis, kidney function can be assessed by creatinine level which may be measured regularly after the operation. Hence, it is incorporated in the model as a time-dependent covariate with many potential change points.

The cornea is the clear part that constitutes the anterior structure of the fibrous tunic of the eye (Ingle, 2004). When the cornea stops performing its function, as a result of a disease or traumatic injury, a corneal transplant becomes necessary. The grafting is performed to develop the vision and improve the quality of the eye as a substantial clinical consequence (Stuart *et al.*, 1997). In the case of receiving a corneal transplant, many factors may affect the survival time of the grafted cornea. These factors include recipient and donor age, donor sex, storage time for the organ, number of previous transplanted organs for the recipient and corneal vascularisation. To model these data, all the factors are included in the model as fixed covariates. On the other hand, the effect of the second graft in one eye on the survival time of the other eye may be significant, so that second graft effect might be measured using time-dependent covariate with one change.

The heart and cornea transplant data sets supplied by NHS Blood and Transplant are used as examples to illustrate the proposed models introduced in this thesis. The initial step to study the two data sets is to use the two basic approaches, the Cox proportional hazard model and the alternative parametric models, to study the effects of the different predictors on the survival time after the transplantation surgery. Secondly, the extended Cox model will be applied where some covariates are allowed to change over time. In the heart data set, the creatinine level that is measured regularly will be incorporated in the model as a time-dependent covariate. Similarly, the effect of the second eye graft on survival time of the first eye graft will be studied by a binary time-dependent covariate. In this context, it is proposed to introduce a parametric model as a possibly good alternative to the Cox model where time-dependent covariates are included in the model. The suggested Weibull model with time-dependent covariate may poorly fit these data sets, and then it is of interest to extend the Weibull model by splines function achieving more flexibility. The proposed two extensions will be examined to assess their efficiency relative to the alternative approaches and their adequacy to fit the data sets on hand. Evaluating these approaches will initially depend upon residual analysis given the applied data. A subsequent stage will be running simulations to assess general performance and suitability for studying survival time after heart and cornea transplants with the proposed methods. Hence, the aim of this study is to extend the flexible Weibull model introduced by Royston and Parmar (2002) with time-dependent covariates and examining the extended model in fitting survival times after heart and cornea transplants, particularly when the data have time-dependent covariates.

1.8 Organisation of the thesis

In chapter two, semi-parametric and parametric survival models that incorporate time-dependent covariates are reviewed. This review includes a brief discussion of spline functions in the context of survival models. In addition methods for simulating survival data are discussed. Finally, we review survival studies of heart and cornea patients.

Chapter three will include details of the likelihood functions that will be used to fit the Weibull, log-logistic and log-normal models and the adjustments that are executed to fit these models in the presence of time-dependent covariates. Furthermore, the mathematical functions that can be used to construct the likelihood function of the Weibull spline model with different number of knots will be described. Finally, the derivation of the likelihood function of the proposed Weibull spline model with time-dependent covariates will be described.

Chapter four will contain heart transplant model. Description for the heart transplant data and the factors particularly kidney functions that may affect the hazard after heart transplant operations will be introduced. Then, procedures of model building will be applied through simple parametric survival models. Moreover, the results of fitting the time-dependent models, the Cox and parametric, will be discussed. Also, the results of applying the Weibull spline models when creatinine level is included as a fixed covariate and discuss in the same manner the results when the same covariate is treated as time-dependent. Graphical assessment will be used as a helpful tool to explain the results. Final process will be the residual analysis that can be applied for the models in order to assess the adequacy of the applied models as an initial step to compare the competitive approaches.

Chapter five is specified to study graft survival time after corneal transplantation. This chapter will start with explaining the factors that may affect failure of the grafted cornea with focus on the second eye graft that will be used as a fixed and a time-dependent covariate. In a similar manner to chapter four, the initial analysis step will be model building, and then applying the two modelling approaches with no time-dependent covariate. Following the models will be applied including the second eye graft as a time-dependent covariate. Then, the results of the Weibull spline model in the two cases will be discussed with their necessary graphical assessments. Finally, residual analysis will be performed for all the models to evaluate them and determine their appropriateness for the illustrated data set.

Chapter six will introduce a discussion for the methods that can be used to generate survival times from the Weibull spline model. In this chapter difficulties in generating observations from the Weibull spline model will be considered and methods to select the number of knots to be used in the Weibull spine model will be discussed using a simulation experiment.

In chapter seven, a simulation design for the applied models based on the two real data sets in order to mimic the properties of the heart and cornea transplant data will be executed. The first group of results will be for the Weibull spline model with time-fixed covariates. Secondly, the results of simulating the Weibull standard model with time-dependent covariates. Finally, the results of simulating the Weibull spline model with time-dependent covariates will be introduced. The chapter will aim to perform three comparisons to evaluate

- The most efficient Weibull spline model where no time-dependent covariate is included.
- The relative efficiency of the Cox, Weibull models and log-logistic where time-dependent covariates are included.
- The most efficient Weibull spline model where time-dependent covariates are included.

Chapter eight will contain a discussion for the performance of each proposed model, in addition to some suggestions that may improve the adopted models as a future work.

Chapter 2

Survival modelling with time-dependent covariates

To use survival models, the first issue is to specify the possibility of assuming a certain probability distribution to the survival times. The first case arises when no particular distribution is specified, and then semi-parametric modelling is adopted with no specified form for the hazard function. This approach is easily extended to allow for one or more covariates to change over time and such models may be fitted using standard packages. However, if a particular distribution can be specified for the survival data, parametric modelling may be the appropriate approach. In this case, the estimates obtained from the parametric model will be more accurate and the model will increase the relative efficiency against semi-parametric models. Similar to the semi-parametric models, the parametric models may be extended to accommodate time-dependent covariates but with possibly more efficient performance than the semi-parametric models. The two approaches may be extended to achieve more flexibility by including splines functions. These functions represent the covariate effects and yield smoother hazard functions. In order to validate any adopted approach, residual analysis may be useful to assess model adequacy. However, more evaluations will be important to compare two or more modelling approaches. These evaluations can be executed using simulation studies to evaluate the performance of each model in different situations. In this chapter, section 2.1 will discuss semi-parametric modelling with time-dependent covariates. Section 2.2 will discuss the alternative parametric modelling with time-dependent covariates. In section 2.3, splines functions that are usually used in survival modelling are explained besides the methods of adjusting survival models by splines functions. Section 2.4 will introduce different algorithms that may be used to generate survival times following particular models, in addition to the detailed procedures to perform simulation studies. The studies that have been applied to survival times after heart and cornea transplantation will be briefly revived in section 2.5.

2.1 Semi-parametric modelling with time-dependent covariates

2.1.1 Modelling time-dependent covariates in Cox model

In section 1.4 we introduced the Cox model. We now extend it to incorporate time-dependent covariates. This model is one of the most widespread applied models in survival data modelling. In this model, it is proposed that the effects of covariates on hazard are measured through multiplying the hazard function by a function of such covariates (Fisher and Lin, 1999). Therefore, the hazard rate, $h(t)$, in (1.11) is the product of a parametric function of the explanatory variables $\exp(\beta^T x)$ and the non-parametric baseline hazard function, $h_0(t)$ (Thiebaut and Benichov, 2004).

In many cases, one or more covariates may be collected and recorded over long time. For example, suppose a group of patients is followed up after surgery for 10 years and during this period blood pressure, kidney function and weight are monitored and recorded at pre-determined time points. These covariates have values that change over time and the Cox regression model is no longer appropriate to handle such covariates and must be extended to include the time varying covariates (Fisher and Lin, 1999).

The form of fixed covariates must be determined before considering their changes over time. Different functional forms for the time-varying covariate may be followed depending on the nature of the covariate and the adopted biological hypothesis. For example, in a study of the effect of smoking on survival, the covariate of interest may be the current smoking status. The most common approach to model this covariate is the step function which takes the value 1 for smoking and 0 otherwise within each follow-up interval (Fisher and Lin, 1999). However, Cavender *et al.* (1992) studied the effect of smoking status on death after coronary artery bybass graft surgery as a time varying covariate that changes each 6 months. After using the smoking status as a step function, the result was surprisingly found that no important effect for smoking on hazard. This result was found because some patients might die while their last status was non-smoking and then effect of smoking on hazard did not appear in the analysis. They introduced two suggestions in order to solve this problem. Firstly, it was proposed a time-lagged covariate at the subsequent intervals. Secondly, the percentages of the follow-up times that have smoking status to be 1 were used. The two methods led to a significant effect for smoking on hazard. In a different example, suppose that a continuous variable that might be recorded at regular times (e.g. blood pressure) to measure its effect on hazard. The time varying values for such a variable could be included in the model using different forms. One of these forms, is to record its values at each time point as a step function. Fisher and Lin (1999) suggested modelling this covariate as a moving weighted average particularly over long time intervals. A third approach that might be followed is to assume continuous increasing (e.g. linearly) over the whole study period or until death. Furthermore, the time-dependent covariate can be formed from the interaction between a fixed covariate and time. In this case, the model will include the original covariate as a fixed and the interaction with time as time-dependent covariate. To illustrate this case, the hazard function for the model that includes one covariate x is

$$h_i(t) \quad = \quad \exp(\beta_1 x_i + \beta_2 x_i t) h_0(t).$$

This method can be used to test the proportionality assumption, since if the time-dependent covariates in the previous hazard function are significant, the Cox model is no longer a proportional hazard model(Allison, 2004).

In our study, two time-dependent covariates are used. The first one, introduced in chapter 4, is glomerular filtration rate (GFR). This covariate is measured after heart transplant surgery as a step function every 1 year and then introduced as a many changes time-dependent covariate. The second, introduced in chapter 5, is the second eye graft status which is recorded as a step function that takes the value 1 once the second eye graft has been done and 0 otherwise.

2.1.2 Cox model with time-dependent covariates

According to the Cox proportional hazards model described in section (1.4), the hazard function of the ith individual can be written as

$$h_i(t) = \exp\left\{\beta^T x_i\right\} h_0(t), \tag{2.1}$$

where

$$\beta^T x_i = \beta_1 x_{i1} + \ldots + \beta_p x_{ip},$$

β^T is a vector of coefficient for the fixed covariates, $i = 1, 2, \ldots, n$ and $h_0(t)$ is the baseline hazard function.

The hazard function in (2.1) can be extended to incorporate time-dependent covariates to become

$$h_i(t) = \exp\left\{\zeta_{ij}\right\} h_0(t),$$

where ζ_{ij} is the parameter function for p fixed covariates x_i and q time-dependent covariates y_{ij} for the individual i at time t_j, where

$$\beta^T x_i = \beta_1 x_{i1} + \ldots + \beta_p x_{ip},$$

and

$$\eta^T y_{ij} = \eta_1 y_{ij1} + \ldots + \eta_q y_{ijq},$$

where η^T is parameters vector of the time-dependent covariates y_{ijq} for the ith individual at time segment j. Thus, the hazard function that includes fixed and time-dependent covariates can be written as

$$h_{ij}(t) = \exp\left\{\beta^T x_i + \eta^T y_{ij}\right\} h_0(t). \tag{2.2}$$

In this hazard function, $h_0(t_i)$ is the hazard of the ith individual with covariates values 0 from $t = 0$ and remain constant over time. On the other hand, the hazard function $h(t_i)$ is no longer proportional to $h_0(t_i)$, because the covariates y_{ij} depend on time and so the relative hazard $h(t_i)/h_0(t_i)$ changes over time. The coefficient η can be interpreted as the log hazard ratio for two individuals whose time-dependent covariate values differ by unit, given that they have the same values for the other explanatory variables at that time (Collett, 2003). In order to estimate the extended Cox model, the partial likelihood function in (1.12) is adapted for time-dependent covariates to become

$$L = \prod_{i=1}^{n} \left\{ \frac{\exp(\zeta_{ij})}{\sum_{\iota \in R(t_i)} \exp(\zeta_{lj})} \right\}^{\delta_i}, \tag{2.3}$$

where ζ_{ij} is the covariates function that includes the fixed covariates x_i and the time-dependent covariates y_{ij}, $R(t_i)$ is the risk set at time t_i and δ_i is the censoring indicator. The partial likelihood function in (2.3) can be maximised numerically using the Newton-Raphson method. In the Newton-Raphson algorithm, the observed information matrix $I(\hat{\beta})$ and the vector of efficient scores $U(\hat{\beta})$ are computed. Hence, the vector of β parameters at the $(v+1)th$ cycle of the iterative procedure, $\hat{\beta}_{v+1}$, is given by

$$\hat{\beta}_{v+1} = \hat{\beta}_v + I^{-1}(\hat{\beta}_v) \cdot U(\hat{\beta}_v) \tag{2.4}$$

In this model, the baseline survivor function $S_0(t)$ is estimated using the baseline cumulative hazard function $H_0(t)$ which is defined for fixed and time-dependent covariates as

$$\tilde{H}_0(t) = -\log \tilde{S}_0(t) = \sum_{m=1}^{k} \frac{d_m}{\sum_{l \in R(t_m)} \exp\{\beta^T x_l + \eta^T y_{lj}\}}, \tag{2.5}$$

where the times are ordered as $t_k \leq t < t_{k+1}$, $k = 1, 2, \ldots, r-1$, and y_{lj} is the vector of the values of the explanatory variables for individual l at time point j, and d_m is the number of events at the mth event time, $m = 1, 2, \ldots, r$. Using the relationships in section (1.2), the survivor function for the ith individual can be defined as

$$S_i(t) = \exp\left\{-\int_0^t \exp\left[\beta^T x_i + \eta^T y_{ij}\right] h_0(u)du\right\}. \tag{2.6}$$

This function depends on the baseline hazard function, $h_0(t)$, the fixed covariates and the time-dependent covariates from time 0 to t. Hence, $S_i(t)$ depends on the future values for the time-dependent covariates which are unknown. In this case, the conditional probability of surviving for individual i from t to $t+\Delta$ given that surviving beyond t, $P(T_i \geq t+\Delta | T_i \geq t)$, can be employed. Assuming that the time-dependent covariates are constant within each interval, the approximate conditional probability becomes

$$\begin{aligned} P_i(t, t+\Delta) &= \frac{S_i(t+\Delta)}{S_i(t)} \\ &= \frac{\exp\left\{-\exp[\beta^T x_i + \eta^T y_{ij}] \int_0^{t+\Delta} h_0(u)du\right\}}{\exp\left\{-\exp[\beta^T x_i + \eta^T y_{ij}] \int_0^{t} h_0(u)du\right\}}, \end{aligned}$$

and then the estimated approximate conditional probability of surviving within the interval $(t, t+\Delta)$ is

$$\tilde{P}_i(t, t+\Delta) = \exp\left[-\left\{\tilde{H}_0(t+\Delta) - \tilde{H}_0(t)\right\} \exp\left(\beta^T x_i + \eta^T y_{ij}\right)\right], \tag{2.7}$$

where $\tilde{H}_0(t)$ is the estimated baseline cumulative hazard function based on the fitted Cox regression model that includes fixed covariate x_i and time-dependent covariates y_{ij} for the ith individual (Altman and De Stavola, 1994).

The expected number of events in the interval $(t, t+\Delta)$ can be estimated by

$$1 - \tilde{P}(t, t+\Delta)$$

when this probability is multiplying by the total number of observations at risk. An informal assessment of model adequacy can be evaluated by comparing the the observed number of events with their expected number in the interval $(t, t+\Delta)$ (Collett, 2003).

2.1.3 Different semi-parametric approaches to model time-dependent covariates

Giorgi and Gouvernet (2005) extended the regressive relative survival model of Esteve *et al.* (1990) to allow for time-dependent covariates. This extension was achieved by using a counting process approach to the covariates that change over time. According to the relative survival regression model proposed by Esteve *et al.* (1990), the observed hazard for total mortality, h, at time t for an individual with age a at diagnosis and a vector of explanatory variables $x's$ can be written as

$$h(t, x, a) = h_e(t, a, x_s) + h_d(t, x),$$

where $h_e(t, a, x_s)$ is the expected hazard function that has been obtained from the overall mortality in general population depending on covariates of sub-vector x_s^T and the published age mortality rate, a, (Esteve *et al.*, 1990). The second term $h_d(t, x)$ represents the hazard function of the disease mortality which is calculated from the data under study, this function is defined for the ith individual as

$$h_d(t_i, x) = \sum_{l=1}^{r} h_{0(l)} I_l(t_i) \exp(\beta^T x_i),$$

where $h_{0(l)}$ is the baseline hazard for mortality at the lth time-segment, $l = 1, \dots, r$, I_l is an indicator function that takes the value 1 if $t_{l-1} < t_i < t_l$ and 0 otherwise and β^T is the coefficients vector of x_i fixed-in-time covariates. This hazard function is extended to include time-dependent covariates to become

$$h_d(t_i, x, y) = \sum_{l=1}^{r} h_{0(l)} I_l(t_i) \exp(\beta^T x_i + \eta^T y_{ij}), \tag{2.8}$$

where η^T are the coefficients of the time-dependent covariates y_{ij}.

Based on this extension, the likelihood function for n individuals is written as

$$L = \prod_{i=1}^{n} \left\{ [h_d(t_i, x_i, y_{ij})]^{\delta_{ij}} \times \left[\exp\left(- \int_{t_i(j)}^{t_{i(j+1)}} h(u) du \right) \right] \right\}, \tag{2.9}$$

where δ_{ij} is the right censoring indicator for individual i at time interval j, $j = 1, \dots, k_i$. This indicator function takes the value 1 for an uncensored observation and 0 otherwise. Estimation through this likelihood depends on properties of the counting process approach. Each subject consists of number of intervals based on the number of the time-dependent covariate values for that subject. The fixed-in-time covariates remain constant through all the intervals. The censoring indicator δ_{ij} takes the value 0 for each interval while last interval takes the original censoring indicator for the subject. This approach will be illustrated in detail in section 3.2. Although this approach introduces estimates for the time-dependent covariates in relative survival models, semi-parametric modelling with time-dependent covariates can be achieved in different frameworks.

Another study by Gao *et al.* (2007) introduced a method to achieve a non-parametric estimation for baseline hazard function with time-dependent covariates. The proposed method depends on approximating baseline hazards and covariate effects as step-functions. This method complements the Cox proportional hazard model, since it is fitted to explore the potential survival data structure instead of performing hypothesis tests. To illustrate the method, let $t_i = \min(T_i, C_i)$ be the observed time for the ith individual, where Y_i and C_i are the potential survival and censoring times respectively. In the presence of time-dependent covariates y_{ij}, the observed data can be denoted as
$\{(t_i, \delta_i), y_{ij}, i = 1, 2, \dots, n, j = 1, 2, \dots, k_i\}$, where t_i is the observed survival time, δ_i is the censoring indicator and y_{ij} is the time-dependent covariate value for individual i at the jth time. In this case, the hazard function can be written as

$$h_i(t|y_{ij}) = \psi(y_{ij}) h_0(t),$$

where $h_0(t)$ is the baseline hazard function and $\psi(y_{ij})$ is an unspecified non-negative function that models the hazards when covariate values change over time. According to the proposed approach, the estimates for covariate effects and baseline hazard function were developed by the tree-type algorithm of Huang *et al.* (1998). In order to approximate the survival experience of an individual, step functions for $h_0(t)$ and $\psi(y_{ij})$ are used. Following this model, the survival time for individual i has a piecewise exponential distribution, and then the density function is defined as

$$f_i(t) = \begin{cases} h_{i1}\exp\{-h_{i1}t\}, & 0 < t \le t^*_{i,1} \\ h_{i2}\exp\{t_{i1}(h_{i2}-h_{i1}) - h_{i2}t\}, & t^*_{i,1} < t \le t^*_{i,2} \\ \vdots & \vdots \\ \vdots & \vdots \\ h_{i(J+1)}\exp\left\{\sum_{j=1}^{J} t_{i,j}(h_{i(j+1)}-h_{ij}) - h_{iJ}t\right\}, & t^*_{i,J} < t < \infty, \end{cases} \tag{2.10}$$

where h_{i1} and $h_{i1}t$ are the hazard and the cumulative hazard functions at the interval $0 < t \le t^*_{i,1}$, and using δ_i as the censoring indicator that takes the value 1 for uncensored observation and 0 otherwise and $t^*_{i,1}, t^*_{i,2}, \ldots, t^*_{1,j}$ are jumps for the piecewise exponential distribution, the full log likelihood for the *ith* individual is

$$logL = \begin{cases} \delta_i\log(h_{i1}) - h_{i1}t, & 0 < t_i \le t^*_{i,1} \\ \delta_i\log(h_{i2}) + t^*_{i1}(h_{i2}-h_{i1}) - h_{i2}t, & t^*_{i,1} < t_i \le t^*_{i,2} \\ \vdots & \vdots \\ \vdots & \vdots \\ \delta_i\log(h_{i(J+1)}) + \sum_{j=1}^{J} t^*_{i,j}(h_{i(j+1)}-h_{ij}) - h_{iJ}t, & t^*_{i,J} < t_i < \infty \end{cases} \tag{2.11}$$

The method was applied to model the withdrawal risk in a clinical trial to evaluate anti-depression treatment in studying the development of clinical depression. The results showed that the suggested algorithm produces accurate approximations for the baseline hazard and covariate effects. On the other hand, the Cox model may produce more accurate estimates, particularly when correct specification for the covariate structure is obtained. Consequently, this method could be considered as a complementary step for the usual extended Cox model that includes time-dependent covariates.

2.1.4 Model comparison and validation

Model checking procedures for models containing time-dependent covariates are similar to the checking procedures in the models with fixed covariates. Cox-Snell residuals can be employed to test the adequacy for the fitted model. The idea is to calculate the residuals for each subject using the last record for this subject (Dupont, 2002). Also, martingale residuals can be employed to check the models with time-dependent covariates. For each subject, martingale residuals can be computed for each record separately. Then the residuals for any subject i is the sum of the residuals at all its records (Therneau and Gambsch, 2000). What is more, the influential observations can be examined following the same manner when no time-dependent covariates in the model. It is done by the $delta - beta$ technique, in order to measure the effect of neglecting the influential observations on the parameter estimates, particularly the time dependent covariate estimate (Collett, 2003). In the presence of a time-dependent covariate, there is a difficulty to assess the functional form of such covariate, because each subject has more than one value for the covariate, so that it is not obvious which value should be plotted with the martingale residual. However, the method of Therneau and Gambsch (2000) can be a reasonable solution. A final issue in time-dependent covariate models is the interpretation of the treatment effect that may be hidden (Sparling *et al.*, 2006). This may occur when the time-dependent covariate masks the treatment effect in the time-dependence modelling process; see Collett (2003) and Sparling *et al.* (2006). Many studies have applied the extended Cox model with time-dependent covariates. One of such study is Grohn *et al.* (1998) in which the extended Cox model was applied using the effect of disease status on culling rate of cows as a time-dependent covariate.

The Cox model is one of the most widely used in survival analysis. It enables the effects of covariates on the hazard to be estimated without specifying the form of the baseline hazard function $h_0(t)$ (Nelson *et al.*, 2007).

On the other hand, Cox model may be unsuitable in some cases

- When the assumption of one of the known probability distributions such as: exponential, Weibull, log-logistic and log normal is valid, the inferences based on such distributions leads to smaller standard errors for the hazard ratios and the survival time quantities, comparing to the semi-parametric model.

- Royston and Parmar (2002) reported that the estimated baseline hazard function is highly erratic and its estimates are high dimensional.

- Collett *et al.* (2006) reported the difficulty of estimating survival rates at a certain time in addition to percentiles of survival distribution, since the survivor function is constant between death times and extrapolation is not available.

- In maximization of the partial likelihood function, the values of each covariate must be known at each death time which is not possible. Although, they can be estimated using linear interpolation method, approximation the time-dependent covariate values may cause measurement errors or intrinsic variation.

2.2 Parametric modelling for time-dependent covariates

In section 2.1 it was shown that the Cox proportional hazards regression model is easily extended to incorporate one or more covariates whose values are subject to change over time. Moreover, this model is straightforwardly fitted in many statistical packages. On the other hand, an alternative and potentially more efficient approach is to use simple parametric accelerated failure time model with standard survival distributions such as the Weibull, log-logistic and log-normal. Again these models may be extended to incorporate time-dependent covariates. The accelerated failure time model will be introduced in this section and then how to extend it to include time-dependent covariates. The performance of the parametric model will be investigated in chapters 4, 5 and 7 using the NHS Blood and Transplant data sets, with residual analysis and a simulation study.

2.2.1 Accelerated failure time model

In parametric survival modelling, the proportional hazards model is widely applicable. However, there are few standard distributions that satisfy proportional hazards, such as the Weibull and Gompertz distributions, and there may be a need to use different distributions. Furthermore, the proportional hazards assumption may be invalid, and then this model becomes inappropriate (Collett, 2003). In such cases an alternative model with distributions will possibly not be a monotonic is the accelerated failure time model.

The term accelerated failure time is extracted from accelerated life testing, particularly in reliability applications. In such applications, designs depend on extrapolations (e.g., increasing stress levels in step-stress models) to attain rapid failure at some conditions. The adjusted time-scale provides the proposed link between the effects of different stress levels. Moreover, the model is applicable in many situations in biostatistics (James, 2005).

To illustrate the model, let $T_1, \ldots, T_n$ be random variables that represent survival times for n individuals, and assume that $(x_{i1}, \ldots, x_{ip})^T$ is a vector of explanatory variables x_i for the ith individual. Thus, the general regression survival model is

$$\log T_i = \beta^T x_i + \epsilon_i,$$

where β^T is the vector of regression coefficients, $\beta^T = (\beta_1, \ldots, \beta_p)$ and the ϵ_i are independent, identically distributed random variables. Then

$$T_i = \exp(\beta^T x_i)\sigma_i,$$

where $\sigma_i = \exp \epsilon_i$. Thus

$$\sigma_i = T_i \exp(-\beta^T x_i).$$

The distribution of σ_i is known as the baseline survival distribution, and the $T_i \exp(-\beta^T x_i)$ are identically distributed. In this model the baseline time axis is rescaled by the explanatory variables. For example, the individual whose covariate value is higher by a factor of 2 progresses along the baseline time axis twice as slowly as the individual with the lower value. The previous example can be graphically explained with the survivor functions in Figure 2.1 and the hazard functions in Figure 2.2.

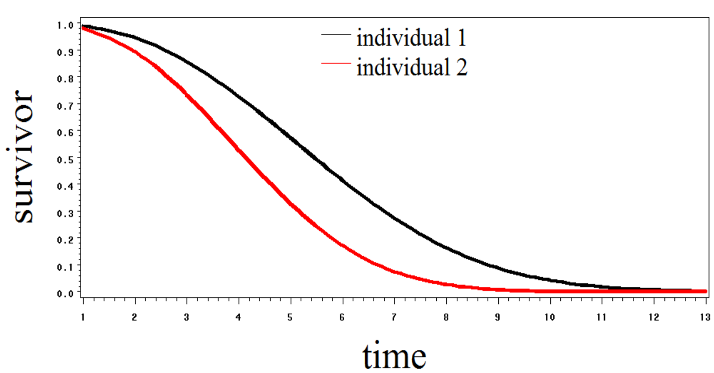

Figure 2.1: The survivor functions for two individuals whose values of $\exp(\beta^T x_i)$ differ by a factor of 2

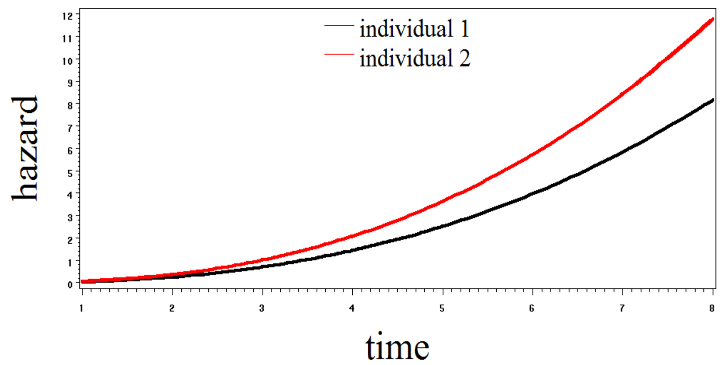

Figure 2.2: The hazard functions for two individuals whose values of $\exp(\beta^T x_i)$ differ by a factor of 2

For the AFT model, the general density, survivor, hazard and cumulative hazard functions can be defined as

$$\begin{aligned} f_i(t) &= \exp(-x_i^T\beta) f_0(\exp[-\beta^T x_i]t), \\ S_i(t) &= S_0(\exp[-\beta^T x_i]t), \\ h_i(t) &= \exp\left[-\beta^T x_i\right] h_0\left(\exp[-\beta^T x_i]t\right) \\ H_i(t) &= H_0\left(\exp[-\beta^T x_i]t\right), \end{aligned}$$

where f_0, S_0, h_0 and H_0 are the baseline density, survivor, hazard and cumulative hazard functions.

2.2.2 Parametric models with time-dependent covariates

Parametric models may achieve better performance than the Cox model, particularly if the correct probability distribution is specified. In this case, the fitted parametric model often produces more efficient parameter estimates. Furthermore, in small samples the loss of precision from fitting parametric models is less than the Cox model (Cox and Oakes, 1984). In the case of including one or more covariate as a time-dependent, parametric models may be good alternatives to the semi-parametric approach.

One of the studies that depends on modelling time-dependent covariates in a parametric framework is that of Petersen (1986). In this study a fully parametric model has been extended to allow for time-dependent covariates. His methodology relied on the Gauss-Newton technique for non-linear least squares estimation in order to estimate his model using maximum likelihood. To illustrate the model, suppose that t is a non-negative continuous random variable that refers to the survival time. This time is the number of months an employee spends in a certain job before leaving it. Also, let x be a fixed variable that refers to the marital status of an employee. This variable takes the value 1 for a married individual and 0 otherwise. The second factor in the model is the labour force experience which is defined by $O(t)$, $O(t) = O + t$, where O is the value of the variable when the observation is entered to the study. The third factor is the duration of staying at the job which can be measured by the time t. The values of the time-dependent covariates change in the beginning of each interval and stay constant, and then jump to the new value at beginning of the next interval. In this empirical study, an extension of the Gompertz model was used, and then the hazard function is

$$h(t|x, O(t)) = \exp\left[\beta x + \eta(O + t) + \pi t\right] \tag{2.12}$$

In order to define the survivor function for the model, the hazard functions at two sequential intervals t_{j-1} and t_j are defined as

$$\begin{aligned} h(t_{j-1}|x, (O + t_{j-1})) &= \exp\left[\beta x + \eta(O + t_{j-1}) + \pi t_{j-1}\right], \\ h(t_j|x, (O + t_j)) &= \exp\left[\beta x + \eta(O + t_j) + \pi t_j\right]. \end{aligned}$$

Consequently, the cumulative hazard function of the model for the *ith* individual is defined by

$$H(t_i|x_i, O(t_{ij}), t_{ij}) = [1/(\eta + \pi)] \sum_{j=1}^{k_i} \left\{h(t_{i(j)}) - h(t_{i(j-1)})\right\}, \tag{2.13}$$

where x_i is the marital status, $O(t_{ij})$ is the labour force experience for the *ith* individual at time t_{ij} and $j = 1, \ldots, k_i$. For this model, the likelihood function with right censoring is

$$L = \prod_{i=1}^{n} \left\{h(t_i|x_i, O(t_{ij}), t_{ij})\right\}^{\delta_i} \left\{\exp\left[-H(t_i|x_i, O(t_{ij}), t_{ij})\right]\right\}, \tag{2.14}$$

where δ_i is the right censoring indicator. In order to apply this function, multiple records were created for each observation based on time intervals. The model was applied to a sample of 6998 jobs, yielding 10198 records, depending on the updated changes in the time-dependent covariates.

Methodology of fitting parametric survival models for interval-censored data with time-dependent covariates have been introduced in the study of Sparling *et al.* (2006). A family of regression models for Weibull, negative binomial and log-logistic distributions was developed as special cases that can be derived from general form of a suggested hazard function. Following Odell *et al.*, (1992), the general likelihood function for right, left and interval censoring was expressed as

$$L = \prod_{i=1}^{n} \left\{ f_i(t_i)^{\delta_{E_i}} F_i(t_{L_i})^{\delta_{L_i}} \left[1 - F_i(t_{R_i})\right]^{\delta_{R_i}} \left[F_i(t_{R_i}) - F_i(t_{L_i})\right]^{\delta_{I_i}} \right\} \tag{2.15}$$

where

δ_{R_i}= 1 if right censored at time t_i, 0 otherwise;
δ_{L_i}= 1 if left censored at time t_i, 0 otherwise;
δ_{I_i}= 1 if interval censored at time t_i, 0 otherwise;
δ_{E_i}= 1 if uncensored at time t_i, 0 otherwise.

Since $\delta_{E_i} = 1-(\delta_{R_i}+\delta_{L_i}+\delta_{I_i})$ for any subject $i = 1, \ldots, n$, $f(t)$ defined the probability density function for the event times and $F(t)$ defined the distribution function. In the presence of both fixed and time-dependent covariates, the likelihood function can be written as

$$\begin{aligned} L \;=\; & \prod_{i=1}^{n} \left\{ f_i(t_i|x_i, y_{i[(t_i)]})^{\delta_{E_i}} F_i(t_i|x_i, y_{i[(t_i)]})^{\delta_{L_i}} \left[1 - F_i(t_i|x_i, y_{i[(t_i)]})\right]^{\delta_{R_i}} \Big[F_i(t_i|x_i, y_{i[(t_i)]}) \right. \\ & \left. - F_i(t_i|x_i, y_{i[(t_i)]})\Big]^{\delta_{I_i}} \right\}, \end{aligned} \tag{2.16}$$

where $x_i = (x_{i1,...}, x_{ip})^T$ is the vector of p fixed covariates and $y_{ij} = (y_{ij1}, \ldots, y_{ijq})^T$ is the vector of q time-dependent covariates for subject i at the jth update time. Then maximization of the likelihood function was executed by Newton-Raphson method in order to obtain the parameter estimates and their standard errors. From the proposed models, Weibull model was applied on 1316 patients with 3934 records according their updated values at each follow-up time. The time-dependent covariate, HbA_{1c} which is the level of glucose exposure (glycemia) over the preceding 6-8 weeks, was highly significant with small relative risk. To check the fitted model, the deviance was computed as a fitting diagnostic value with p=0.624 that indicated model adequacy.

The two studies introduce approaches to extend parametric survival models to allow for time-dependent covariates. In our study, a similar approach to Sparling *et al.* (2006) is adopted. However, the cumulative hazard function in this study should be modified to calculate the function when the time exceeds the end of time intervals, more details will be introduced in section (3.2). Furthermore, the model in our study will be extended by natural cubic splines to gain more flexibility. Evaluations for the model before and after adding splines will be introduced using model checking procedures and a simulation study which is based on the NHS Blood and Transplant data sets.

2.3 Splines in survival modelling

The Cox proportional hazards model is a tool to obtain the covariate estimates and log hazard ratios without need to estimate the baseline hazard parametrically (Nelson *et al.*, 2007). In the hazard function of this approach, the response variable is the failure hazard rate which is transformed to the log hazard ratio of covariates in linear form. On the contrary, a non-linear smooth function may achieve a better representation for the covariates effects and then it will be more precise comparing to the linear form (Sleeper and Harrington, 1990). Furthermore, parametric models may be good alternatives to the Cox model. However, the restrictions of the hazard function shape may affect the model adequacy. What is more, many distributional forms may fail to fit hazard functions particularly in observed transplantation data. For example, in Collett *et al.*, (2006), it was found that the hazard function in the Weibull spline model decreases swiftly compared to the hazard in the standard Weibull model after kidney transplantation. Both the Cox and parametric models can be re-expressed to allow for spline interpolation functions to obtain more flexible hazard function and possibly a more suitable model.

2.3.1 Spline interpolation

Interpolation is the creation of a curve in order to connect a set of data points. The first interpolation approach is to use global interpolation which relies on a single polynomial function to fit all the data points (Kruger, 2002). However, this method may lead to erratic behaviour for the created curve when many data points are interpolated. Even though use of a global polynomial often interpolates the data sets with higher range of points, this function does not usually interpolate all the data points (Levine and McKinley, 2009).

On the other hand, piecewise interpolation constructs polynomial functions between each pair of data points, so that this approach achieves smoother curves and introduces solutions to the previous problems in the global polynomial technique. If the piecewise polynomial is first degree, then it is called linear interpolation. When the piecewise polynomial is of higher degree, it is called spline interpolation (e.g. quadratic splines if the polynomial is second

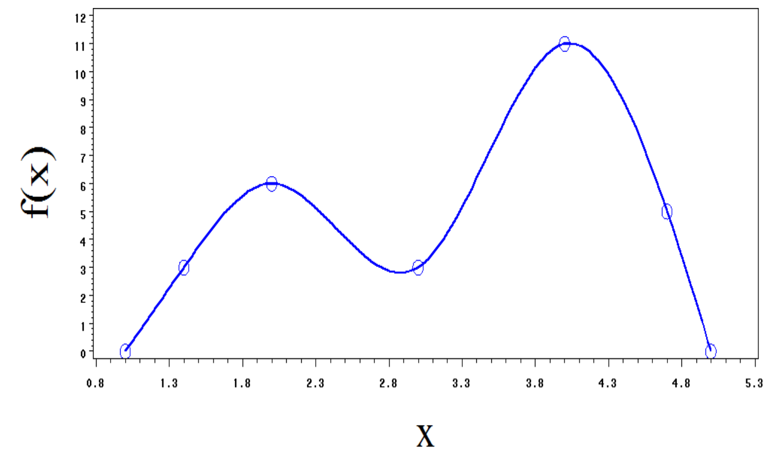

Figure 2.3: Natural cubic splines curve through seven data points.

degree and cubic splines for the third degree polynomial). The idea of splines, one of the most widely used technique in data analysis, is to interpolate between certain data points without knowing the original function information. Increasing the polynomial order leads to smoother curves (Kruger, 2003).

The mathematical cubic spline technique is applied by using numerical values for the points and the cubic polynomial coefficients as weights. The line is inverted by these coefficients through all the data points smoothly and continuously. The piecewise function in cubic splines $M(x_i)$, for any data points $x_1, \ldots, x_n$ that are assumed to be ordered, has four basic characteristics (McKinley and Levine, 2000):

1. The function $M(x_i)$ interpolates all the data points from x_1 to x_n.

2. $M(x_i)$ is continuous on the interval $[x_1, x_n]$.

3. The first derivative $M'(x_i)$ is continuous on the interval $[x_1, x_n]$.

4. The second derivative $M''(x_i)$ is continuous on the interval $[x_1, x_n]$.

There are three basic types of cubic splines:

- Parabolic spline. The second derivatives at the end points, x_0 and x_n, are the same at the adjacent points, $M''(x_0) = M''(x_1)$ and $M''(x_n) = M''(x_{n-1})$, and then the smoothed curve is parabolic at the end points.

- Cubic run out splines. The smoothed curve is adjusted by single cubic curve over the last two intervals, since the second derivatives at the end points are $M''(x_0) = 2M''(x_1) - M''(x_2)$ and $M''(x_n) = 2M''(x_{n-1}) - M''(x_{n-2})$.

- Natural cubic spline. The second derivatives are equal to zero at the end points, $M''(x_1) = M''(x_n) = 0$, so that the natural cubic splines curve becomes linear outside the interval $[x_1, x_n]$. This property is shown in the natural cubic splines curve in Figure 2.3. This figure shows interpolation of seven data points by natural cubic spline curve that has extended lines outside the end points.

Natural cubic splines can be used in survival models in order to obtain a more flexible model by smoothing the survival functions (Jimenez, 2006). The baseline cumulative hazard function for the Weibull model, $H_0(t)$, can be approximated by the natural cubic splines function. This approximation can be applied in the Weibull survival model that includes both fixed and time-dependent covariates to obtain a more flexible model. More details will be introduced in the next section and in chapter 3.

2.3.2 Cox model with cubic splines

The Cox proportional hazard model can be approximated using cubic splines in order to smooth the hazard function. In this case, the model will retain its basic advantages such as, the possibility to be applied through several packages and the non-determinable hazard shape property, i.e. the non-parametric hazard function. Sleeper and Harrington (1990) approximated the Cox model by B-splines that was described originally by De Boor (1978, 2001) to produce a more flexible model. The B-splines are applied as basis functions to fit smoothed curve. In this technique, data points are divided into intervals with end points that are converted to knots with smoothness conditions. Their method was based on transforming the continuous covariates into the B-splines vector, and then the corresponding hazard function of the extended model was defined by

$$h(t|x) = h_0(t) \exp\left[\sum_{j=1}^{p} \beta_j x_j + \sum_{j=p+1}^{p+q} M(x_j)\right],$$

where $h_0(t)$ is the baseline hazard function, the first covariates group, $x_1, \ldots, x_p$, include the categorical covariates while the continuous covariates, $x_{p+1}, \ldots, x_{p+q}$, are transformed into the B-splines basis function $M(x_j)$.

Gray (1992) used a limited number of fixed knots to model a flexible Cox model with B-splines function and then he used a penalized partial likelihood function to estimate the parameters. In his proposed model, the hazard function for the *ith* subject was defined as

$$h_i(t|x_i, z_i) = h_0(t) \exp\left[\beta^T x_i + f_j(z)\right],$$

where β^T is the vector of unknown parameters for the explanatory variables x_i and $f_j(z)$ is the splines term that can be written as

$$f_j(z) = \gamma_{j0}(z) + \sum_{k=1}^{m+2} \gamma_{jk} B_{jk}(z),$$

where $\gamma_{j0}, \gamma_{j1}, \ldots, \gamma_{jk}$ are the spline parameters, m is the number of internal knots and $\sum_{k=1}^{m+2} \gamma_{jk} B_{jk}(z)$ is the sum of cubic B-spline basis functions as defined by De Boor (1978).

LeBlanc and Crowley (1999) used the multivariate adaptive regression splines of Friedman (1991) to modify the Cox model by terms that represent the effect of covariates with splines basis functions. The P-splines can be defined as regression splines when the coefficients of the piecewise polynomial are penalised by controlling influence of the included knots instead of discarding them. Eisen *et al.* (2004) used penalised splines with the Cox model by adding a smooth function that represents the P-splines degree to the hazard function. Amorim *et al.* (2008) estimated time-dependent coefficient rates model with B-splines function. In this study, the hazard function that describes the recurrent average in a certain period for the ith individual was defined as

$$d\mu_i(t) = \exp\left\{\beta^T x_i + \eta(t) y_i(t)\right\} d\mu_0(t),$$

where $d\mu_0(t)$ is the baseline hazard function and $\eta(t)$ is a time-dependent coefficient for possibly time-dependent covariate $y(t)$. By approximating the $\eta(t)$ by its B-splines function, the previous rate model becomes

$$d\mu_i(t) = \exp\left\{\beta^T x_i + \gamma^T \tilde{Y}(t)\right\} d\mu_0(t),$$

where $\tilde{Y}(t)$ is the time-dependent term that incorporates the B-splines basis functions.

In the study of Heinzl *et al.* (1996), the Cox model was adapted by binary time-dependent covariate using cubic splines function. The hazard function of the ith individual in this model is written as

$$h(t_i) = h_0(t_i) \exp(\eta y_{ij}),$$

where the binary time-dependent covariate, y_{ij}, at time τ_{ij} is defined as

$$y_{ij} = \begin{cases} 0, & 0 < t_i < \tau_{ij} \\ 1, & t_i \geq \tau_{ij}. \end{cases}$$

To increase the model flexibility, the hazard function was modified to become

$$h(t_i) = h_0(t_i) \exp\left(\eta y_{ij} M(t_i - \tau_{ij})\right), \tag{2.17}$$

and the log hazard ratio function is

$$\log\left[h_i(t_i)/h_0(t_i)\right] = \eta_1 y_{ij} + \eta_2(t_i - \tau_i) + \sum_{j=1}^{m-2} \gamma_j M_j(t_i - \tau_{ij}), \tag{2.18}$$

where the spline function $M_j(t_i - \tau_{ij}) = 0$ for $t_i < \tau_{ij}$, $j = 1, \ldots, m-2$.

The restricted cubic spline function, $M(t_i - \tau_{ij})$, is a development of the cubic spline function that was introduced by Durrleman and Simon (1989) and Hess (1994). This standard cubic spline function for m knots with $0 \leq \kappa_1 \leq \kappa_2 \leq \cdots \leq \kappa_m$ can be written as

$$M(u) = \beta_0 + \beta_1 u + \beta_2 u^2 + \beta_3 u^3 + \sum_{j=1}^{m} \gamma_j (u - \kappa_j)_+^3,$$

where $(u - \kappa_j)_+^3 = max\left\{0, (u - \kappa_j)^3\right\}$. The function $M(u)$ is unstable before the first knot κ_1 and after the last knot κ_m. To treat the instability in the tails, the condition $M''(u) = 0$ is set for $u \leq \kappa_1$ and $u \geq \kappa_m$, and then the function will be linear in the tails when β_1 and β_2 are set equal to zero. In this case, the function $M(u)$ will transform from

$$M(u) = \beta_0 + \beta_1 u + u^3 \sum_{j=1}^{m} \gamma_j - 3u^2 \sum_{j=1}^{m} \gamma_j \kappa_j + 3u \sum_{j=1}^{m} \gamma_j \kappa_j^2 - \sum_{j=1}^{m} \gamma_j k_j^3,$$

to

$$M(u) = \beta_0 + \beta_1 u + \sum_{j=1}^{m-2} \gamma_j M_j(u).$$

The number of knots was suggested by Durrleman and Simon (1989) and Hess (1994) to be from 3 to 5, and these knots can be placed at certain quintiles of the observed follow-up times, often not close to the extreme times or distributed uniformly. Following these proposals, the model was applied to the kidney transplant and the Stanford heart transplant programme data sets (Cox and Oakes, 1984). The results obtained from the two data sets showed that the spline model with 3 knots is the best model, based on $-2\log\hat{L}$ criteria.

The method achieved flexibility in the Cox model, retained the advantage of the non-specified functional form for the hazard function and is easy to fit in standard packages. However, this method should not be the final outcome, since it can be used as an exploratory procedure that may lead to use a parametric modelling as a following analysis step when certain distribution can be assumed. Also, the achieved model flexibility increases and more sensible results are obtained when larger samples are studied. These results will be investigated in chapters 6 and 7.

Denis and Molinari (2010) proposed a method to use the Reversible Jump Markov Chain Monte Carlo (RJMCMC) algorithm (Metropolis *et al.*, 1953; Hastings, 1970; Green, 1995) to estimate the B-spline Cox model. The aim of the study was to use the algorithm to determine the number of knots and their locations where the effect of X covariate in the Cox model is represented by the B-splines smooth non-linear function. The B-splines function is defined as

$$M(X,\gamma,\kappa) = \sum_{j=1}^{d+1+m} \gamma_j B_j(X),$$

where $\gamma = (\gamma_1, \ldots, \gamma_{d+1+k})$ are the spline coefficients for the basis functions $B_1, \ldots, B_{d+1+m}$ based on the internal knots $\kappa_1 < \kappa_2 < \ldots < \kappa_m$. Here $d = 1$ for linear splines. Hence the spline partial likelihood function can be written as

$$L(\gamma) = \prod_{i=1}^{n} \left\{ \frac{\exp[M(X_i,\gamma,\kappa)]}{\sum_{j\in R(t_i)} \exp[M(X_j,\gamma,\kappa)]} \right\}. \tag{2.19}$$

The RJMCMC algorithm can be employed to simulate from a specific target distribution based on spaces of available variable dimensions. This technique is based on Metropolis-Hastings algorithms [Hastings (1970) and Gamerman (2002)]. In the proposed method, the B-splines function with degree $d = 1$ is described as

$$M(X,\gamma,\kappa) = \sum_{i=1}^{m+2} \gamma_i B_i(X,\kappa).$$

The RJMCMC algorithm is applied to achieve the best adjustment based on specific number and positions for the spline knots. Changes in knot numbers and positions are determined by calculating acceptance probabilities that select any of these changes. For example, to move a certain knot from position v to position v', an acceptance probability for this move step is calculated as

$$\alpha_1 = min\left\{1, \frac{p[(y|(m,v')n(v)]}{p[(y|(m,v)n(v')]}\right\},$$

where $\frac{p[(y|(m,v')]}{p[(y|(m,v)]}$ is the likelihood ratio for the new model, $\frac{n(v)}{n(v')}$ is the proposal ratio for the move from v to v' and $n(v)$ is number of the moveable knots.

Further change may be executed for the function dimension when the number of knots is adjusted. In this case, an acceptance probability to increase the number of knots from m to

$m + 1$ is given by

$$\alpha_2 = min\left\{1, \frac{p(y|z')}{p(y|z)} \times \frac{p(m+1)}{p(m)}\frac{m+1}{K} \times \frac{d_{m+1}(K-m)}{b_m(m+1)}\right\},$$

where $\frac{p[y|z']}{p[y|z]}$ is the likelihood ratio for the new model z' that contains the new number of knots, against the null model z that contain the previous number of knots, m is the number of knots, K is the possible number of emplacements and $b_m = d_m = 1/3$ for internal knots where b_m and d_m are the probabilities to add and delete an internal knot respectively.

The algorithm's performance was compared with the two classic alternative AIC and BIC criteria. The result showed that the AIC overestimated the number of significant covariates, while the BIC underestimated. The RJMCMC tended to be in the middle of the two criteria. Even though the proposed algorithm is a successful tool for selecting knots number and locations, the basic advantage over the two criteria is the possibility to investigate the best adjustment for the knots in the spline functions in one stage. Consequently, this method may be more efficient, particularly compared to AIC and BIC, which are performed in two stages: selecting prior choice for number and positions of knots followed by the stage of estimating and evaluating the model based on this prior choice.

2.3.3 Parametric models with cubic splines

The role of the Weibull distribution in parametric survival analysis is similar to that of the normal distribution in linear modelling (Collett, 2003). The Weibull proportional hazard model is widely used in medical research, since it is good alternative to the Cox proportional hazard model, particularly when the survival data indicate that the Weibull probability distribution is tenable. On the other hand, a more flexible model may be employed in order to achieve better performance. This flexible model was introduced by Royston (2001) for censored survival data, depending on the direct modelling of the baseline hazard function. The flexibility in the hazard function shape increased when a natural cubic spline function is used compared with the standard model without splines (Nelson *et al.*, 2007).

Royston and Parmar (2002) have introduced flexible parametric proportional hazards and proportional odds models. To obtain a parametric alternative to the Cox proportional hazard model, the Weibull and log-logistic models could be extended by using natural cubic splines. The spline function increases flexibility of the log baseline cumulative hazard function in Weibull model and the log baseline cumulative odds failure function in log-logistic model. To illustrate the methodology of the proposed proportional hazard model, suppose that the general proportional hazard model is

$$h(t) = h_0(t)\exp(x^T\beta) \tag{2.20}$$

where $h_0(t)$ is the baseline hazard function and x^T is the vector of the explanatory variables. Then the cumulative hazard function can be written as

$$H(t) = H_0(t)\exp(x^T\beta) = \left(\int_0^t h_0(u)du\right)\exp(x^T\beta). \tag{2.21}$$

When the survival time t has a Weibull distribution with parameters λ and ρ, the baseline cumulative hazard function may be defined as

$$H_0(t) = \lambda t^\rho \tag{2.22}$$

and then the log baseline cumulative hazard function is

$$\log H_0(t) = \log \lambda + \rho \log t = \gamma_0 + \gamma_1 \chi \tag{2.23}$$

where $\chi = \log t$. In the presence of the fixed covariate vector x^T, the Weibull proportional hazards model with splines is

$$\log H(t|x) = \log H_0(t) + \beta x^T = M(\chi, \gamma) + \beta x^T \tag{2.24}$$

where

$$M(\chi, \gamma) = \gamma_0 + \gamma_1 \chi + \gamma_2 v_1(\chi) + \ldots + \gamma_m v_m(\chi) + x^T \beta \tag{2.25}$$

For $r = 1, \ldots, m$, the rth basis function is defined as

$$v_r(\chi) = (\chi - k_r)_+^3 - \lambda_r(\chi - k_{\min})_+^3 - (1 - \lambda_r)(\chi - k_{\max})_+^3 \tag{2.26}$$

where

$$\lambda_r = \frac{k_{\max} - k_r}{k_{\max} - k_{\min}}. \tag{2.27}$$

The external knots $k_{\min}$, $k_{\max}$ and the internal knots $k_1, \ldots, k_m$ are specified prior to the study at different percentiles for the uncensored log survival times distribution in order to set approximately equal number of events in each interval (Hess, 1994). To estimate the model, the likelihood function based on smoothing the log cumulative hazard function for an uncensored observation is

$$l = \frac{1}{t} \frac{dM(\chi, \gamma)}{d\chi} \exp(\varrho - \exp \varrho) \tag{2.28}$$

and for a censored observation is

$$l = \exp(-\exp \varrho) \tag{2.29}$$

where $\varrho = \log H(t|x)$, and

$$\frac{dM(\chi, \gamma)}{d\chi} = \gamma_1 + \sum_{j=2}^{m} \gamma_j \frac{dv_j(\chi)}{d\chi}. \tag{2.30}$$

Starting values are necessary to obtain maximum likelihood estimates of the parameters. Royston (2001) suggested to determine these values by fitting Cox model using the uncensored observations. The baseline survivor function is computed and evaluated at the covariate values x_p and transformed to the cumulative hazard function. Then a least squares regression model is applied to the log cumulative hazard function with x_p covariate values and the splines basis function. In the study of Royston and Parmar (2002) the Weibull spline model was applied to 720 patients to study node-positive primary breast cancer. Three prognostic groups, poor, medium and good, were used in which the good outcome values formed the reference group. Different nested models were compared via AIC, and using plots for the hazard functions for models with different number of knots.

Collett *et al.* (2006) have applied a flexible Weibull survival model to estimate the hazard of organ failure after kidney transplantation. The model was applied to a data set of 3511 adult patients who had first kidney transplants. In this study the time from the transplantation to the time of graft failure or death was estimated in which six fixed covariates were included in the model. Six Weibull models with from 0 to 5 knots were compared using the likelihood ratios. The spline model with 5 knots was specified as the best model based on the $-2 \log \widehat{L}$. A graphical assessment of the baseline survivor functions was executed to evaluate the proposed Weibull spline model as an alternative to the Cox model. Additionally, the baseline hazard functions for the flexible model were plotted. It was found that the hazard function in the spline model decreased faster than in the standard model. The study concluded that the Weibull model with splines introduced more flexibility and smoother hazard curves as the number of observations increases.

Nelson *et al.* (2007) proposed an extension for the relative survival model to study the mortality rate associated with heart diseases. The Royston and Parmar (2002) methodology was adopted to extend their model. To illustrate the proposed model, let $R(t)$ be the relative survival, defined as the ratio between the observed survival $S(t)$ and the expected survival $S_e(t)$. Thus

$$R(t) = \frac{S(t)}{S_e(t)},$$

and the hazard function is

$$h(t) = h_e(t) + h_d(t), \tag{2.31}$$

where $h_e(t)$ is the expected hazard (mortality) rate and $h_d(t)$ is the excess mortality rate for the disease of interest.

Using (2.12), the likelihood function for that model can be written as

$$L = \prod_{i=1}^{n} \{h_e(t_i) + h_d(t_i)\}^{\delta_i} \{S_e(t_i)R(t_i)\},$$

As $S_e(t_i)$ does not involve any unknown parameter, it can be cancelled from the likelihood function to become

$$L = \prod_{i=1}^{n} \{h_e(t_i) + h_d(t_i)\}^{\delta_i} \{R(t_i)\}. \tag{2.32}$$

The cumulative hazard function, $H(t)$, in the model is

$$H(t) = H_e(t) + H_d(t),$$

where $H_e(t)$ is the expected cumulative hazard and $H_d(t)$ is the cumulative excess hazard that can be defined for coefficient vector β^T that is estimated for covariates x as

$$H_d(t) = t^{\rho} \exp(\beta^T x).$$

The log excess cumulative hazard is approximated using cubic splines function described in (2.24) to become

$$\log H_d(t) = M(\chi, \gamma) + \beta^T x,$$

where $M(\chi, \gamma)$ is the spline basis function as described in (2.25). The hazard function in (2.31) can be derived from $\log H_d(t)$ to become

$$h(t) = h_e(t) + \frac{1}{t}\frac{dM(\chi, \gamma)}{d\chi} \exp(\varrho),$$

and the the survival rate can be written as

$$R(t) = \exp[-\exp(\varrho)],$$

where $\varrho = M(\chi, \gamma) + \beta^T x$. Thus, the likelihood function for the flexible model is

$$L = \prod_{i=1}^{n} \left\{ h_e(t) + \frac{1}{t} \frac{dM(\chi,\gamma)}{d\chi} \exp(\varrho) \right\}^{\delta_i} \{\exp[-\exp(\varrho)]\} . \tag{2.33}$$

It was found that the estimates obtained from the flexible model are smoother in comparison to the estimates of the other standard relative survival methods (e.g. piecewise approach). Furthermore, there was no splitting of the timescale (continuous survival time) instead of using split-time data. The 5 knots model was chosen as the best model based on the AIC criterion.

The study of Royston and Parmar (2002) introduced a methodology to extend both of proportional hazards and proportional odds models by natural cubic splines functions to gain more flexibility. In our study, the same methodology will be followed to extend the Weibull model for the heart and cornea transplant survival data where no time-dependent covariates is used. Also, the same methodology will be adopted to increase flexibility of the applied Weibull model to the same data sets where some covariates are allowed to change over time. Then simulation will be used to evaluate performance of these extensions.

2.4 Simulation in survival modelling

Simulation is the use of computer intensive procedures to test certain hypotheses and determine the adequacy and accuracy of different statistical models. The results obtained from such procedures are compared to the known truth about the population under study to assess the model performance (Angelis *et al.*, 1998). In survival modelling, simulation techniques can be applied to the Cox model, parametric models and flexible survival models that are approximated by spline functions. These models may be evaluated, for example, by graphical assessment to assess model suitability and residual analysis is used to assess model adequacy. However, these procedures are considered as an initial process to evaluate the model and they are insufficient particularly if the aim is to compare alternative statistical methods and determine the relative efficiency of such models. In this section, simulation procedures for different survival models will be described together with the methods of generating censored survival times based on these models.

The initial step in the simulation must be the clear determination of the aim of the study. The clear aim helps to build up the appropriate design and then specify the procedures and the scenarios that need to be followed. For example, when the aim is to investigate more than one statistical methodology, more complications may be added to the dependence level of the simulated data sets. In this case, moderately independent simulation strategy may be adopted. Such strategy is employed by using the same simulated data sets for all the methods at each scenario while different data sets are used for the different scenarios (Burton *et al.*, 2006). In other situations, where one method is evaluated and robustly examined, an independent simulation is followed when completely independent data sets are generated for each method and each scenario.

An essential procedures in any simulation study is random number generation. Details of several methods that may be used to generate random numbers are given in Marsaglia (2003) and L'Ecuyer (2004). An identical set of random numbers are reproduced by setting the same starting values "seeds" in the beginning of the generating process. The dependence level of the simulation strategy specifies the method of setting the starting seeds. For instance, when moderately independent simulation is performed, the same starting seeds are set for the same scenario of the different methods and are changed for the new scenarios (Masuda *et al.*, 1996).

To simulate survival data sets, a survival distribution for the data is assumed besides more specifications about the parameters in the simulated model. These specifications have to be determined carefully in order to reflect reality. Using a real data set as a base is a good approach to borrow the realistic structure of the data to generate statistically similar samples. When a survival data set is generated, it can be verified through several methods such as distribution summarising and Kaplan-Meier survival curves (Burton *et al.*, 2006).

The number of the performed simulations can be determined by

$$B = \left(\frac{z_{1-(\alpha/2)}\sigma}{\delta}\right)^2$$

where δ is the acceptable error value in the estimate of interest which can be calculated as a percentage, 5% at most, from this estimate value, and $z_{1-(\alpha/2)}$ is the $1-(\alpha/2)$ quantile of the standard normal distribution and σ^2 is the variance of the estimate (Lachin, 1998). In the simulations of our study, this formula can be used to determine the number of simulated data (replications) depending on estimates of the time-dependent covariates in the two data sets on hand when δ is taken to be 1% from the estimate of these estimates and σ^2 is the estimated variance of such covariates. Now details of the methods that might be used to generate various survival models will be discussed.

2.4.1 Generating data sets in survival models

Univariate data can be generated as a vector of random numbers from a certain distribution. This can be achieved using a variety of statistical packages. Demirtas (2005) showed how to use generated random numbers from uniform distribution to simulate samples from several univariate distributions.

Multivariate data are commonly used in survival modelling to study the effects of different prognostic factors on survival times. In reality, covariates are often correlated, so that this correlation is employed to generate their values. Multivariate normal distribution has basic role in generating multivariate data sets with specific means, variances and correlation structure that are involved in their variance-covariance matrix. This approach is also applied to generate any non-normal continuous variables by transforming it to validate normality assumption. MacCallum *et al.* (2002) described the method of generating binary covariates as a latent normal, by generating such covariates as continuous and dichotomizing them to the original form.

Tennenbaum *et al.* (2006) introduced two methods, discrete and continuous, to simulate correlated continuous and categorical covariates using a single multivariate distribution. The discrete method depends upon involving both categorical and continuous covariates in separate multivariate normal distribution for each combination that derived from the categories values. For example, if the model contains two categorical variables, sex and smoking status, in addition to age as a continuous variable, there will be four combinations (male with smoking, male with non-smoking, female with smoking and female with non-smoking), and hence four multivariate normal distributions are used for the combinations with the matched age values to generate vectors for the three covariates.

Due to the limitations that arise when the discrete method is used, the continuous method is preferable to generate both categorical and continuous covariates. In this method, the categorical covariates are treated as continuous, more details are found in Ghosh and Henderson (2000) and Kaut *et al.* (2003). To apply this method, all the covariate values are generated from multivariate log-normal distribution in order to avoid any negative outcomes. This can be executed by defining the variance-covariance matrix in terms of logarithms of covariate values. Then, after generating the covariate values, they are exponentiated to obtain the required values. As a result of considering the categorical covariates as continuous, a further step is done to dichotomize the values of the continuous covariates according the original categories. This can be achieved by the continuous critical value (CrV) that is determined based on the inverse of the log normal distribution using the mean, the standard deviation and the cumulative probability for the simulated covariate (Lapin, 1983). Thus, for a categorical covariate X with m categories, CrV is defined as

$$CrV(\mu, \sigma, p_i) = \exp\left\{\mu + \sigma.NORMINV(p_i)\right\},$$

where $\mu = mean[\ln(x)]$, $\sigma = SD[\ln(x)]$, p_i is the proportion of subjects in the empirical distribution with categorical value $X_i (i \leq m)$ and NORMINV is the inverse of the standard normal distribution. Applications of this method and more details will be described in chapter 7.

Liu and Craig (2006) described a method to generate time-dependent covariates. To illustrate their method, suppose $y_i(t)$ is a single time-dependent covariate that is defined as

$$y_i(t) = \eta^T g(t) + A_i + W_i(t),$$

where η^T is a vector of p unknown parameters, $g(t) = (g_1(t), \ldots, g_p(t))$ is a vector of functions of t which describes the trend component, A_i is the random subject effect, $A_i \sim N(0, \sigma_A^2)$, and $W_i(t)$ is a stationary random effect with mean 0 and variance σ_A^2. The random effect $W(t)$ can be approximated by AR(1) as

$$W(t) \quad = \quad \rho W(t - \frac{1}{24}) + \sigma\varepsilon(t), \tag{2.34}$$

where the starting value of $W(t)$ is generated from standard normal distribution, with mean 0 and variance σ_W^2 and then assumed to be a step function that jumps every $\frac{1}{24}$ year (every 15 days). Also, the values of $\varepsilon(t)$ over time are independent standard normal random variables and ρ is the assumed AR(1) parameter.

In survival modelling, the outcome is the time to a certain event. This time is often censored. Hence, the simulation procedures depend upon two distributions, one for the survival times and the other for introducing the censoring mechanism. Generating a specific proportion of non-informative right censoring can be performed when one of the distributions such as exponential and Weibull are assumed with no covariates. The parameter values for the employed distribution determine the censoring ratio that is targeted through the simulation scenarios (Miloslavsky *et al.*, 2004). More details about these procedures are introduced via the algorithms of generating survival times for the Cox model in the following section as well as the algorithms that will be introduced in chapter 7 of this thesis.

2.4.2 The Cox proportional hazards model simulation

The widely used Cox model and the corresponding partial likelihood function can be robustly investigated through simulation methodology so that bias and efficiency of the model parameter estimates are assessed (Cox, 1975). Some difficulties arise when simulation of the Cox model is designed. In linear regression model simulation, it is sufficient to determine the true regression coefficients. On the other hand, in the Cox model, the covariate effects are derived from the hazard function that must be assumed. One method to solve this issue is to assume a constant baseline hazard function and then generate exponentially distributed survival times (Bender *et al.*, 2003). Alternatively, Weibull distribution may be used to simulate survival times based on the Cox model. Schemper (1992) introduced a method to use Weibull distributed survival times to investigate different analyses with the Cox model.

In some applications, it might be necessary to assume different distribution for the survival data. An example for this application is human mortality study which is modelled using Gompertz distribution (Lee and Go, 1997). Bender *et al.,* (2003) proposed method to generate survival times using exponential, Weibull and Gompertz distributions to simulate the Cox model with known regression parameters. The method is based on developing the relationships of cumulative hazard and survivor functions with the survival times. To clarify this method, let the survivor function in the Cox model be

$$S(t|x) \quad = \quad \exp\left\{-H_0(t)\exp(\beta^T x)\right\},$$

and the model distribution function is

$$F(t|x) \quad = \quad 1-\exp\left\{-H_0(t)\exp(\beta^T x)\right\}.$$

Let Y be a random variable that has a distribution function F and then function $F(Y)$ follows uniform distribution, $U \sim Uni[0,1]$. Also, the survivor function $1-F(Y)$ follows $U \sim Uni[0,1]$. Consequently, the survivor function is written as

$$U = \exp\left[-H_0(T)\times\exp(\beta^T x)\right], \tag{2.35}$$

where T is the survival time that can be generated using the the inversion of the equation (2.35) as well as the baseline cumulative hazard function $H_0(T)$ that depends upon the assumed distribution. For example, when the Weibull distribution is assumed, the baseline cumulative hazard is defined as

$$H_0(t) \quad = \quad \lambda t^\rho,$$

where λ and ρ are the Weibull scale and shape parameters. Thus,

$$U \quad = \quad \exp\left[-\lambda t^\rho \times \exp(\beta^T x)\right],$$

and then the survival times are generated by

$$T = \left[\frac{-\log(U)}{\lambda} \times \frac{1}{\exp(\beta^T x)}\right]^{\frac{1}{\rho}}, \tag{2.36}$$

and the exponential generated survival times can be obtained from (2.36) when $\rho = 1$ as

$$T = \frac{-\log(U)}{\lambda \times \exp(\beta^T x)}. \tag{2.37}$$

2.4.3 Parametric model simulation

Parametric survival models can be described in two manners: proportional hazards and accelerated failure time. The simple survival distributions that can be modelled in proportional hazards are exponential, Weibull and Gompertz. On the other side, there are many distributions that may be modelled in accelerated failure time model such as Weibull, log-logistic and log-normal. To simulate the two modelling types, the method of Bender et al., (2003) can be used. However, there is a difference when an accelerated failure time model is simulated.

Leemis (1987) proposed various algorithms to generate survival times from proportional hazards and accelerated failure time models. To differentiate between the generation from the two models, he described the generated survival model based on proportional hazards as

$$T = H_0^{-1}\left(\frac{-\log(U)}{\exp(\beta^T x)}\right),$$

and for accelerated failure time as

$$T = \frac{H_0^{-1}\left(-\log(U)\right)}{\exp(\beta^T x)},$$

where $U \sim Uni[0,1]$ and H_0^{-1} is the inverse baseline cumulative hazard function for time t. To clarify the difference between the two formulas, let $H_0 = \lambda t^{\rho}$ be the baseline cumulative hazard function for the Weibull distribution, where $\exp(\beta^T x)$ is the covariate function. Thus, in proportional hazards model, the survival times are generated as

$$T = \left[\frac{-\log(U)}{\lambda \times \ \exp(\beta^T x)}\right]^{\frac{1}{\rho}}, \tag{2.38}$$

and in AFT model as

$$T = \left[\frac{-\log(U)}{\lambda}\right]^{\frac{1}{\rho}} \left[\exp(\beta^T x)\right]. \tag{2.39}$$

Generating from other distributions such as log-logistic are described in (Leemis *et al.*, (1990).

2.4.4 Simulation for the Cox model with time-dependent covariates

The approaches that can be used to simulate this model will be more complicated than the approach that was described in section 2.4.2. There are a variety of algorithms that are applicable to simulate the model that contains one or more covariates that change over time. Leffondre *et al.* (2003) used the permutational algorithm (PA) proposed by Abrahamowicz *et al.* (1996) and validated by MacKenzie and Abrahamowicz (2002), through five steps as

1. Generate n survival times $T_i^*, (i = 1, \ldots, n)$ from a specified marginal distribution.

2. Generate n censoring times $C_i, (i = 1, \ldots, n)$ from specified marginal distribution.

3. Determine the survival times t_i as $t_i = min(T_i^*, C_i)$ and the censoring indicator as $\delta_i = I(T_i^* \leq C_i)$.

4. Generate vectors for both fixed and time-dependent covariates at each time t_i.

5. Assign randomly each covariate vector to the corresponding survival time t_i based on the partial likelihood function in (2.3). If $\delta_i = 0$ then the censored individual is selected by simple random sampling with equal probability. Otherwise, if $\delta_i = 1$ the uncensored individual is selected by the probability that is proportional to his/her hazard ratio at time t_i.

Sylvestre and Abrahamowicz (2008) described this probability for individual s at time t_i as

$$P_{s,t_i} = \frac{\exp[\beta^T y_s(t_i)]}{\sum_{j\in R(t_i)} \exp[\beta^T y_j(t_i)]}, \tag{2.40}$$

where $y_s(t_i)$ is the covariate value for individual s at time t_i.

Due to the intensive computation of the permutational algorithm and low efficiency, particularly when the sample size is large or contains high number of uncensored subjects, Sylvestre and Abrahamowicz (2008) suggested the modified permutational algorithm with rejection sampling (PARS) using the following steps

1. Sample a covariate vector $Y_s(t_i)$ from the risk set R_i at time t_i with equal probability $1/size[R(t_i)]$.

2. Generate U as $U \sim Uni[0, 1]$.

3. Calculate the hazard ratio associated with the covariate vector Y_s at time t_i, $h(Y_s(t_i)) = \exp[\beta^T y_s(t_i)]$.

4. If $U \leq h(Y_s(t_i))/c_{t_i}$ assign the covariate vector $Y_s(t_i)$ to the event time t_i. Otherwise, go back to step 1, c_{t_i} is a predefined constant that can be specified as

   $$c_{t_i} = \max\left\{\exp[\beta^T y_j(t_i)]\right\}$$

   where $j \in R_i$.

Further, they introduced an algorithm based on a binomial model through the following steps

1. Calculate the conditional probability $p_{i,t}$ for the ith individual based on the binomial model with parameters β_j, $j = 1, \ldots, w$ as

   $$p_{i,1} = logit\left[\beta_0 + \sum_{j=1}^{w} \beta_j y_{ij}(t)\right], \tag{2.41}$$

   where the parameter β_0 represents the baseline risk that can be assumed constant to yield exponential distributed survival times. Otherwise, it could be time-dependent to achieve increasing hazard.

2. Generate U as $U_{i,t} \sim Uni[0, 1]$.

3. If $U_{i,t} \leq p_{i,1}$, match an event to individual i at time t and stop follow-up for this individual. Otherwise, increase the time t by one unit and go to step 1.

A validation for the three algorithms was done by generating survival times conditional on time-dependent covariates. The results showed that the PARS and the binomial algorithms are more efficient that the PA algorithm. However, the PARS has easier implementation than the binomial algorithms that may have difficulties in the intercept parameter calibration (Sylvestre and Abrahamowicz, 2008).

For the proposed parametric model with time-dependent covariates, a method for generating survival times condition on both of one change and many changes time-dependent covariates will be described in chapter 7.

2.4.5 Evaluating the performance of different methods

In simulation designs, all the parameter estimates, for both fixed and time-dependent covariates, are stored besides their standard errors in order to calculate performance and uncertainty measures. For each covariate, the average estimate over B simulations $\bar{\hat{\beta}}$ is taken to be a measure of the true estimate for such a covariate, and the standard deviation of the estimate, $\hat{\beta}_\iota$, over the B simulations is used as a the standard error of this estimate $SE(\hat{\beta})$ (Burton *et al.*, 2006). Hence, for B simulations

$$\bar{\hat{\beta}} = \sum_{\iota=1}^{B} \hat{\beta}_\iota / B$$

and

$$SE(\hat{\beta}) = \sqrt{[1/(B-1)] \sum_{\iota=1}^{B} (\hat{\beta}_\iota - \bar{\hat{\beta}})^2}$$

The required estimates will be stored, after the simulations are completed, and then measures that reflect the considered criteria are calculated in order to evaluate method performance (Collins *et al.*, 2001). The measures are often used to assess the bias, accuracy, power, type I and type II error probabilities and coverage.

2.4.5.1 Bias assessment

The bias is defined as the difference between the estimate $\bar{\hat{\beta}}$ and the true value β, which specifies the performance of the method being evaluated. The second method is to calculate the percentage of the bias as (Burton *et al.*, 2006)

$$\left(\frac{\bar{\hat{\beta}} - \beta}{\beta} \right) \times 100.$$

The standardized bias is

$$\left(\frac{\bar{\hat{\beta}} - \beta}{SE(\hat{\beta})} \right) \times 100$$

The efficiency, coverage and error rates of parameter estimate are adversely affected, when the standardized bias exceeds 40% in any direction (Collins *et al.*, 2001).

2.4.5.2 Accuracy assessment

The overall accuracy of the estimate can be assessed by the mean square error (MSE)

$$(\bar{\hat{\beta}} - \beta)^2 + (SE(\hat{\beta}))^2$$

2.4.5.3 Power and type I and type II error probabilities

The empirical power can be calculated as the proportion of the simulated samples with rejected null hypothesis at a certain significance level, when this null hypothesis is false and then the empirical type II error probability is 1-power. The empirical type I error probability can be determined as the proportion of $p-values$ that are less than the determined significance level, usually 5% when the null hypothesis is true (Burton *et al.*, 2006).

Finally, a comparison between the two approaches of generating survival times will be performed to assess the accuracy and the efficiency of these two approaches. In chapter 7, evaluations for each of the proposed models will be performed by calculating these assessment tools, particularly the empirical power for parameters of interest.

2.5 Study of survival times after heart and cornea transplantations

Many survival studies have focused on studying survival time after heart transplantation. Most of these studies used the Cox proportional hazards model to investigate the effects of different factors on survival after the surgery. Some studies used the extended Cox model with one or more time-dependent covariates. For example, Aydemir *et al.* (1999) considered several time-dependent covariates in the extended Cox model of the Stanford heart transplant data. In the study of Gioargi and Gouvernet (2005), a regressive survival model was applied to same data in which prognostic factors were accommodated in the model as time-dependent. Jimenez (2006) applied logistic regression to model heart failure after transplant surgery using the data of NHS Blood and Transplant. Heart transplant data was used in the study of Nardi and Schemper (2003) to compare the Cox model and parametric models by analysing residual methods to assess goodness of fit in each model. Further, more flexible survival models were introduced to model this type of data. For example, Heinzl et al. (1996) used the Stanford data by considering the Cox model with cubic spline functions where binary time-dependent covariates are incorporated in the model. These previous studies of heart transplant survival data have covered a wide area of modelling approaches. However, the proposed modelling approaches may add new investigations for the heart transplant data analysis.

After cornea transplantation the graft survival time was modelled through traditional approaches. One approach to study cornea survival time was the Cox proportional hazards model to measure the effects of different factors on hazard of failure; see for example, Yang *et al.* (1998) and Maier (2011). In a different study, Anshu *et al.* (2011) studied the effects of the factors of post operative complications and operation procedures after the surgery as time-dependent covariates in the extended Cox model. Also, in the study of Ingle (2004), the effect of the second eye graft was considered as a time-dependent covariate with other fixed covariates on the first eye graft survival time using the extended Cox model and illustrated by the data of NHS Blood and Transplant.

A variety of models can be employed to study the two data sets on hand. The first type of models is the Cox and parametric models that treat all the covariates as fixed. Secondly, the previous group of models can be extended to allow for one or more covariates to change over time. Thirdly, these two modelling approaches are modified in order to gain more flexibility by including spline functions. The three approaches will be applied to the heart and cornea transplant data sets, and then evaluation of their performance and efficiency will be discussed through the next chapters of this thesis.

Chapter 3

Mathematical model specification

The aim of this chapter is to describe the models that will later be applied to the two real data sets. These models are introduced as alternative approaches to the Cox model when the data contain one or more covariates that change over time. Section 3.1 will discuss the general accelerated failure time model, and the method of constructing the full likelihood function for that model when there is right censoring.

The likelihood functions for the accelerated failure time models of the Weibull and log-logistic distributions are derived in section 3.2. In section 3.3, derivation of the cumulative hazard functions in the presence of time-dependent covariates is explained. Then, the likelihood functions for the Weibull and the log-logistic AFT models that allow for time-dependent covariates are presented. These likelihood functions are applied to the transformed data in counting process input style in which multiple records for each observation are set to allow for the changes in the values of the time-dependent covariates.

The standard AFT Weibull model can be extended using natural cubic spline functions. This extension leads to a more flexible model but one which, unlike the traditional Cox model, retains the advantages of a parametric framework. In section 3.4, the hazard and the cumulative hazard functions for the AFT Weibull spline model are described in cases of using fixed and time-dependent covariates. Consequently, the likelihood function to estimate the Weibull spline model, with different number of knots, is described.

3.1 General accelerated failure time model

The accelerated failure time (AFT) model is a general survival model which assumed the acceleration property for the explanatory variables. According to this model, the explanatory variables for any individual affect survival time multiplicatively. Generally, the hazard function for individual i at time t is

$$h_i(t|x_i) = \exp\left[-\beta' x_i\right] h_0\left(\exp\left[-\beta' x_i\right] t\right), \tag{3.1}$$

where $x_i = (x_{i1}, \ldots, x_{ip})'$ contains the explanatory variables for the ith individual, $i = 1, 2, \ldots, n$, $\beta = (\beta_1, \ldots, \beta_p)'$ is a vector of regression coefficients and $h_0(t)$ is the baseline hazard function. For the ith individual, the survivor function is

$$S_i(t|x_i) = S_0\left(\exp\left[-\beta' x_i\right] t\right), \tag{3.2}$$

where $S_0(t)$ is the baseline survivor function, and the cumulative hazard function is

$$H_i(t|x_i) = H_0\left(\exp\left[-\beta' x_i\right] t\right), \tag{3.3}$$

where $H_0(t)$ is the baseline cumulative hazard function.

This model is fitted using maximum likelihood. The likelihood function is constructed for n independent observations with possibly right censored survival times $t_1, t_2, \ldots, t_n$ as

$$L = \prod_{i=1}^{n} \{f_i(t_i|x_i)\}^{\delta_i} \{S_i(t_i|x_i)\}^{1-\delta_i} \tag{3.4}$$

where f_i is the probability density function and δ_i is the censoring indicator function that takes the value 1 for an uncensored observation and 0 otherwise. Hence,

$$\begin{aligned} L &= \prod_{i=1}^{n} \{h_i(t_i|x_i)S_i(t_i|x_i)\}^{\delta_i} \{S_i(t_i|x_i)\}^{1-\delta_i} \\ &= \prod_{i=1}^{n} \{h_i(t_i|x_i)\}^{\delta_i} \{S_i(t_i|x_i)\} \\ &= \prod_{i=1}^{n} \{h_i(t_i|x_i)\}^{\delta_i} \{\exp[-H_i(t_i|x_i)]\}. \end{aligned} \tag{3.5}$$

3.2 AFT model with fixed-time covariates

3.2.1 Weibull AFT model with fixed-time covariates

In the Weibull survival model with shape parameter ρ, the probability density function is defined as

$$f(t) = \rho t^{\rho-1} \exp\{-t^{\rho}\},$$

and the survivor function is

$$S(t) = \exp\{-t^{\rho}\}.$$

Using the the relationship in (1.5), the hazard function is therefore

$$\begin{aligned} h(t) &= \frac{f(t)}{S(t)} \\ &= \rho t^{\rho-1}. \end{aligned}$$

This hazard function is the baseline hazard function when no covariate values is included in the model. In the Weibull model that incorporates fixed covariates only, let β' be the coefficient vector. Then, for the ith individual

$$\beta' x_i = \beta_1 x_{i1} + \cdots + \beta_p x_{ip}$$

Let α_i be

$$\alpha_i = \exp(\theta + \beta' x_i), \tag{3.6}$$

where θ is the intercept parameter. In the Weibull AFT model, the hazard function is

$$h_i(t) = \rho \left(\frac{1}{\alpha_i}\right)^{\rho} t^{\rho-1}, \tag{3.7}$$

and the cumulative hazard function is

$$H_i(t) = \left(\frac{1}{\alpha_i}\right)^{\rho} t^{\rho}. \tag{3.8}$$

Thus, the likelihood function in (3.5) is applied using the hazard and cumulative hazard functions in (3.7) and (3.8).

3.2.2 Log-logistic AFT model with fixed-time covariates

The probability density function for the log-logistic model with shape parameter ρ is

$$f(t) = \frac{\rho t^{\rho-1}}{(1+t^{\rho})^2},$$

and the survivor function is defined as

$$S(t) \quad = \quad (1+t^{\rho})^{-1}.$$

Using (1.5), the hazard function is defined by

$$h(t) = \frac{\rho t^{\rho-1}}{(1+t^{\rho})}.$$

This hazard function is considered as the baseline hazard function of the log-logistic model without covariates. In the log-logistic AFT model that includes p fixed covariates x_i, the hazard function is written as

$$h_i(t) = \frac{\rho(\frac{1}{\alpha_i})^{\rho} t^{\rho-1}}{\left[1+(\frac{1}{\alpha_i})^{\rho} t^{\rho}\right]}, \tag{3.9}$$

and the cumulative hazard function is

$$H_i(t) = \log\left[1+(\frac{1}{\alpha_i})^{\rho} t^{\rho}\right]. \tag{3.10}$$

From the hazard and the cumulative hazard functions in (3.9) and (3.10), the likelihood function is applied using (3.5).

3.3 AFT model with time-dependent covariates

The AFT model can be extended by incorporating time-dependent covariates. Even though the Cox model can be extended easily to model such covariates, the AFT models provide a parametric alternative. Petersen (1986) and Sparling *et al.* (2006) have described the methodology to extend parametric models to include time-dependent covariates. In this section, derivations of the hazard and the cumulative hazard functions for the Weibull and the log-logistic models will be presented in order to constitute the likelihood function of these two extended models.

Suppose that additional time-dependent covariates are updated at a sequence of follow-up times $\tau_{i0}, \ldots, \tau_{ik_i}$, where τ_{i0} is the first follow-up time (usually zero) (Sparling *et al.*, 2006). Sometimes, patients may be followed up after operations at certain times. For example, heart transplant patients are followed up to measure their kidney function every year. Let $y_{ij} = (y_{ij1}, \ldots, y_{ijq})'$ be a vector of q time-dependent covariates that are updated at discrete points at those times. Then the likelihood function becomes

$$L = \prod_{i=1}^{n} \left\{h_i(t_i|x_i, y_{i[t_i]})\right\}^{\delta_i} \left\{\exp[-H_i(t_i|x_i, y_{i[t_i]})]\right\}, \tag{3.11}$$

where $y_{i[t_i]}$ is the time-dependent covariate value for the ith individual at time t_i.

3.3.1 Weibull AFT model with time-dependent covariates

In the Weibull model that incorporates fixed and time-dependent covariates, let β' and η' be the coefficient vectors for the p fixed covariates x_i and q time-dependent covariates y_{ij} respectively. Then, for the ith individual

$$\beta' x_i = \beta_1 x_{i1} + \cdots + \beta_p x_{ip}$$

and

$$\eta' y_{ij} = \eta_1 y_{ij1} + \cdots + \eta_q y_{ijq},$$

where y_{ijq} is the value of the time-dependent covariate q of the ith individual at time segment j. Let α_{ij} be

$$\alpha_{ij} = \exp(\theta + \beta' x_i + \eta' y_{ij}), \tag{3.12}$$

where θ is the intercept parameter.

Assuming that $\tau_{ij} = (\tau_{i0}, \ldots, \tau_{ik_i})$, $j = 0, \ldots, k_i$ and k_i is the number of update times for the ith individual, since each time t is divided in counting process style into intervals which start at τ_{ij} and end at $\tau_{i(j+1)}$ (see Table 3.2). In this modelling approach, it is assumed that time-dependent covariate values are updated at the beginning of each interval and stay constant to the end of the interval. Then the hazard function including time-dependent covariates becomes

$$h_i(t|x_i, y_{i[t]}) = \rho \left(\frac{1}{\alpha_{ij}} \right)^{\rho} t^{\rho-1}, \tag{3.13}$$

where $h_i(t|x_i, y_{i[t]})$ is the hazard function that is evaluated for the ith individual at the beginning of each interval, at $t = \tau_{ij}$, $y_{i[t]}$ is the time-dependent covariate and α_{ij} is the parameter function at the same time segment τ_{ij}.

The cumulative hazard function including the time-dependent covariate, y_{ij}, for the ith individual at time t is

$$H_i(t|x_i, y_{i[t]}) = \sum_{j=0}^{k_i-1} \left[I_{\left\{\tau_{i(j+1)} \le t\right\}} \int_{\tau_{i(j)}}^{\tau_{i(j+1)}} \rho \left(\frac{1}{\alpha_{ij}} \right)^{\rho} u^{\rho-1} du \right] \tag{3.14}$$

where the time-dependent covariate values are updated at τ_{ij} and stay constant to the end of the interval at τ_{j+1}, where $j = 0, 1, \ldots, k_i$, and $I_{\{\omega\}}$ is the indicator function that takes the value 1 if $\{\omega\}$ is true and 0 otherwise. This indicator function was introduced by Sparling *et al.* (2006) as $I_{\left\{\tau_{i(j+1)} = t_i\right\}}$. Using this function, the cumulative hazard is calculated for $t_i = \tau_{i(j+1)}$ only and ignores the intervals in which $t_i > \tau_{i(j+1)}$. For that reason, it was amended in (3.14) to $I_{\left\{\tau_{i(j+1)} \le t_i\right\}}$. Using the hazard and the cumulative hazard functions, $h(t_i|x_i, y_{i[t]})$ and $H(t_i|x_i, y_{i[t]})$, as in (3.13) and (3.14) for the ith individual, the likelihood function is applied using the previous formula in (3.5).

3.3.2 Log-logistic AFT model with time-dependent covariates

When the log-logistic model is extended to accommodate time-dependent covariates, the hazard function at time $t_i = \tau_{ij}$ and using the parameter function in (3.12) becomes

$$h_i(t|x_i, y_{i[t]}) = \frac{\rho \left(\frac{1}{\alpha_{ij}} \right)^{\rho} t^{\rho-1}}{1 + \left(\frac{1}{\alpha_{ij}} \right)^{\rho} t^{\rho}} \tag{3.15}$$

As described in section (3.3.1), the hazard function in (3.15) is evaluated at the beginning of each interval τ_{ij} using the the values of the time-dependent covariates that is updated at τ_{ij}. where $y_{i[t]}$ is the time-dependent covariates at time τ_{ij} . Then, the cumulative hazard function at time t, for the ith individual with y_{ij} time-dependent covariate, is

$$H_i(t|x_i, y_{i[t]}) = \sum_{j=0}^{k_i-1} \left[I_{\{\tau_{i(j+1)} \leq t\}} \int_{\tau_{i(j)}}^{\tau_{i(j+1)}} \frac{\rho \left(\frac{1}{\alpha_{ij}}\right)^{\rho} u^{\rho-1}}{1 + \left(\frac{1}{\alpha_{ij}}\right)^{\rho} u^{\rho}} du \right]. \tag{3.16}$$

The same likelihood function in (3.5) can be applied where $h(t_i|x_i, y_{i[t]})$ and $H(t_i|x_i, y_{i[t]})$ are the hazard and the cumulative hazard functions in (3.15) and (3.16).

3.3.3 Counting process style of input

In typical survival data analysis, each subject takes one record. This record is a vector of the sort $(T, \delta, ...)$ where T has the value of time since the origin point until event $(\delta = 1)$ or censoring $(\delta = 0)$ (Ake and Carpenter, 2003). On the other hand, in order to compute the functions of the survival models with time-dependent covariates, a counting process style of input that was originated by Therneau (1994) is followed. The method represents each subject with multiple records according the number of time-dependent covariate changes for that subject. Each record defines one interval with (T_1, T_2, δ, x, y) when T_1 is the time at the beginning of the interval, T_2 is the time at which the interval ends, δ is the censoring indicator that takes 0 in each interval, where subject is still censored, while it is defined in the last interval according to the status of the subject in the original data, x is the fixed covariate which remains constant through all the intervals and y is the time-dependent covariate that changes when the interval starts and remains constant to the end of the interval.

For example, suppose that the data of two patients with fixed covariate x and time-dependent covariate y that changes every 100 days are defined as in Table 3.1.

Table 3.1: Survival data of two patients including follow-up covariate values

patient	time	status	x	y_1	y_2	y_3	y_4	y_5
1	270	0	40	8	9	10	-	-
2	480	1	60	11	12	15	18	22

The data of these two patients are formulated in the counting process style as shown in Table 3.2.

3.4 Flexible Weibull AFT model

The Weibull AFT model may yield a good tool to fit survival data with time-dependent covariates. However, this model can be developed to achieve a better performance when flexibility is added to the original model. The flexible Weibull model is obtained when the standard model is extended to allow for the natural cubic spline function. The log of baseline cumulative hazard function including the splines function was described by Royston and Parmar (2002) as

$$\log H(t) = \theta + \rho t + \gamma_1 \upsilon_1(t) + \cdots + \gamma_m \upsilon_m(t), \tag{3.17}$$

where the rth basis function is defined for $r = 1, \ldots, m$ as

$$\upsilon_r(t) \quad = \quad (\log t - \kappa_r)^3_+ - \lambda_r (\log t - \kappa_{min})^3_+ - (1 - \lambda_r)(\log t - \kappa_{max})^3_+$$

Table 3.2: Data formulated following counting process style

patient	time	T_1	T_2	status	x	y
1	270	0	100	0	40	8
1	270	100	200	0	40	9
1	270	200	270	0	40	10
1	270	270	270	0	40	10
2	480	0	100	0	60	11
2	480	100	200	0	60	12
2	480	200	300	0	60	15
2	480	300	400	0	60	18
2	480	400	480	0	60	22
2	480	480	480	1	60	22

with

$$\lambda_r = \frac{\kappa_{max} - \kappa_r}{\kappa_{max} - \kappa_{min}}$$

and

$$(t-a)_+^3 = max\{0, (t-a)^3\}.$$

In order to estimate the function $\upsilon_r(t)$, Royston (2001) suggested setting external knots κ_{min} and κ_{max} at the minimum and the maximum value of the uncensored survival times, and the m internal knots $\kappa_1 < \cdots < \kappa_m$ with $\kappa_1 > \kappa_{min}$ and $\kappa_m < \kappa_{max}$. Table 3.3 shows the internal knots that are placed at the centiles of the distribution for the uncensored log survival times.

Table 3.3: Internal knot placement for spline models with different one to five knots

No. of knots	Centile positions
1	50
2	33 67
3	25 50 75
4	20 40 60 80
5	17 33 50 67 83

3.4.1 Fixed covariates model

The cumulative hazard functions for the Weibull accelerated failure time model with fixed covariates only were defined in (3.8). The log of this function is

$$\log H_i(t|x_i) = \rho \log(\frac{1}{\alpha_i}) + \rho \log t,$$

where $\alpha_i = \exp(\theta + \beta' x_i)$. Hence

$$\log H_i(t|x_i) = \rho(-\theta - \beta' x_i) + \rho \log t, \quad (3.18)$$

and the log cumulative hazard function of the Weibull spline model becomes

$$\log H_i(t|x_i) = \rho(-\theta - \beta' x_i) + \rho \log t + \gamma_1 \upsilon_1(t) + \cdots + \gamma_m \upsilon_m(t), \tag{3.19}$$

and then,

$$H_i(t|x_i) = \exp\left\{\rho(-\theta - \beta' x_i) + \rho \log t + \gamma_1 \upsilon_1(t) + \cdots + \gamma_m \upsilon_m(t)\right\}. \tag{3.20}$$

The hazard function for the model is

$$\begin{aligned} h_i(\tau_{i(j)}|x_i, y_{ij}) &= \{\rho(-\theta - \beta' x_i) + \rho \log t + \gamma_1 \upsilon_1(t) + \cdots + \gamma_m \upsilon_m(t)\} \times \left\{ \left(\frac{\rho}{\tau_{i(j)}}\right) \right. \\ &\quad + \sum_{r=1}^{m} \frac{3\gamma_r}{\tau_{i(j)}} \Big[(\log \tau_{i(j)} - \kappa_r)_+^2 - \lambda_r (\log \tau_{i(j)} - \kappa_{min})_+^2 \\ &\quad \left. - (1 - \lambda_r) \left(\log \tau_{i(j)} - \kappa_{max}\right)_+^2 \Big] \right\} \end{aligned} \tag{3.21}$$

Then, the likelihood function in (3.5) can be applied to the Weibull spline model with fixed covariates using (3.20) and (3.21).

3.4.2 Time-dependent covariates model

The cumulative hazard function of the Weibull accelerated failure time model with time-dependent covariates in (3.14) is

$$H_i(t|x_i, y_{i[t]}) = \sum_{j=0}^{k_i - 1} \left[I_{\{\tau_{i(j+1)} \leq t\}} \int_{\tau_{i(j)}}^{\tau_{i(j+1)}} \rho \left(\frac{1}{\alpha_{ij}}\right)^{\rho} u^{\rho - 1} du \right].$$

In the Weibull spline model with time-dependent covariates, using the basis function, $\upsilon_r(\tau_{i(j)})$, which is calculated at time $\tau_{i(j)}$ for the natural cubic spline, the functions $\Lambda_{\tau_{i(j)}}$ and $\Lambda_{\tau_{i(j+1)}}$ are defined at times $\tau_{i(j)}$ and $\tau_{i(j+1)}$ respectively as

$$\Lambda_{\tau_{i(j)}} = \exp\left[\rho(-\theta - \beta' x_i - \eta' y_{ij}) + \rho \log \tau_{i(j)} + \gamma_1 \upsilon_1(\tau_{i(j)}) + \cdots + \gamma_m \upsilon_m(\tau_{i(j)})\right] \tag{3.22}$$

$$\Lambda_{\tau_{i(j+1)}} = \exp\left[\rho(-\theta - \beta' x_i - \eta' y_{i(j+1)}) + \rho \log \tau_{i(j+1)} + \gamma_1 \upsilon_1(\tau_{i(j)}) + \cdots + \gamma_m \upsilon_m(\tau_{i(j)})\right] \tag{3.23}$$

These functions define the cumulative hazards at $\tau_{i(j)}$ and $\tau_{i(j+1)}$ respectively. Hence, the cumulative hazard function for the Weibull accelerated failure time with time-dependent covariates and m knots can be written as

$$H_i(t|x_i, y_{i[t]}) = \sum_{j=0}^{k_i - 1} \left(I_{\{\tau_{i(j+1)} \leq t\}} \left[\Lambda_{\tau_{i(j+1)}} - \Lambda_{\tau_{i(j)}}\right] \right), \tag{3.24}$$

In order to fit the model, the data input style is used as described in Table 3.2. The values of the external knots, κ_{min} and κ_{max}, are the minimum and the maximum log uncensored survival times at the beginning of each interval, τ_{ij}. Similarly, the internal knots, $\kappa_1 < \ldots < \kappa_m$, are calculated based on the same values. The next step is to calculate the basis function $\upsilon_r(\tau_{i(j)})$ which is evaluated based on the values of $\tau_{i(j)}$. From the differentiation of the function $\lambda_{\tau_{i(j)}}$ with respect to $\tau_{i(j)}$, the hazard function of the ith individual at time $\tau_{ij} = \log t$ with m knots is defined as

$$\begin{aligned}
h_i(\tau_{i(j)}|x_i, y_{ij}) \quad = \quad & \left\{\Lambda_{\tau_{i(j)}}\right\} \times \left\{\left(\frac{\rho}{\tau_{i(j)}}\right)\right. \\
& + \sum_{r=1}^{m} \frac{3\gamma_r}{\tau_{i(j)}} \Big[(\log \tau_{i(j)} - \kappa_r)_+^2 - \lambda_r(\log \tau_{i(j)} - \kappa_{min})_+^2 \\
& \left. - (1-\lambda_r)\left(\log \tau_{i(j)} - \kappa_{max}\right)_+^2\Big]\right\}
\end{aligned} \tag{3.25}$$

The likelihood function for the flexible Weibull model with the time-dependent covariate y_{ij} and m knots is obtained from the cumulative hazard and the hazard functions in (3.24) and (3.25) respectively.

As an illustration, suppose a model with one internal knot κ_1, and external knots κ_{min} and κ_{max}, the Weibull AFT model with splines and time-dependent covariates is applied as follows.

1. Insert the survival data in counting process style as described in Table 3.2.

2. Calculate the value of λ_1 as

$$\lambda_1 \quad = \quad \frac{\kappa_{max} - \kappa_1}{\kappa_{max} - \kappa_{min}},$$

   where κ_1 is the median of the uncensored log survival times which is calculated from the values of time at the beginning of each interval t_1 as described in Table 3.2.

3. Calculate the first knot basis function $\upsilon_1(t)$ as

$$\upsilon_1(t) \quad = \quad (\log t - \kappa_1)_+^3 - \lambda_1(\log t - \kappa_{min})_+^3 - (1-\lambda_1)(\log t - \kappa_{max})_+^3,$$

   where $t = t_1$.

4. Calculate the functions Λ_{t_1} and Λ_{t_2} as

$$\begin{aligned}
\Lambda_{t_1} \quad &= \quad \exp\left[\rho\left(-\theta - \beta' x_i - \eta' y_{ij}\right) + \rho \log t_1 + \gamma_1 \upsilon_1(t)\right], \\
\Lambda_{t_2} \quad &= \quad \exp\left[\rho\left(-\theta - \beta' x_i - \eta' y_{ij}\right) + \rho \log t_2 + \gamma_1 \upsilon_1(t)\right].
\end{aligned}$$

5. Calculate the cumulative hazard function $H_i(t|x_i, y_{i[t]})$ as

$$H_i(t|x_i, y_{i[t]}) = \sum_{j=0}^{k_i-1} \left(I_{\left\{\tau_{i(j+1)} \le t\right\}} \left[\Lambda_{t_2} - \Lambda_{t_1}\right]\right),$$

6. The hazard function is evaluated at the end of each interval and encountered at each

event time to become

$$
\begin{aligned}
h_i(t_1|x_i, y_{i[t]}) &= \{\Lambda_{t_1}\} \times \Bigg\{ \left(\frac{\rho}{t_1}\right) \\
&+ \sum_{r=1}^{m} \frac{3\gamma_1}{t_1} \Big[(\log t_1 - \kappa_1)_+^2 - \lambda_1 (\log t_1 - \kappa_{min})_+^2 \\
&- (1 - \lambda_1)\,(\log t_1 - \kappa_{max})_+^2 \Big] \Bigg\}
\end{aligned}
$$

7. The likelihood function is calculated using the hazard and the cumulative hazard functions in 5 and 6.

In this chapter, the standard Weibull AFT model has been extended in two ways: incorporation of time-dependent covariates, and adding natural cubic spline functions. These two extensions modify the standard model to be more attractive to potential users and possibly more appropriate to fit a variety of survival data. In the next two chapters, the models that have been described in this chapter will be applied to the heart transplant survival data in chapter four and for the cornea transplant survival data in chapter five. These two data sets will be used to apply different models using fixed and time-dependent covariates.

Chapter 4

Heart transplant model

Heart failure is physiologically the condition in which the heart fails to pump the normal rate of the blood to achieve the requirements of metabolizing tissues (Zevitz, 2006). There are many reasons for heart failure such as coronary artery disease (heart attack), hypertension, heart valve problems, infections (e.g. viruses), alcohol and illicit drug use (such as cocaine) and congenital heart disease (Jurt *et al.*, 2002). Heart transplantation is the technique of replacing the failing heart by another suitable donated heart. This procedure is executed for end-stage congestive heart failure cases, for patients who urgently need the operation and who have not responded to the stipulated medical therapy (Mancini, 2009). Transplantation surgery has become an essential procedure for heart failure patients, particularly in the absence of the availability of other medications. This technique has been developed by improving three aspects: surgical procedures, immunosuppressive drugs and the network of the transplantation centres (Janeway, 1994). NHS Blood and Transplant is the organ donor organization which is responsible for allocating the available donated organs to the appropriate recipients in the UK. Table 4.1 shows the number of heart transplants in the UK from 2001 to 2010 (NHS Blood and Transplant, 2010).

Table 4.1: Heart transplants in the UK from 2001 to 2010

Year	***Number of heart transplants***
2001	176
2002	158
2003	148
2004	165
2005	154
2006	141
2007	156
2008	128
2009	130
2010	120

Table 4.2 presents the survival estimates with confidence intervals for one, two, five and ten years after heart transplant (NHS Blood and Transplant, 2010).

Table 4.2: Long-term patient survival after first adult heart only transplant in the UK, 1 January 1996 - 31 December 2008

Year of transplant	No. at risk on day 0	% Patient survival (95% confidence interval)			
		One year	Two year	Five year	Ten year
1996-1998	708	81 (78-84)	79 (76-82)	72 (68-75)	57 (54-61)
1999-2001	501	80 (76-83)	77 (73-80)	69 (65-73)	
2002-2004	387	80 (76-84)	78 (74-82)	70 (65-74)	
2005-2008	429	83 (79-86)			

Figure 4.1 shows the patient survival in days for adult ($\geq$ 16 years) recipients after first heart transplant from 1995 to 2006 (NHS Blood and Transplant, 2010).

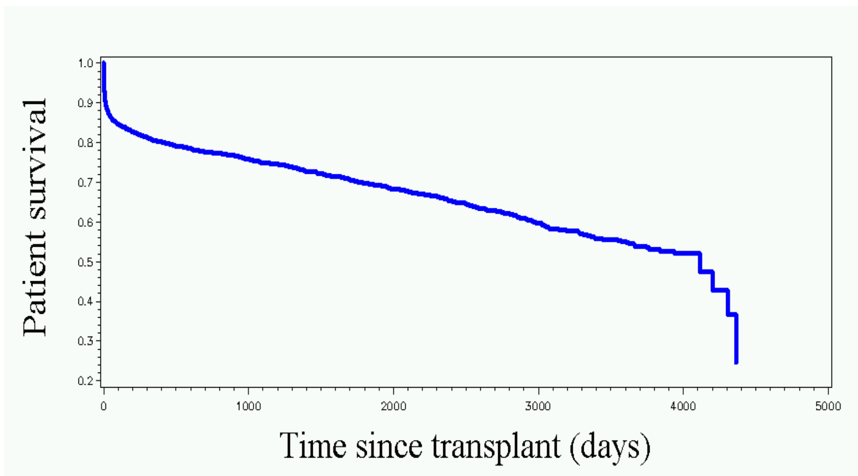

Figure 4.1: Survivor function (days) for adult ($\geq$ 16 years) recipients after first heart transplant from 1995 to 2006.

4.1 Heart transplant survival data

The first survival analysis for heart transplant aimed to clarify whether the technique really improved the life expectancy of patients (Turnbull *et al.*, 1974). Many studies based on the Cox model have been done to investigate the important explanatory variables and find suitable models that fit heart transplant survival data well (Villar *et al.*, 2007). Also, parametric models have been applied to study survival times after heart transplant (Jimenez, 2006 and Nelson *et al.*, 2007). However, the aim here is to study the same type of data using parametric models which allow for creatinine level (to measure kidney function) as a time-dependent covariate. The data used in the analysis were supplied by NHS Blood and Transplant for 1845 patients including all deceased heart beating and orthotropic heart only transplants in the UK for adult patients ($\geq$ 16 years at time of transplant operation) between 1 April 1995 and 31 March 2006, excluding multi-organ and re-transplant operations. The fixed covariates that may affect survival times for patients after heart transplant may be divided into four groups which are related to recipient, donor, transplant and immunosuppressant variables. In addition creatinine level is used as a time-dependent covariate.

4.1.1 Recipient variables

Most of the previous studies have agreed that the important recipient factors are sex, age, physical conditions (e.g. weight and height), recipient primary cardiotherapies disease, diabetes status and urgency status of the patient before the operation, Cimato and Jessup (2002). Table 4.3 describes the recipient variables.

Table 4.3: Description of heart transplant recipient variables

Variable	***Description***
RSEX	Recipient sex (1=Male, 2=Female)
RBG	Recipient blood group (1=O, 2=A, 3=B, 4=AB)
TX-WEIGHT	Recipient weight at transplant (kg)
REG-HEIGHT	Recipient height at registration (cm)
CMV	Recipient cytomegalovirus infection test result (1=Negative, 2=Positive)
PCD	Recipient primary cardiotherapies disease (group=1 for code 310, group=2 for codes from 313 to 319, group=3 for code 341 and group=4 for other codes)*
TX-IN HOSP	Recipient in hospital/ITU immediately prior to transplant (1=No, 2=Yes)
TX-VENT	Recipient ventilated at transplant (1=No, 2=Yes)
TX-NYHA	Recipient activity status according to New York Health Association classification at transplant(1=No limitation of activity, 2=Slight limitation, 3=Marked limitation, 4=Confined to bed/chair)
VASCULAR DISEASE	Peripheral vascular disease with intervention performed or planned (1=No, 2=Yes)
DIABETES	Diabetes status (1=No, 2=Yes-insulin dependent, 3=Yes-not insulin dependent)
PREV-HEART SURGERY	Number of previous open heart surgery operations
RAGE	Recipient age (years)
R-ETHNIC	Ethnicity (groups=1 for white, group=2 for Asian/Asian-British or Black/Black-British and group=3 for other)
WEIGHT-DIFF	Difference of the recipient weights at registration and transplantation (kg)

*See PCD codes in the Appendix A1.

4.1.2 Donor variables

Donor age and sex seem to be important variables (Ganesh, 2005). Also, cause of death, particularly if the donor suffered from explosive brain death, may affect survival times after heart transplant operation (Mehra *et al.*, 2004). NHS Blood and Transplant (2008) reported that donor blood group and CMV test result may influence survival times for transplanted organ. Table 4.4 shows the description of the heart donor variables.

*See DCOD codes in the Appendix A1.

4.1.3 Transplant variables

Three transplant variables are studied. The first is donor-recipient blood group match and the second is the urgency status before transplantation. Ischaemic time is defined as the time

Table 4.4: Description of heart donor variables

Variable	***Description***
DSEX	Donor sex (1=Male, 2=Female)
DAGE	Donor age at donation (years)
DPAED	Donor paediatric/adult indicator (0=Adult $>$ 14 years, 1= Paediatric $\leq$ 14 years)
DBG	Donor blood group (1=O, 2=A, 3=B, 4=AB)
DCMV	Donor CMV test result (1=Negative, 2=Positive)
DCOD	Donor cause of death (groups=1 for codes 10 and 11, group=2 for codes 12 and 13, group=3 for codes from 20 to 39 and group=4 for codes from 40 to 99)*
DCOUNTRY	Country of donor hospital(1=UK, 2=Republic of Ireland, 3=overseas)

between organ removal and surgery. It has been reported that survival time is affected by ischaemic time (Jimenez, 2006). Table 4.5 describes the three variables.

Table 4.5: Description of heart transplant variables

Variable	***Description***
ABOMATCH	Donor - recipient blood group match (1=Identical, 2=Compatible, 3=Incompatible)
URGENT	Urgency status of transplant (0=Non-urgent, 1=Urgent)
IT	Total ischaemic time, warm and cold (hours)

4.1.4 Immunosuppression variables

Patients after transplantation are at risk of several complications with the possibility of short survival. In the immediate post transplantation period, the most frequent reasons for death are: infections and critical organ rejection (Jurt *et al.*, 2002). In order to decrease these risks, many kinds of immunosuppressant drugs are applied within the 30 days post transplant. These medications help to treat cholesterol (statins), prevent infection, treat high blood pressure and other complications which potentially occur after transplant (Jurt *et al.*, 2002). Table 4.6 presents a list of these drugs.

4.1.5 The time-dependent variable

Creatinine is a chemical waste product from muscle metabolism and generated from creatine. About 2% of creatine is converted to creatinine daily and is carried through the bloodstream to the kidneys. Most of the creatinine is filtered out by the kidneys to be disposed of in the urine. Serum creatinine is commonly used to assess renal function in adults (Di Filippo *et al.*, 2007). Renal dysfunction may occur after heart transplantation and impact on long-term prognosis. The study focuses on recipient serum creatinine level which is measured at registration, one day after transplantation, 90 days later and at then subsequently every year. This variable is involved as a time-dependent covariate with many changes. Also, it may be treated either as a continuous variable or as a categorical variable (see section 4.2.2).

Creatinine level depends on body mass, which is affected by age, sex and ethnicity. So rather than use creatinine level itself, glomerular filtration rate (GFR) is the actual variable

Table 4.6: Description of immunosuppression variables

Variable	***Description***
CYCLO	Cyclosporin (1=No, 2=Yes)
AZATH	Azathioprine (1=No, 2=Yes)
CORTI	Corticosteroids (1=No, 2=Yes)
ALG-IND	ALG/ATG Induction/Prophylactic (1=No, 2=Yes)
ALG-REJ	ALG/ATG for Rejection (rejection resistant) (1=No, 2=Yes)
OKT3-IND	OKT3 Induction/Prophylactic (1=No, 2=Yes)
OKT3-REJ	OKT3 for Rejection (rejection resistant) (1=No, 2=Yes)
FK506	FK506 (1=No, 2=Yes)
TLI	TLI (1=No, 2=Yes)
METHO	Methotrexate (1=No, 2=Yes)
OTHER	Other drug at transplant (1=No, 2=Yes)

that features in our models. GFR may be estimated as follows. Suppose we have the creatinine measurement c in $\mu mol/l$ of a patient, then an estimate of GFR for a patient aged a years at measurement can be calculated as (NHS Blood and Transplant, 2008).

$$GFR = 186 \left(\frac{c}{88.4}\right)^{-1.154} a^{-0.203} \left(1 - 0.258 I_F\right) \left(1 + 0.21 I_B\right), \tag{4.1}$$

where $I_F = 1$ if the patient is female, 0 otherwise, and $I_B = 1$ if the patient is from the black ethnic group, 0 otherwise. So GFR is used in place of the creatinine level as a continuous time-dependent variable (note that the age, a, will change for a patient at each measurement time). Finally, a discrete version of GFR, used by NHS Blood and Transplant, might be applied where each GFR value was put into one of the following categories: > 89 (normal kidney function), $60 - 89$ (mildly reduced kidney function), $30 - 60$ (moderately reduced kidney function) and < 30 (severely reduced kidney function). Based on survival time in days of adult (≥ 16 years) heart transplant recipients, product-limit estimate of the survivor function of these risk groups are shown in Figure 4.2. The estimated survival for the severely reduced kidney function group is obviously low comparing to the other three groups.

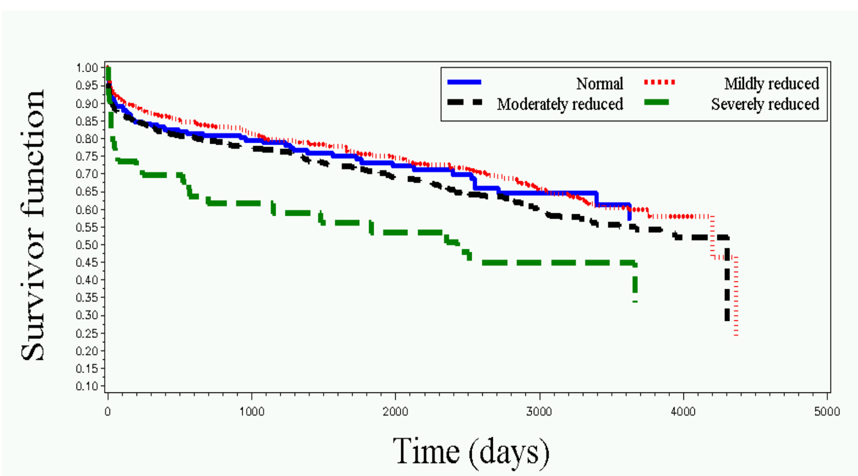

Figure 4.2: Product-limit survival estimates of heart transplant patients with normal, mildly, moderately, severely reduced kidney function (measured at transplantation day).

4.2 Model building

4.2.1 Model selection procedures for the fixed covariates

Model selection aims to find a parsimonious standard model. Hence a model selection strategy described by Collett (2003) was used. This strategy started with the identification of all the potential explanatory variables that might be related to the hazard after heart transplant data set. As described in section 3.1, the data included 35 variables in addition to the GFR as a time-dependent variable. Instead of using automatic variable selection procedures, a different general method was applied.

The aim of the project is to estimate the effect of the GFR as a time-dependent covariate on the hazard function. To achieve this aim, the first stage focused on modelling all the significant fixed covariates in one model to test them with the GFR in the next steps. The first step in this method was to test the significance of the variables at 10% significance level. This step was applied for all the 35 variables by fitting single Weibull models including one variable for each model and comparing them with the null model. The difference in the value of the likelihood ratio test $-2\log\hat{L}$ statistic between the one variable model and the null model was determined. There were 15 variables with significant difference in $-2\log\hat{L}$ at 10% significance level, so that these variables were fitted in one model. Table 4.7 summaries the results for the variables that gave significant difference $-2\log\hat{L}$ at 10% significance level.

Table 4.7: Results of the significant variables for the Weibull model at 10% based on one variable model

Model	Change in -2log$\hat{L}$	*df*	*P*
DSEX	3.98	1	0.0460
DAGE	24.46	1	$<$ 0.0001
DPAED	2.74	1	0.0979
DCMV	9.51	2	0.0087
DCOD	8.32	3	0.0398
URGENT	4.31	1	0.0379
IT	2.92	1	0.0875
RAGE	4.84	1	0.0278
PCD	14.48	3	0.0023
TX-IN HOSP	3.16	1	0.0755
CYCLO	72.02	1	$<$ 0.0001
CORTI	3.78	1	0.0519
OKT3-REJ	8.22	1	0.0042
FK506	3.61	1	0.0578
OTHER	4.76	1	0.0291

The second step is to examine the significant variables at 10% significance level from the first step. The 15 variables model was constructed and the variables were omitted in turn. Those variables that did not significantly increase the value of $-2\log\hat{L}$ at 5% significance level were omitted from the model. After omitting any variable, the other variables were examined by dropping them in the absence of this variable. To retain any variable in this method, it must be significant in the full model and in the absence of any other variable. For instance, this procedure started with dropping DAGE which significantly increased the value of $-2\log\hat{L}$. After dropping DAGE, all the other variables were dropping from the model that did not contain DAGE to examine them in the absence of DAGE. The resulting model from this stage contained the variables that are significant in presence and the absence of the other components. The significant variables were: DAGE, DCMV, PCD, CYCLO, FK506 and OTHER.

In the third step, all the discarded variables in the second step were added to the result 6 variables model, one at a time, to examine them in the presence of these six variables only. There were no changes in the significance of the discarded variables. A final check was done: all the dropped variables from the first and the second steps were added to the model with six variables modelling in order to be sure that no significant variable was omitted from the model. This final confirmation that there were six important variables in the heart transplant data set. Table 4.8 summaries the results values of $-2\log\hat{L}$ statistic and the p values that result from dropping each variable in the six variables model.

Table 4.8: Results of the significant variables in the six variable Weibull model

Model	Change in -2log$\hat{L}$	*df*	P
DAGE	8.05	1	0.0046
DCMV	10.81	2	0.0045
PCD	14.52	3	0.0023
CYCLO	154.01	1	< 0.0001
FK506	90.2	1	< 0.0001
OTHER	7.01	1	0.0081

In the previous model, DAGE is used as a continuous covariate. However, to test the linearity of the effect of, DAGE, a four factor version of DAGE was added to the model containing DCMV, PCD, CYCLO, FK506 and OTHER. The change in the value of $-2\log\hat{L}$ for the two models with DAGE as a factor with 4 levels and with linear trend was 0.89 on 2 df (p=0.64) which showed that DAGE should be used as a linear covariate.

Considering the hierarchy principle, after modelling all the single significant variables, two factor interactions between factors were examined. There were five mixed terms between DAGE and the other five factors and ten interaction terms among the five factors. The results showed only two significant interactions for CYCLO with FK506, $INTER_1$, with p=0.0003 and CYCLO with OTHER, $INTER_2$, p=0.003.

4.2.2 Model selection procedures including the time-dependent covariate

At this stage GFR was added to the model with six fixed covariates and two interactions. In this case, a counting process input style was used. The original survival times were divided to intervals according to the times of the creatinine test (i.e., it is assumed that creatinine test is done at regular times for each patient). The first interval starts with the GFR at registration and remains constant to the end of the interval (i.e., this interval starts at day zero and continues for one day). Thus, the second interval starts with the second GFR value, at transplant date (i.e. at day one), up to the end of this interval and so on.

The next step was estimating all the nine variables in one model, using the second step in the manual model selection way. Each variable was dropped from the complete model to examine its significance in the presence of all the nine variables. The omitted variables with significant increase in the value of $-2\log\hat{L}$ were retained in the model. For example, DAGE is retained in the model if it is significant in the complete model and in the reduced models (with one variable is dropped in turn). All the nine variables significantly increased the value of $-2\log\hat{L}$ when dropped from the complete model. Hence the model must contain the seven variables DAGE, DCMV, PCD, CYCLO, FK506, OTHER, GFR and the two interaction variables, CYCLO*FK506 (INTER1) and CYCLO*OTHER (INTER2).

4.3 Fixed covariate models

Following heart transplantation, the hazard of death tends to be high during the first days after the operation, and then decreases gradually with time as the body accepts the transplanted heart. Hence the hazard function can be represented by the AFT Weibull and log-logistic models when their shape is less than one. The AFT log-normal model may be used but it often tends to be similar to the log-logistic model (Collett, 2003). Consequently, it was suggested to use the Weibull and the log-logistic models only as alternatives to the Cox model. In this section, the results of fitting the suggested models using all the covariates as fixed including the baseline value for GFR are discussed. This stage will help to compare the performance of the Cox, standard Weibull, log-logistic and Weibull spline models to fit the data when no covariates are included as time-dependent.

4.3.1 Fixed covariates model using GFR as a continuous covariate

In this section the results of applying Cox, log-logistic, standard Weibull and Weibull spline models, using GFR as a continuous covariate, will be discussed.

4.3.1.1 Cox regression model

The first approach to model heart transplant data was the Cox model. This model is straightforward to fit using Proc Phreg in SAS. The results of the Cox model with GFR as a fixed continuous covariate are shown in Table 4.9.

Table 4.9: Cox model estimates and tests including GFR as a fixed continuous covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
DAGE(β_1)	0.0112	0.0035	10.3009	0.0013	10.3200	0.0013
DCMV1(β_2)	0.8148	0.5088	2.5644	0.1093	3.3450	0.0674
DCMV2(β_3)	1.0440	0.5099	4.1916	0.0406	5.8930	0.0152
PCD1(β_4)	0.2161	0.1049	4.2441	0.0394	4.3080	0.0379
PCD2(β_5)	0.1042	0.1552	0.4509	0.5019	0.4440	0.5052
PCD3(β_6)	-0.1490	0.1258	1.4029	0.2362	1.4100	0.2351
CYCLO(β_7)	-6.8690	0.7909	75.4228	<0.0001	47.6740	<0.0001
FK506(β_8)	-5.8844	0.8092	52.8824	<0.0001	39.0650	<0.0001
OTHER(β_9)	-2.2886	0.6038	14.3653	0.0002	15.7770	0.0001
INTER1(β_{10})	2.7468	0.5623	23.8596	<0.0001	15.7980	0.0001
INTER2(β_{11})	1.1028	0.3200	11.8773	0.0006	12.7180	0.0004
GFR(β_{12})	-0.0046	0.0023	4.1101	0.0426	4.2240	0.0399

Table 4.9 includes the MLE estimates of the parameters with their standard errors and the relative hazard for each covariate in addition to Wald and likelihood ratio tests. It is clear from these results that the covariates DCMV1, PCD2 and PCD3 are non-significant at the 5% significance level. However, these covariates should be retained in the model because the changes in $-2\log\hat{L}$ when they are extracted from the model are 8.956 on 2 df and 12.117 on 3 df and the corresponding p-values are .011 and 0.007 for DCMV and PCD respectively. The estimated relative hazard of death for GFR level for a patient is 0.995 which means that the increase in the value of that covariate by one unit (keeping the values of the other covariates fixed) decreases the hazard by 0.005.

4.3.1.2 Log-logistic model

After heart transplantation, the hazard of death is usually high during the first days as the result for body updating for the transplanted heart. In the following period, the hazard starts to decrease while the body responses for the new organ (Collett, 2003). The log-logistic AFT model with shape less than one, described in section (3.2.2,), may be an appropriate model for the monotonically decreasing hazard case. This model is straightforward to be estimated using Proc Lifereg, in addition to the possibility to use Proc Nlp in SAS. Table 4.10 shows the results of fitting the log-logistic model to the heart transplant data.

As in the Cox model results, DCMV1, PCD1, PCD2 and PCD3 are not significant at the 5% significance level, but likelihood ratio test for excluding them tells that the changes of dropping DCMV and PCD from the model are 8.548 on 2 df and 9.857 on 3 df with p-values 0.0139 and 0.0198 respectively. GFR covariate is significant with p-value 0.0454 which is very close to the Cox model result. In the log-logistic model, the acceleration factor for GFR is .991 which means that decreasing GFR level by one unit accelerates the survival time by about 1.009 when the other covariates have the same values.

Table 4.10: Log-logistic model estimates and tests including GFR as fixed continuous covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept(β_0)	-24.8569	3.4132	-	-	-	-
DAGE(β_1)	-0.0217	0.0077	7.9700	0.0048	8.0100	0.0047
DCMV1(β_2)	-1.7687	1.2278	2.0800	0.1497	2.5150	0.1128
DCMV2(β_3)	-2.2407	1.2295	3.3200	0.0684	4.2260	0.0398
PCD1(β_4)	-0.3925	0.2298	2.9200	0.0875	2.9460	0.0861
PCD2(β_5)	-0.1220	0.3380	0.1300	0.7181	0.1290	0.7195
PCD3(β_6)	0.3735	0.2667	1.9600	0.1614	1.9720	0.1602
CYCLO(β_7)	17.3501	1.7973	93.1900	<0.0001	64.3190	<0.0001
FK506(β_8)	15.1914	1.7190	78.1000	<0.0001	56.4790	<0.0001
OTHER(β_9)	5.5052	1.5296	12.9500	0.0003	13.2340	0.0003
INTER1(β_{10})	-7.0715	1.1517	37.7000	<0.0001	24.4540	<0.0001
INTER2(β_{11})	-2.5540	0.7956	10.3100	0.0013	10.4240	0.0012
GFR(β_{12})	0.0094	0.0048	3.9200	0.0478	4.0050	0.0454
Shape(ρ)	0.5575	0.0682	-	-	-	-

4.3.1.3 Standard Weibull model

The standard Weibull AFT model may be a good alternative to fit the heart transplant data. The model was applied using Proc Lifereg and Proc Nlp in SAS. Table 4.11 shows the results that have been obtained.

Significance of the parameters in the standard Weibull model are very close to the significance level of the parameters in the Cox and the log-logistic models. Even though the PCD2 and PCD3 seem to be not significant at the 5% significance level, the likelihood ratio test for excluding the PCD suggests to retain this covariate. The GFR is significant with (p=0.03) and the acceleration factor for this covariate is about 0.99 which is equivalent to its acceleration factor in the log-logistic model. This may refer to approximately analogous results for the three models when GFR is treated as a fixed and continuous covariate.

4.3.1.4 Weibull spline model

The Weibull spline model, described in section (3.4.1), was applied using Proc Nlp in SAS with the codes given in Appendix B. The models with more than 5 knots are expected to produce unstable curves (Royston and Parmar, 2002). Models with 0, 1, 2, 3, 4 and 5 knots were fitted using the knot positions as defined in Table 4.12 for the log uncensored survival times.

Based on the AIC values for the six models that are shown below, the best model is the 5 knots model. The results of fitting this model are given in Table 4.13.

The results in Table 4.13 are similar to the results that have been obtained from the other three models. The p-values of the different covariates were very similar to the calculated p-values in the Cox, log-logistic and the standard Weibull model. Also, it was noticed that the shape parameter changed to about 0.6 in the Weibull model with 5 knots. The MLE estimates and their standard errors for the different spline models are included in Table 4.14.

The Weibull spline models with 0, 1, 2, 3, 4 and 5 knots were estimated. The survival function decrease rapidly during the first days after heart transplantation while it is slightly

Table 4.11: Standard Weibull model estimates and tests including GFR as a fixed continuous covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept(β_0)	-17.8709	3.0001	-	-	-	-
DAGE(β_1)	-0.0230	0.0075	9.4600	0.0021	9.5230	0.0020
DCMV1(β_2)	-1.9519	1.0984	3.1600	0.0756	4.2410	0.0395
DCMV2(β_3)	-2.4530	1.1019	4.9600	0.0260	7.1780	0.0074
PCD1(β_4)	-0.4528	0.2262	4.0000	0.0454	4.0770	0.0435
PCD2(β_5)	-0.2197	0.3342	0.4300	0.5109	0.4260	0.5140
PCD3(β_6)	0.3293	0.2720	1.4700	0.2260	1.4790	0.2239
CYCLO(β_7)	14.3076	1.7022	70.6500	<0.0001	45.6130	<0.0001
FK506(β_8)	12.5966	1.7474	51.9700	<0.0001	38.8330	<0.0001
OTHER(β_9)	4.6353	1.3009	12.7000	0.0004	13.9730	0.0002
INTER1(β_{10})	-5.7770	1.2103	22.7800	<0.0001	15.2630	0.0001
INTER2(β_{11})	-2.0957	0.6871	9.3000	0.0023	9.9030	0.0017
GFR(β_{12})	0.0101	0.0049	4.2500	0.0392	4.3860	0.0362
Shape(ρ)	0.4642	0.0807	-	-	-	-

Table 4.12: Knot positions for survival times after heart transplants and the AIC values for the six estimated models

No. of knots	Centile positions	Heart transplant survival times (days)	AIC
0	-	-	9992.12
1	50	398.5	9988.83
2	33, 67	59, 1272.5	9913.86
3	25, 50, 75	19.25, 398.5, 1734	9897.29
4	20, 40, 60, 80	9, 154, 935, 2085	9885.92
5	17, 33, 50, 67, 83	10, 59, 398.5, 1276.5, 2262.5	9864.15

flat with the larger times. Even though the 5 knots model has more knots than the lower degree models (e.g., 4 knots or less models) to represent the function while it changes fast, it was found that the knots that are placed at large times are necessary to improve the model. Placing knots at suitable locations is another issue. In the case of heart transplant data, the hazard function decreases rapidly after a time between 10 and 50 days. Thus, it was supposed that select knot location at 10, 50, 100 and 150 days may improve the spline models. However, it was found that the model significance did not change when different knots model was estimated using these knot locations. Table 4.14 shows the MLE estimates and their standard errors for the different models. The shape parameter increased from about 0.46 in the Weibull spline model with 0 knots to 0.61 in the Weibull spline model with 5 knots. This means that the hazard shape of the model changes as the number of knots increases as described in Figure 4.7.

As a result to the difference in scales of parameters between the Cox and the parametric models, it is not suitable to compare parameter estimates and their estimated variances. In this case, standardized variability, which analogous to the coefficient of variation, can be used to compare efficiency of parameter estimates across Cox, parametric and spline models. Nardi and Schemper (2003) defined this measure for parameter estimate $\hat{\beta}$ as $[sv = \hat{\sigma}_\beta/|\hat{\beta}|]$. These values were calculated for the GFR, GFR1, GFR2 and GFR3 in the fixed and the time-dependent models (see Table 4.37). For the fixed continuous GFR case, the sv values were

Table 4.13: Weibull spline (5 knots) estimates and Wald tests including GFR as a fixed continuous covariate

Covariate	MLE	SE	Wald	
			χ^2	P
Intercept(β_0)	-14.2626	2.2512	-	-
DAGE(β_1)	-0.0188	0.0057	10.9239	0.001
DCMV1(β_2)	-1.4046	0.8334	2.8404	0.0921
DCMV2(β_3)	-1.7734	0.8355	4.5056	0.0339
PCD1(β_4)	-0.3395	0.1716	3.9144	0.048
PCD2(β_5)	-0.1593	0.2539	0.3937	0.5305
PCD3(β_6)	0.2603	0.2061	1.5956	0.2067
CYCLO(β_7)	11.4729	1.2936	78.6592	<0.0001
FK506(β_8)	9.8242	1.3237	55.0846	<0.0001
OTHER(β_9)	3.8156	0.9886	14.8966	0.0001
INTER1(β_{10})	-4.5837	0.9207	24.787	<0.0001
INTER2(β_{11})	-1.8398	0.5238	12.3375	0.0005
GFR(β_{12})	0.0076	0.0037	4.2107	0.0403
First knot (γ_1)	0.1106	0.019	33.7689	<0.0001
Second knot (γ_2)	-0.4077	0.1567	6.7688	0.0094
Third knot (γ_3)	2.1091	0.614	11.7979	0.0006
Fourth knot (γ_4)	-7.3005	1.6646	19.2344	<0.0001
Fifth knot (γ_5)	7.8828	1.8274	18.6080	<0.0001
Shape(ρ)	0.611	0.1149	-	-

calculated for parameter estimates through the spline models with 0 to 5 knots. According to this measure there was a small difference among the six models for all parameter estimates. However, the 1 knot model appears to have the lowest sv-values for all parameter estimates of the explanatory covariates.

Table 4.14: MLE estimates and standard errors for the Weibull spline models from 0 to 5 knots including GFR as a fixed continuous covariate

Covariate	0 Knots		1 Knot		2 Knots		3 Knots		4 Knots		5 Knots	
	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE
Intercept(β_0)	-17.871	2.997	-20.563	3.393	-17.226	2.748	-15.947	2.525	-14.614	2.313	-14.263	2.252
DAGE(β_1)	-0.023	0.009	-0.027	0.010	-0.023	0.008	-0.021	0.007	-0.019	0.007	-0.019	0.007
DCMV1(β_2)	-1.952	1.099	-2.181	1.259	-1.746	1.018	-1.546	0.934	-1.425	0.855	-1.405	0.833
DCMV2(β_3)	-2.453	1.101	-2.756	1.262	-2.189	1.020	-1.955	0.936	-1.8	0.857	-1.773	0.835
PCD1(β_4)	-0.453	0.226	-0.515	0.259	-0.408	0.210	-0.373	0.193	-0.349	0.176	-0.34	0.172
PCD2(β_5)	-0.22	0.334	-0.241	0.383	-0.178	0.310	-0.165	0.284	-0.159	0.261	-0.159	0.254
PCD3(β_6)	0.329	0.272	0.381	0.311	0.324	0.252	0.301	0.231	0.265	0.212	0.26	0.206
CYCLO(β_7)	14.307	1.696	16.263	1.946	13.735	1.578	12.727	1.450	11.736	1.328	11.473	1.293
FK506(β_8)	12.596	1.739	14.367	1.995	11.752	1.616	10.92	1.484	10.063	1.360	9.824	1.324
OTHER(β_9)	4.635	1.300	5.106	1.489	4.58	1.208	4.216	1.108	3.89	1.015	3.816	0.989
INTER1(β_{10})	-5.777	1.211	-6.602	1.388	-5.473	1.124	-5.098	1.031	-4.695	0.946	-4.584	0.921
INTER2(β_{11})	-2.096	0.688	-2.332	0.788	-2.188	0.640	-2.029	0.587	-1.877	0.538	-1.84	0.524
GFR(β_{12})	0.01	0.004	0.012	0.005	0.009	0.004	0.008	0.004	0.008	0.003	0.008	0.003
Shape(ρ)	0.464	0.081	0.405	0.181	0.5	0.139	0.545	0.127	0.595	0.118	0.611	0.115
First knot (γ_1)	-	-	-0.006	0.003	0.280	0.036	0.187	0.029	0.093	0.015	0.111	0.157
Second knot (γ_2)	-	-	-	-	-0.758	0.097	-0.413	0.259	-0.128	0.190	-0.408	0.019
Third knot (γ_3)	-	-	-	-	-	-	0.088	0.472	0.212	0.873	2.109	0.614
Fourth knot (γ_4)	-	-	-	-	-	-	-	-	-0.661	1.392	-7.301	1.665
Fifth knot (γ_5)	-	-	-	-	-	-	-	-	-	-	7.883	1.827

Table 4.15: Standardized variability of parameter estimates for the Weibull spline models from 0 to 5 knots including GFR as a fixed continuous covariate

Covariate	0 Knots	1 Knot	2 Knots	3 Knots	4 Knots	5 Knots
Intercept(β_0)	0.165	0.165	0.160	0.158	0.158	0.158
DAGE(β_1)	0.375	0.366	0.348	0.349	0.354	0.345
DCMV1(β_2)	0.563	0.577	0.583	0.604	0.600	0.593
DCMV2(β_3)	0.449	0.458	0.466	0.479	0.476	0.471
PCD1(β_4)	0.500	0.503	0.515	0.517	0.506	0.505
PCD2(β_5)	1.518	1.588	1.742	1.724	1.638	1.595
PCD3(β_6)	0.825	0.817	0.778	0.768	0.799	0.793
CYCLO(β_7)	0.119	0.120	0.115	0.114	0.113	0.113
FK506(β_8)	0.138	0.139	0.138	0.136	0.135	0.135
OTHER(β_9)	0.280	0.292	0.264	0.263	0.261	0.259
INTER1(β_{10})	0.210	0.210	0.205	0.202	0.202	0.201
INTER2(β_{11})	0.328	0.338	0.293	0.289	0.287	0.285
GFR(β_{12})	0.431	0.412	0.444	0.459	0.420	0.409
Shape(ρ)	0.175	0.447	0.278	0.233	0.198	0.188

4.3.2 Fixed covariates model using GFR as a categorical covariate

Following the categorization of GFR that was described in section 4.2.2, the suggested models were applied including the three covariates $GFR1$, $GFR2$ and $GFR3$ which correspond to GFR levels: > 89 (normal kidney function), $60 - 89$ (mildly reduced kidney function) and $30 - 60$ (moderately reduced kidney function) respectively.

4.3.2.1 Cox regression model

Table 4.16 shows the results of the Cox model with GFR as a fixed categorical covariate. The table includes the MLE estimates with their standard errors and the relative hazard for each covariate in addition to the tests of Wald and likelihood ratio. As in the continuous case, it is noticed that the covariates DCMV1, PCD2 and PCD3 are non-significant at 5% level. However, these covariates should be retained in the model because the changes in $-2\log\hat{L}$ when they are extracted from the model are 9.935 on 2 df and 13.758 on 3 df and the corresponding p-values are .007 and 0.003 for DCMV and PCD respectively. For the kidney functions covariates $GFR1$, $GFR2$ and $GFR3$, the p-values are greater than 0.05 which indicate to low significance and then it is preferable to use it as a continuous. The estimated relative hazards of death for $GFR1$, $GFR2$ and $GFR3$ for a patient, with the same values for the other covariates, are 0.87, 0.76 and 0.88 respectively which reflect the hazard of death for patients who in the three groups relative to the hazard of death for patients with low kidney function (GFR <15).

Table 4.16: Cox model estimates and tests including GFR as a fixed categorical covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
DAGE(β_1)	0.0112	0.0035	10.3083	0.0013	10.3300	0.0013
DCMV1(β_2)	0.8754	0.5122	2.9208	0.0874	3.8580	0.0495
DCMV2(β_3)	1.1126	0.5136	4.6930	0.0303	6.6770	0.0098
PCD1(β_4)	0.2415	0.1050	5.2901	0.0214	5.3770	0.0204
PCD2(β_5)	0.0998	0.1554	0.4127	0.5206	0.4070	0.5235
PCD3(β_6)	-0.1461	0.1260	1.3458	0.2460	1.3530	0.2448
CYCLO(β_7)	-6.7398	0.7973	71.4662	<0.0001	46.1690	<0.0001
FK506(β_8)	-5.7411	0.8150	49.6280	<0.0001	37.4510	<0.0001
OTHER(β_9)	-2.3034	0.6041	14.5379	0.0001	15.9690	0.0001
INTER1(β_{10})	2.6555	0.5653	22.0699	<0.0001	17.5760	<0.0001
INTER2(β_{11})	1.1038	0.3201	11.8904	0.0006	13.2940	0.0003
GFR1(β_{12})	-0.1367	0.2290	0.3564	0.5505	0.3530	0.5524
GFR2(β_{13})	-0.2779	0.1912	2.1133	0.1460	1.9830	0.1591
GFR3(β_{14})	-0.1265	0.1889	0.4481	0.5033	0.4350	0.5095

Figure 4.3 shows the estimated survival function for two patients with normal and low kidney functions in the Cox model. The two estimated survival functions are based on the average values for all the other covariates in order to reflect the effect of changing kidney functions level on the survival time of the patient after the heart is transplanted. It is obvious that the patient with normal kidney functions has higher survival than the patient with low kidney functions.

4.3.2.2 Log-logistic model

In the same manner of the continuous case, the results of applying the log-logistic model are described in Table 4.17. It was found that the covariates $DCMV1$ (according to Wald test) and $PCD1$ were not significant at the 5% significance level. However, the three covariates $GFR1$, $GFR2$ and $GFR3$ were significant at the same significance level.

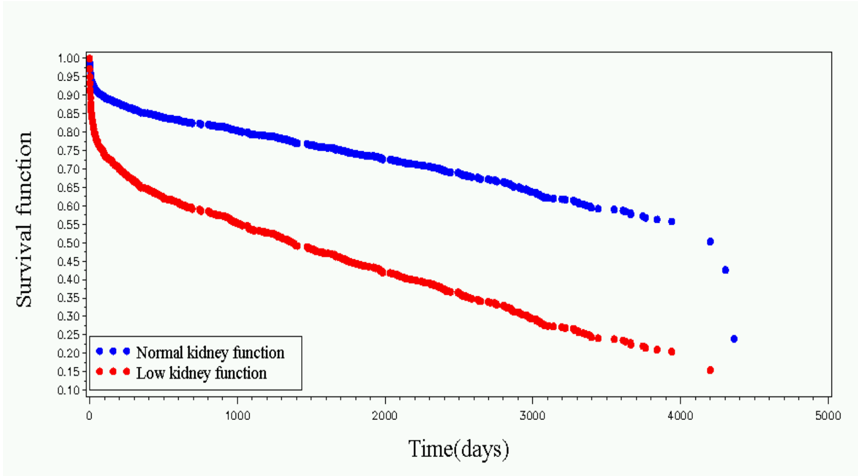

Figure 4.3: Estimated survival function for normal and low kidney function patients in the Cox model based on the average values for the other covariates.

Table 4.17: Log-logistic model estimates and tests including GFR as a fixed categorical covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept(β_0)	-25.2757	3.4458	-	-	-	-
DAGE(β_1)	-0.0222	0.0077	8.3300	0.0039	8.3700	0.0038
DCMV1(β_2)	-1.8016	1.2350	2.1300	0.1446	2.6030	0.1067
DCMV2(β_3)	-2.2781	1.2368	3.3900	0.0655	4.3650	0.0367
PCD1(β_4)	-0.3992	0.2297	3.0200	0.0823	3.0480	0.0808
PCD2(β_5)	-0.0882	0.3384	0.0700	0.7945	0.0680	0.7943
PCD3(β_6)	0.3873	0.2668	2.1100	0.1466	2.1200	0.1454
CYCLO(β_7)	17.3337	1.8023	92.5000	<0.0001	64.1170	<0.0001
FK506(β_8)	15.0442	1.7258	75.9900	<0.0001	55.5470	<0.0001
OTHER(β_9)	5.7198	1.5388	13.8200	0.0002	14.1230	0.0002
INTER1(β_{10})	-6.9368	1.1560	36.0100	<0.0001	30.6060	<0.0001
INTER2(β_{11})	-2.6606	0.8001	11.0600	0.0009	15.0080	0.0001
GFR1(β_{12})	1.0655	0.5279	4.0700	0.0435	4.0370	0.0445
GFR2(β_{13})	1.1225	0.4488	6.2500	0.0124	6.0170	0.0142
GFR3(β_{14})	0.8958	0.4473	4.0100	0.0452	3.8910	0.0485
Shape(ρ)	0.5580	0.0681	-	-	-	-

4.3.2.3 Standard Weibull model

The results of applying the standard Weibull AFT model are shown in Table 4.18. The results of this model are very close to the results of the Cox when GFR is treated as a fixed categorical covariate. Figure 4.4 shows the estimated log hazard functions for the two patients with normal and low kidney functions in the standard Weibull model. Given that they have the same average values for the other covariates, it is noticed that the hazard is higher for the patient with lower kidney functions.

Table 4.18: Standard Weibull model estimates and tests including GFR as a fixed categorical covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept(β_0)	-17.0870	3.0019	-	-	-	-
DAGE(β_1)	-0.0232	0.0075	9.5200	0.0020	9.5710	0.0020
DCMV1(β_2)	-2.1050	1.1088	3.6000	0.0576	4.8970	0.0269
DCMV2(β_3)	-2.6251	1.1128	5.5600	0.0183	8.1410	0.0043
PCD1(β_4)	-0.5104	0.2268	5.0600	0.0244	5.1670	0.0230
PCD2(β_5)	-0.2173	0.3351	0.4200	0.5166	0.4150	0.5194
PCD3(β_6)	0.3184	0.2726	1.3600	0.2427	1.3770	0.2406
CYCLO(β_7)	14.1003	1.7194	67.2500	<0.0001	44.2910	<0.0001
FK506(β_8)	12.3521	1.7621	49.1400	<0.0001	37.3810	<0.0001
OTHER(β_9)	4.6926	1.3041	12.9500	0.0003	14.2610	0.0002
INTER1(β_{10})	-5.6158	1.2179	21.2600	<0.0001	16.6110	<0.0001
INTER2(β_{11})	-2.1078	0.6887	9.3700	0.0022	10.3510	0.0013
GFR1(β_{12})	0.2550	0.4968	0.2600	0.6077	0.2620	0.6087
GFR2(β_{13})	0.5165	0.4152	1.5500	0.2135	1.4750	0.2246
GFR3(β_{14})	0.2228	0.4097	0.3000	0.5866	0.2900	0.5902
Shape(ρ)	0.4636	0.0810	-	-	-	-

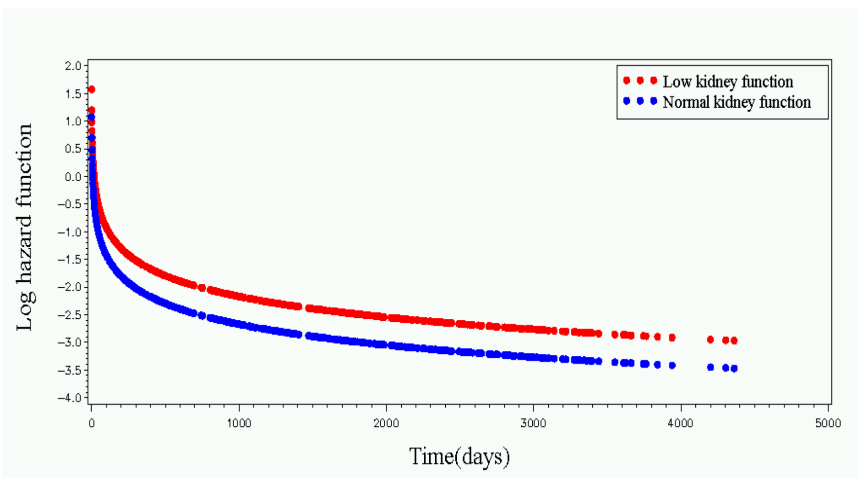

Figure 4.4: Estimated log hazard function for normal and low kidney function patients in the standard Weibull model based on the average values for the other covariates.

4.3.2.4 Weibull spline model

The Weibull spline model was applied to fit the same data that incudes GFR as a categorical covariate. Six models with 0, 1, 2, 3, 4 and 5 knots were fitted using the same method of the continuous case and the same knot positions as defined in Table 4.12.

The AIC values for the six models, that are shown in the Table 4.19, are approximately the same when GFR was treated as a continuous. These AIC values give to the 5 knots model as the best model. The results of this model are given in Table 4.18.

The results in Table 4.20 show that the p value of GFR3 decreased from 0.59 in the standard Weibull model to less than 0.001 in the Weibull spline model. The other results are similar in the two models. The MLE estimates and their standard errors for the different

Table 4.19: The AIC values for the six estimated models

Number of knots	AIC
0 knots	9993.45
1 knot	9989.98
2 knots	9914.24
3 knots	9897.75
4 knots	9886.52
5 knots	9864.88

spline models are included in Table 4.21. These results will be investigated using residuals analysis in section 4.5. Figure 4.5 shows the difference in the estimated hazard functions between the patients with normal and low kidney function in the Weibull spline model with 5 knots, where the other covaraites were held fixed.

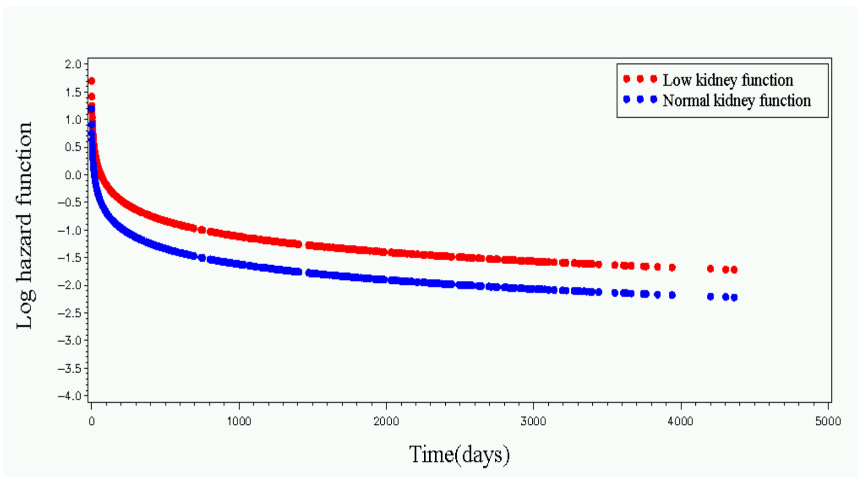

Figure 4.5: Estimated log hazard function for normal and low kidney function patients in the Weibull spline (5 knots) model where the same value for the other covariates are used.

The Weibull spline models with 0, 1, 2, 3, 4 and 5 knots were estimated. Table 4.21 shows the MLE estimates and their standard errors for the different models when GFR was treated as a categorical. There is no important change in the results of table 4.14.

Table 4.22 presents the sv-values of parameter estimates for the Weibull spline models from 0 to 5 knots when GFR was treated as a fixed categorical covariate. The six models produce similar values, with a tendency towards lower values in the 1 knot model.

Table 4.20: Weibull spline (5 knots) model estimates and tests including GFR as fixed categorical covariate

Covariate	MLE	SE	Wald	
			χ^2	P
Intercept(β_0)	-13.7007	2.2553	-	-
DAGE(β_1)	-0.0190	0.0057	10.9688	0.0009
DCMV1(β_2)	-1.5194	0.8428	3.2501	0.0716
DCMV2(β_3)	-1.9034	0.8453	5.0708	0.0245
PCD1(β_4)	-0.3841	0.1724	4.9658	0.0260
PCD2(β_5)	-0.1556	0.2552	0.3717	0.5422
PCD3(β_6)	0.2537	0.2070	1.5023	0.2205
CYCLO(β_7)	11.3262	1.3093	74.8274	<0.0001
FK506(β_8)	9.6411	1.3382	51.9082	<0.0001
OTHER(β_9)	3.8697	0.9930	15.1878	0.0001
INTER1(β_{10})	-4.4612	0.9286	23.0819	<0.0001
INTER2(β_{11})	-1.8553	0.5260	12.4422	0.0004
GFR1(β_{12})	0.1955	0.3771	0.2688	0.6042
GFR2(β_{13})	0.4240	0.3146	1.8159	0.1780
GFR3(β_{14})	0.1802	0.3108	0.3361	0.5621
First knot (γ_1)	0.1100	0.0190	33.5250	<0.0001
Second knot (γ_2)	-0.4033	0.1567	6.6283	0.0101
Third knot (γ_3)	2.1074	0.6151	11.7363	0.0006
Fourth knot (γ_4)	-7.3195	1.6706	19.1956	<0.0001
Fifth knot (γ_5)	7.9050	1.8357	18.5435	<0.0001
Shape(ρ)	0.6088	0.1157	-	-

4.4 Time-dependent covariates models

To extend the suggested models to allow for a time-dependent covariate with many changes, the regular measures of GFR were used. The extended Cox model in addition to the AFT parametric models that were described in section 3.3 were applied to model the same data when GFR is treated as a continuous and as a categorical covariate. The aim here is to obtain the best model with the best form for modelling that covariate.

4.4.1 Time-dependent covariates model using GFR as a continuous covariate

The results of fitting the extended Cox model and the parametric alternative models are supplied in this section when GFR is treated as a continuous time-dependent covariate.

4.4.1.1 Cox regression model

This model is straightforward to be estimated using Proc Phreg in SAS when the style of data input that was described in 3.3.4 is used. Table 4.23 shows the Cox model estimates and tests. The $DCMV1$, $DCMV2$, $PCD1$, $PCD2$ and $PCD3$ were not significant at the 5% significance level while the other covariates were significant at the same level. The relative hazard for GFR is 0.993, which means that the increase in GFR level by 1 unit will decrease the hazard of death by 0.007. When GFR was treated as a categorical time-dependent

Table 4.21: MLE estimates and standard errors for the Weibull spline models with 0 to 5 knots including GFR as a fixed categorical covariate

Covariate	0 Knots		1 Knot		2 Knots		3 Knots		4 Knots		5 Knots	
	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE
Intercept(β_0)	-17.087	2.953	-19.714	3.394	-16.566	2.757	-15.325	2.529	-14.035	2.315	-13.701	2.255
DAGE(β_1)	-0.023	0.009	-0.027	0.010	-0.023	0.008	-0.021	0.007	-0.019	0.007	-0.019	0.007
DCMV1(β_2)	-2.105	1.108	-2.359	1.272	-1.882	1.030	-1.671	0.945	-1.541	0.865	-1.519	0.842
DCMV2(β_3)	-2.625	1.112	-2.956	1.275	-2.343	1.032	-2.096	0.947	-1.931	0.867	-1.903	0.846
PCD1(β_4)	-0.510	0.226	-0.582	0.260	-0.462	0.211	-0.423	0.193	-0.395	0.177	-0.384	0.172
PCD2(β_5)	-0.217	0.334	-0.237	0.384	-0.174	0.311	-0.161	0.285	-0.154	0.261	-0.156	0.255
PCD3(β_6)	0.318	0.272	0.371	0.312	0.316	0.253	0.294	0.232	0.259	0.212	0.254	0.207
CYCLO(β_7)	14.100	1.713	16.052	1.968	13.546	1.598	12.554	1.466	11.582	1.344	11.326	1.309
FK506(β_8)	12.352	1.752	14.111	2.015	11.520	1.635	10.707	1.499	9.872	1.374	9.641	1.338
OTHER(β_9)	4.693	1.300	5.176	1.495	4.640	1.213	4.273	1.112	3.944	1.019	3.870	0.993
INTER1(β_{10})	-5.616	1.218	-6.427	1.399	-5.320	1.135	-4.956	1.041	-4.568	0.953	-4.461	0.928
INTER2(β_{11})	-2.108	0.688	-2.348	0.792	-2.205	0.643	-2.045	0.589	-1.891	0.540	-1.855	0.525
GFR1(β_{12})	0.255	0.496	0.301	0.569	0.245	0.460	0.217	0.422	0.190	0.388	0.196	0.378
GFR2(β_{13})	0.517	0.414	0.614	0.475	0.533	0.384	0.485	0.352	0.432	0.324	0.424	0.315
GFR3(β_{14})	0.223	0.409	0.270	0.470	0.242	0.380	0.213	0.348	0.182	0.319	0.18	0.311
Shape(ρ)	0.464	0.081	0.404	0.182	0.498	0.140	0.543	0.128	0.593	0.119	0.609	0.116
First knot (γ_1)	-	-	-0.006	0.003	0.282	0.036	0.187	0.029	0.093	0.015	0.110	0.019
Second knot (γ_2)	-	-	-	-	-0.763	0.097	-0.407	0.259	-0.122	0.190	-0.403	0.157
Third knot (γ_3)	-	-	-	-	-	-	0.075	0.474	0.206	0.876	2.107	0.615
Fourth knot (γ_4)	-	-	-	-	-	-	-	-	-0.668	1.399	-7.320	1.671
Fifth knot (γ_5)	-	-	-	-	-	-	-	-	-	-	7.905	1.836

Table 4.22: Standardized variability of parameter estimates for the Weibull spline models from 0 to 5 knots including GFR as a fixed categorical covariate

Covariate	0 Knots	1 Knot	2 Knots	3 Knots	4 Knots	5 Knots
Intercept(β_0)	0.173	0.172	0.166	0.165	0.165	0.165
DAGE(β_1)	0.375	0.367	0.349	0.351	0.355	0.346
DCMV1(β_2)	0.526	0.539	0.547	0.565	0.561	0.555
DCMV2(β_3)	0.424	0.431	0.441	0.452	0.449	0.444
PCD1(β_4)	0.444	0.447	0.456	0.457	0.448	0.449
PCD2(β_5)	1.539	1.619	1.789	1.773	1.697	1.632
PCD3(β_6)	0.854	0.841	0.801	0.789	0.820	0.815
CYCLO(β_7)	0.122	0.123	0.118	0.117	0.116	0.116
FK506(β_8)	0.142	0.143	0.142	0.140	0.139	0.139
OTHER(β_9)	0.277	0.289	0.261	0.260	0.258	0.257
INTER1(β_{10})	0.217	0.218	0.213	0.210	0.209	0.208
INTER2(β_{11})	0.326	0.337	0.291	0.288	0.285	0.283
GFR1(β_{12})	1.944	1.891	1.877	1.943	2.041	1.927
GFR2(β_{13})	0.800	0.774	0.720	0.725	0.749	0.744
GFR3(β_{14})	1.836	1.742	1.568	1.634	1.751	1.718
Shape(ρ)	0.175	0.450	0.281	0.236	0.201	0.190

covariate, INTER2 was non-significant with p=0.42 and then it was discarded from the continuous and categorical time-dependent models.

Table 4.23: Cox model estimates and tests including GFR as a time-dependent continuous covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
DAGE(β_1)	0.0096	0.0036	7.1050	0.0077	7.1130	0.0077
DCMV1(β_2)	0.5619	0.5058	1.2342	0.2666	1.4860	0.2228
DCMV2(β_3)	0.7870	0.5064	2.4151	0.1202	3.1380	0.0765
PCD1(β_4)	0.1715	0.1099	2.4360	0.1186	2.4680	0.1162
PCD2(β_5)	0.1002	0.1592	0.3964	0.5290	0.3910	0.5318
PCD3(β_6)	-0.1529	0.1286	1.4142	0.2344	1.4190	0.2336
CYCLO(β_7)	-4.9116	0.6156	63.6587	<0.0001	34.9290	<0.0001
FK506(β_8)	-5.0117	0.7900	40.2420	<0.0001	31.4050	<0.0001
OTHER(β_9)	-0.0425	0.0188	5.0933	0.0240	9.1690	0.0025
INTER1(β_{10})	2.3441	0.5557	17.7953	<0.0001	12.4430	0.0004
GFR(η_1)	-0.0072	0.0024	8.9601	0.0028	9.4080	0.0022

4.4.1.2 Log-logistic model

The log-logistic model with time-dependent GFR was estimated using Proc Nlp in SAS using the codes that is described in Appendix B. Table 4.24 contains the model estimates and tests. For GFR, the p-value is <0.0001 which refers to higher significance of GFR when treated as a continuous time-dependent in the log-logistic model comparing to the same significance level of the same covariate in the Cox model.

Table 4.24: Log-logistic model estimates and tests including GFR as a time-dependent continuous covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept(β_0)	-27.5181	2.7179	-	-	-	-
DAGE(β_1)	-0.0287	0.0081	12.5790	0.0004	12.6066	0.0004
DCMV1(β_2)	-2.0449	1.1408	3.2133	0.0731	3.496	0.0615
DCMV2(β_3)	-2.7144	1.1431	5.6387	0.0176	4.37	0.0366
PCD1(β_4)	-0.6087	0.2451	6.1669	0.0130	6.6134	0.0101
PCD2(β_5)	-0.5374	0.3670	2.1440	0.1431	2.2828	0.1311
PCD3(β_6)	0.4021	0.2761	2.1212	0.1453	2.272	0.1319
CYCLO(β_7)	17.7089	1.4234	154.7902	<0.0001	106.4128	<0.0001
FK506(β_8)	18.4915	1.7686	109.3161	<0.0001	93.636	<0.0001
OTHER(β_9)	0.2174	0.0437	24.7402	<0.0001	16.4168	0.0001
INTER1(β_{10})	-8.3485	1.1580	51.9746	<0.0001	39.88	<0.0001
GFR(η_1)	0.0198	0.0048	17.1522	<0.0001	19.29	<0.0001
Shape(ρ)	0.4392	0.0627	-	-	-	-

4.4.1.3 Standard Weibull model

The Weibull model with time-dependent covariates was fitted using Proc Nlp in SAS based on the described codes in Appendix B. In Table 4.25, the results of parameter estimates and tests of the model are presented. It was found that the p-value of GFR is 0.0335 which means that the time-dependent GFR is significant at the 5% significance level in the AFT

Weibull model. The acceleration factor of GFR is 0.989 which means that decrease the GFR level by one unit accelerates the survival times by a factor of about 1.01.

Table 4.25: Standard Weibull model estimates and tests including GFR as a time-dependent continuous covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept(β_0)	-10.1907	2.3453	-	-	-	-
DAGE(β_1)	-0.0218	0.0076	8.2244	0.0041	8.2344	0.0041
DCMV1(β_2)	-1.6454	1.1162	2.1731	0.1405	2.7875	0.0950
DCMV2(β_3)	-2.1128	1.1179	3.5719	0.0588	4.9250	0.0265
PCD1(β_4)	-0.4237	0.2340	3.2799	0.0702	3.3287	0.0681
PCD2(β_5)	-0.0154	0.3097	0.0025	0.9601	0.0027	0.9586
PCD3(β_6)	0.4080	0.2759	2.1864	0.1393	2.1974	0.1382
CYCLO(β_7)	10.5081	1.3506	60.5324	<0.0001	33.5722	<0.0001
FK506(β_8)	10.9715	1.7377	39.8659	<0.0001	31.1229	<0.0001
OTHER(β_9)	0.1032	0.0434	5.6542	0.0174	10.8868	0.0010
INTER1(β_{10})	-4.9304	1.2233	16.2436	0.0001	11.5453	0.0007
GFR(η_1)	0.0105	0.0050	4.3630	0.0367	4.5195	0.0335
Shape(ρ)	0.4532	0.0880	-	-	-	-

4.4.1.4 Weibull spline model

The different Weibull spline models with GFR that was treated as a continuous time-dependent were fitted. In Appendix B, the codes of using Proc Nlp in SAS are introduced with the method of setting the starting values to apply these codes. As described in the spline model of the fixed GFR, it was investigated if changing the knot positions to early times, less than 150 days, improves the model but the results suggested that same positions as previously applied are sufficient. Consequently, the same knot positions, as described in Table 4.12, were used to fit the six models with 0, 1, 2, 3, 4 an 5 knots based on the values of t_1 following the counting process style of the data input (see Table 3.2). The AIC values for the six models in Table 4.26 show that the best choice is the 4 knots model. It can be noticed that the AIC value of the 0 knots model is different from that obtained in the fixed model as a result of the method of computing the hazard and the cumulative hazard functions that form the likelihood function. In the time-dependent case, the hazard function is calculated based on the last updated value for the time-dependent covariate GFR while in the fixed case, the baseline value at transplantation day is used. Also, the cumulative hazard function is calculated using the updated GFR values form transplantation to death or being censored, so that contribution of the hazard and the cumulative hazard in the likelihood function changes when GFR is treated as a time-dependent covariate.

Table 4.27 presents the results of fitting the Weibull spline model with 4 knots. It can be noticed from the table that parameter estimates are similar to those obtained in the standard Weibull model. The MLE estimates and their standard errors are shown in Table 4.28. For GFR covariate, it can be seen that the MLE changed from 0.0089 in the 0 knots model to 0.0276 in the 4 knots model. Also, the shape of the model changed from 0.4626 in the 0 knots model to 0.3812 in the 4 knots model.

Table 4.29 presents the sv-values of parameter estimates for the Weibull spline models from 0 to 5 knots when GFR was treated as a continuous time-dependent covariate. Even

Table 4.26: The AIC values for the six estimated spline models with GFR as a continuous time-dependent covariate

Number of knots	AIC
0 knots	11080.74
1 knot	10830.15
2 knots	10692.88
3 knots	10599.98
4 knots	10577.16
5 knots	10614.92

Table 4.27: Weibull spline (4 knots) model estimates and tests including GFR as a time-dependent continuous covariate

Covariate	MLE	SE	Wald	
			χ^2	P
Intercept(β_0)	-13.7495	2.9480	-	-
DAGE(β_1)	-0.0278	0.0090	9.5412	0.0020
DCMV1(β_2)	-2.1005	1.3460	2.4353	0.1186
DCMV2(β_3)	-2.5940	1.3480	3.7031	0.0543
PCD1(β_4)	-0.4687	0.2630	3.1760	0.0747
PCD2(β_5)	0.0267	0.3980	0.0045	0.9465
PCD3(β_6)	0.5790	0.3190	3.2944	0.0695
CYCLO(β_7)	10.9052	1.7540	38.6552	<0.0001
FK506(β_8)	11.8761	2.1990	29.1674	<0.0001
OTHER(β_9)	1.0025	0.2990	11.2416	0.0008
INTER1(β_{10})	-4.8383	1.5980	9.1671	0.0025
GFR(η_1)	0.0276	0.0060	21.1600	<0.0001
First knot (γ_1)	-0.0014	0.0051	0.0754	0.7874
Second knot (γ_2)	0.0254	0.0208	1.4912	0.2231
Third knot (γ_3)	1.2565	0.1718	53.4907	<0.0001
Fourth knot (γ_4)	-2.6164	0.3041	74.0245	<0.0001
Shape(ρ)	0.3754	0.1548	-	-

though sv-values are similar across the six models, the models with 1 and 4 knots have the lowest sv-values comparing to those obtained by the 2, 3 and 5 knots model.

4.4.2 Time-dependent covariates model using GFR as a categorical covariate

In this section, the results of applying the suggested models are presented when GFR is treated as a categorical time-dependent based on the previous GFR categorization.

4.4.2.1 Cox regression model

After preparing GFR groups within the data with the counting process style of the data input, the Cox model was fitted using Proc Phreg in SAS. Table 4.30 shows the MLE estimates and tests. The time-dependent GFR covariates, $GFR1$, $GFR2$ and $GFR3$, it was found that the three covariates are significant with p-values 0.0399, <0.0001 and <0.0001 respectively.

Table 4.28: MLE estimates and standard errors for the Weibull spline models from 0 to 5 knots including GFR as a time-dependent continuous covariate

Covariate	0 Knots		1 Knot		2 Knots		3 Knots		4 Knots		5 Knots	
	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE
Intercept(β_0)	-10.191	2.344	-9.598	2.200	-13.546	2.941	-13.335	2.860	-13.750	2.952	-13.528	2.906
DAGE(β_1)	-0.022	0.007	-0.024	0.006	-0.028	0.008	-0.027	0.008	-0.028	0.008	-0.027	0.008
DCMV1(β_2)	-1.645	1.117	-1.813	1.002	-2.169	1.343	-2.059	1.305	-2.101	1.347	-2.096	1.325
DCMV2(β_3)	-2.113	1.119	-2.219	1.004	-2.663	1.346	-2.540	1.307	-2.594	1.349	-2.584	1.328
PCD1(β_4)	-0.424	0.234	-0.405	0.196	-0.477	0.263	-0.457	0.256	-0.469	0.264	-0.465	0.260
PCD2(β_5)	-0.015	0.311	-0.015	0.295	0.020	0.396	0.023	0.385	0.027	0.397	0.023	0.391
PCD3(β_6)	0.408	0.276	0.414	0.238	0.575	0.319	0.558	0.310	0.579	0.320	0.566	0.315
CYCLO(β_7)	10.508	1.351	9.475	1.301	10.949	1.750	10.655	1.700	10.905	1.755	10.809	1.727
FK506(β_8)	10.972	1.740	10.165	1.632	11.907	2.194	11.594	2.132	11.876	2.203	11.762	2.165
OTHER(β_9)	0.103	0.044	0.596	0.226	1.045	0.298	0.977	0.289	1.003	0.299	0.998	0.294
INTER1(β_{10})	-4.930	1.223	-3.796	1.188	-4.847	1.596	-4.727	1.550	-4.838	1.600	-4.792	1.575
GFR(η_1)	0.010	0.004	0.008	0.004	0.026	0.005	0.027	0.005	0.028	0.005	0.027	0.005
Shape(ρ)	0.453	0.088	0.505	0.094	0.376	0.142	0.387	0.149	0.375	0.155	0.381	0.152
First knot (γ_1)	-	-	-0.012	0.001	0.052	0.005	-0.010	0.005	-0.001	0.005	0.009	0.007
Second knot (γ_2)	-	-	-	-	-0.164	0.013	0.369	0.036	0.025	0.021	-0.050	0.020
Third knot (γ_3)	-	-	-	-	-	-	-0.881	0.077	1.256	0.172	0.514	0.064
Fourth knot (γ_4)	-	-	-	-	-	-	-	-	-2.616	0.304	-0.992	0.222
Fifth knot (γ_5)	-	-	-	-	-	-	-	-	-	-	0.281	0.313

Table 4.29: Standardized variability of parameter estimates for the Weibull spline models from 0 to 5 knots including GFR as a time-dependent continuous covariate

Covariate	0 Knots	1 Knot	2 Knots	3 Knots	4 Knots	5 Knots
Intercept(β_0)	0.230	0.229	0.217	0.215	0.215	0.215
DAGE(β_1)	0.301	0.248	0.285	0.287	0.286	0.292
DCMV1(β_2)	0.679	0.553	0.619	0.634	0.641	0.632
DCMV2(β_3)	0.530	0.452	0.505	0.515	0.520	0.514
PCD1(β_4)	0.552	0.484	0.552	0.560	0.563	0.559
PCD2(β_5)	20.733	19.670	19.814	16.740	14.716	17.003
PCD3(β_6)	0.676	0.574	0.555	0.556	0.553	0.556
CYCLO(β_7)	0.129	0.137	0.160	0.160	0.161	0.160
FK506(β_8)	0.159	0.161	0.184	0.184	0.185	0.184
OTHER(β_9)	0.429	0.379	0.285	0.296	0.298	0.295
INTER1(β_{10})	0.248	0.313	0.329	0.328	0.331	0.329
GFR(η_1)	0.442	0.495	0.205	0.191	0.190	0.194
Shape(ρ)	0.194	0.186	0.378	0.385	0.413	0.399

The relative hazard for the three covariates were 0.65, 0.48 and 0.57 respectively.

4.4.2.2 Log-logistic model

The log-logistic model with GFR as a categorical time-dependent was fitted using Proc NLP in SAS as the same method and codes of the continuous case. Table 4.31 presents the MLE estimates and tests. As in the Cox model results, there were no differences in the results of all the fixed covariates. On the other hand, the noticeable changes were in GFR covariates. The p-values of the covariates, $GFR1$, $GFR2$ and $GFR3$ were 0.2144, 0.0001 and <0.0001

Table 4.30: Cox model estimates and tests including GFR as a time-dependent categorical covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
DAGE(β_1)	0.0098	0.0036	7.4674	0.0063	7.4780	0.0062
DCMV1(β_2)	0.5930	0.5073	1.3663	0.2424	1.6580	0.1979
DCMV2(β_3)	0.8366	0.5082	2.7105	0.0997	3.5680	0.0589
PCD1(β_4)	0.1953	0.1098	3.1618	0.0754	3.2090	0.0732
PCD2(β_5)	0.0964	0.1591	0.3676	0.5443	0.3630	0.5468
PCD3(β_6)	-0.1391	0.1287	1.1682	0.2798	1.1720	0.2790
CYCLO(β_7)	-4.8137	0.6166	60.9402	<0.0001	33.9400	<0.0001
FK506(β_8)	-4.9582	0.7907	39.3187	<0.0001	30.8670	<0.0001
OTHER(β_9)	-0.0406	0.0193	4.4349	0.9035	7.7820	0.0053
INTER1(β_{10})	2.2807	0.5561	16.8231	<0.0001	11.8990	0.0006
GFR1(η_1)	-0.4182	0.2080	4.0414	0.0444	4.2220	0.0399
GFR2(η_2)	-0.7152	0.1476	23.4751	<0.0001	22.5610	<0.0001
GFR3(η_3)	-0.5571	0.1227	20.6139	<0.0001	18.6610	<0.0001

respectively.

Table 4.31: Log-logistic model estimates and tests including GFR as a time-dependent categorical covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept(β_0)	-16.8333	2.5418	-	-	-	-
DAGE(β_1)	-0.0222	0.0079	7.8163	0.0052	7.8285	0.0051
DCMV1(β_2)	-1.7573	1.2528	1.9674	0.1607	2.3660	0.1240
DCMV2(β_3)	-2.2807	1.2547	3.3042	0.0691	4.1903	0.0407
PCD1(β_4)	-0.4905	0.2402	4.1698	0.0412	4.2067	0.0403
PCD2(β_5)	-0.2184	0.3525	0.3837	0.5356	0.3809	0.5371
PCD3(β_6)	0.3085	0.2760	1.2500	0.2636	1.2569	0.2622
CYCLO(β_7)	13.1211	1.3511	94.3128	<0.0001	51.7267	<0.0001
FK506(β_8)	13.6967	1.7131	63.9273	<0.0001	47.9700	<0.0001
OTHER(β_9)	0.1504	0.0448	11.2618	0.0008	10.2725	0.0014
INTER1(β_{10})	-6.1563	1.1651	27.9204	<0.0001	19.2499	<0.0001
GFR1(η_1)	0.5765	0.4736	1.4822	0.2235	1.5415	0.2144
GFR2(η_2)	1.3415	0.3532	14.4284	0.0001	15.7173	0.0001
GFR3(η_3)	1.3171	0.3079	18.2999	<0.0001	19.0994	<0.0001
Shape(ρ)	0.5448	0.0721	-	-	-	-

4.4.2.3 Standard Weibull model

The standard Weibull model using the categorical time-dependent GFR was estimated using proc Nlp in SAS as in the continuous case. The results of the MLE and tests are presented in Table 4.32. As in the Cox and the log-logistic models, there were no essential differences in the results of the fixed covariates between this model and the fixed model. However, the p-values of $GFR1$, $GFR2$ and $GFR3$ decreased from 0.6087, 0.2246 and 0.5902 in the fixed model to 0.1518, <0.0001 and <0.0001 respectively in the time-dependent model.

Table 4.32: Standard Weibull model estimates and tests including GFR as a time-dependent categorical covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept(β_0)	-10.1939	2.3181	-	-	-	-
DAGE(β_1)	-0.0225	0.0059	14.6867	0.0030	8.8497	0.0029
DCMV1(β_2)	-1.7207	0.9210	3.4907	0.1236	3.0681	0.0798
DCMV2(β_3)	-2.2225	0.9717	5.2316	0.0472	5.4981	0.0190
PCD1(β_4)	-0.4782	0.2156	4.9176	0.0407	4.2590	0.0390
PCD2(β_5)	-0.1279	9.0439	0.0002	0.7088	0.1386	0.7097
PCD3(β_6)	0.3754	0.2282	2.7057	0.1732	1.8647	0.1721
CYCLO(β_7)	10.2328	1.4298	51.2165	<0.0001	32.4076	<0.0001
FK506(β_8)	10.7843	1.7461	38.1462	<0.0001	30.3785	<0.0001
OTHER(β_9)	0.0988	0.0339	8.5058	0.0260	9.3058	0.0023
INTER1(β_{10})	-4.7492	1.3359	12.6378	0.0001	10.8899	0.0010
GFR1(η_1)	0.6219	0.4692	1.7567	0.1584	2.0540	0.1518
GFR2(η_2)	1.4230	0.3419	17.3242	<0.0001	20.0632	<0.0001
GFR3(η_3)	0.6043	0.1412	18.3238	<0.0001	19.2450	<0.0001
Shape(ρ)	0.4541	0.0874	-	-	-	-

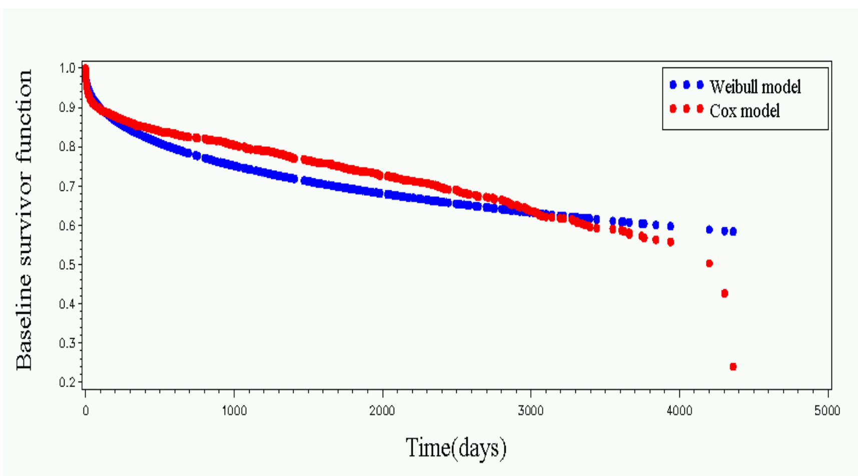

Figure 4.6: Estimated baseline survivor functions for the Cox and the standard Weibull models.

Figure 4.6 compares the baseline survivor functions for the Weibull and the Cox models. It can be seen that the baseline survivor function for the Weibull model is smoother than the survivor function of the Cox model.

4.4.2.4 Weibull spline model

The six Weibull spline models with 0, 1, 2, 3, 4 and 5 knots were fitted to the data that includes the categorical time-dependent GFR . The same knot positions that were assigned for the value of t_1, as in the continuous case in section 4.4.1. The AIC statistic gives the 4 knots model as the best choice as shown in Table 4.33.

Table 4.33: The AIC values for the six estimated spline models with GFR as a categorical time-dependent covariate

Number of knots	AIC
0 knots	11063.32
1 knot	10811.91
2 knots	10673.76
3 knots	10581.88
4 knots	10558.97
5 knots	10605.62

Table 4.34 presents the MLE and tests for the 4 knots model. For all the fixed covariates, there are slight decreases in the p-values in comparison to the other models in all the previous cases. Moreover, the p-values of $GFR1$, $GFR2$ and $GFR3$ were 0.0013, <0.0001 and <0.0001 respectively. The accelerator factors of the three covariates were 0.17, 0.09 and 0.19 respectively.

Table 4.34: Weibull spline (4 knots) model estimates and tests including GFR as a time-dependent categorical covariate

Covariate	MLE	SE	Wald	
			χ^2	P
Intercept(β_0)	-13.5765	2.9166	-	-
DAGE(β_1)	-0.0284	0.0087	10.6928	0.0011
DCMV1(β_2)	-2.163	1.3429	2.5943	0.1073
DCMV2(β_3)	-2.6834	1.3454	3.9778	0.0461
PCD1(β_4)	-0.5331	0.2619	4.1447	0.0418
PCD2(β_5)	0.032	0.3950	0.006	0.936
PCD3(β_6)	0.548	0.3172	2.984	0.084
CYCLO(β_7)	10.663	1.7466	37.273	<0.0001
FK506(β_8)	11.735	2.1882	28.759	<0.0001
OTHER(β_9)	1.106	0.2980	13.764	0.000
INTER1(β_{10})	-4.681	1.5903	8.665	0.003
GFR1(η_1)	1.740	0.5389	10.420	0.001
GFR2(η_2)	2.326	0.3657	40.470	<0.0001
GFR3(η_3)	1.629	0.3014	29.220	<0.0001
First knot (γ_1)	-0.001	0.005	0.035	0.852
Second knot (γ_2)	0.025	0.021	1.373	0.241
Third knot (γ_3)	1.259	0.172	53.446	<0.0001
Fourth knot (γ_4)	-2.620	0.305	73.942	<0.0001
Shape(ρ)	0.3775	0.1516	-	-

Figure 4.7 compares the log baseline survivor functions for the Weibull spline model (4 knots) with the standard Weibull model. It can be seen that the function of the spline model decreases swiftly than the standard model reflecting the difference in flexibility between the two models.

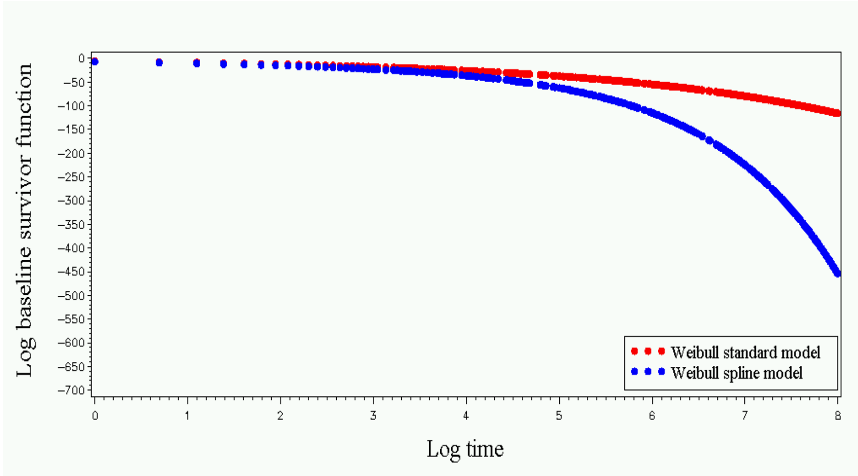

Figure 4.7: Estimated log baseline survivor functions for the standard Weibull and the Weibull spline (4 knots) models.

Table 4.35 contains the MLE and their standard errors for the six Weibull spline models. For $GFR1$, $GFR2$ and $GFR3$, it is noticed that the MLE are similar for the models from 1 to 5 knots, but those estimates are different from the estimates of the 0 knots (standard) model. The shape parameter changed from 0.4541 in the 0 knots model to 0.3775 in the 4 knots model.

Table 4.35: MLE estimates and standard errors for the Weibull spline models from 0 to 5 knots including GFR as a time-dependent categorical covariate

Covariate	0 Knots		1 Knot		2 Knots		3 Knots		4 Knots		5 Knots	
	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE
Intercept(β_0)	-10.194	2.317	-9.978	2.186	-13.421	2.910	-13.176	2.830	-13.577	2.913	-13.184	2.838
DAGE(β_1)	-0.023	0.007	-0.022	0.006	-0.028	0.008	-0.028	0.008	-0.028	0.008	-0.028	0.008
DCMV1(β_2)	-1.721	1.117	-1.722	1.006	-2.230	1.341	-2.118	1.303	-2.163	1.341	-2.130	1.307
DCMV2(β_3)	-2.223	1.121	-2.113	1.008	-2.749	1.344	-2.624	1.306	-2.683	1.344	-2.637	1.309
PCD1(β_4)	-0.478	0.233	-0.394	0.196	-0.540	0.262	-0.520	0.254	-0.533	0.262	-0.523	0.255
PCD2(β_5)	-0.128	0.344	0.029	0.295	0.031	0.394	0.026	0.383	0.032	0.394	0.025	0.384
PCD3(β_6)	0.375	0.275	0.414	0.238	0.546	0.317	0.528	0.308	0.548	0.317	0.528	0.309
CYCLO(β_7)	10.233	1.350	8.558	1.303	10.684	1.743	10.423	1.694	10.663	1.743	10.436	1.698
FK506(β_8)	10.784	1.736	9.346	1.634	11.746	2.183	11.459	2.123	11.735	2.185	11.473	2.129
OTHER(β_9)	0.099	0.044	0.860	0.224	1.145	0.299	1.076	0.290	1.106	0.299	1.083	0.291
INTER1(β_{10})	-4.749	1.222	-3.796	1.188	-4.675	1.587	-4.578	1.542	-4.681	1.587	-4.581	1.546
GFR1(η_1)	0.622	0.441	1.308	0.404	1.633	0.540	1.685	0.522	1.740	0.540	1.676	0.526
GFR2(η_2)	1.423	0.313	1.709	0.273	2.253	0.365	2.250	0.355	2.326	0.365	2.247	0.356
GFR3(η_3)	0.604	0.130	1.212	0.226	1.616	0.302	1.576	0.293	1.629	0.302	1.576	0.294
Shape(ρ)	0.454	0.087	0.505	0.094	0.378	0.139	0.389	0.146	0.378	0.152	0.388	0.146
First knot (γ_1)	-	-	-0.012	0.001	0.053	0.005	-0.010	0.005	-0.001	0.005	0.010	0.007
Second knot (γ_2)	-	-	-	-	-0.165	0.013	0.368	0.036	0.024	0.021	-0.051	0.020
Third knot (γ_3)	-	-	-	-	-	-	-0.880	0.077	1.259	0.172	0.515	0.064
Fourth knot (γ_4)	-	-	-	-	-	-	-	-	-2.620	0.305	-0.993	0.223
Fifth knot (γ_5)	-	-	-	-	-	-	-	-	-	-	0.281	0.314

Table 4.36 presents the sv-values of parameter estimates for the Weibull spline models from 0 to 5 knots when GFR was treated as a time-dependent categorical covariate. The 0

Table 4.36: Standardized variability of parameter estimates for the Weibull spline models from 0 to 5 knots including GFR as a time-dependent categorical covariate

Covariate	0 Knots	1 Knot	2 Knots	3 Knots	4 Knots	5 Knots
Intercept(β_0)	0.227	0.219	0.217	0.215	0.215	0.215
DAGE(β_1)	0.287	0.270	0.283	0.275	0.283	0.276
DCMV1(β_2)	0.649	0.584	0.601	0.615	0.620	0.613
DCMV2(β_3)	0.504	0.477	0.489	0.498	0.501	0.497
PCD1(β_4)	0.488	0.498	0.485	0.489	0.491	0.488
PCD2(β_5)	2.684	10.174	12.715	14.732	12.318	15.361
PCD3(β_6)	0.734	0.574	0.581	0.584	0.579	0.586
CYCLO(β_7)	0.132	0.152	0.163	0.163	0.163	0.163
FK506(β_8)	0.161	0.175	0.186	0.185	0.186	0.186
OTHER(β_9)	0.445	0.260	0.261	0.270	0.270	0.269
INTER1(β_{10})	0.257	0.313	0.340	0.337	0.339	0.338
GFR1(η_1)	0.708	0.309	0.330	0.310	0.310	0.314
GFR2(η_2)	0.220	0.160	0.162	0.158	0.157	0.158
GFR3(η_3)	0.215	0.186	0.187	0.186	0.185	0.186
Shape(ρ)	0.192	0.186	0.368	0.375	0.402	0.376

knots model has the lowest sv-values for parameter estimates of the PCD2, CYCLO, FK506 and the INTER1. As in the continuous time-dependent case, it is noticed that the models with 1 and 4 knots produce the lowest sv-values comparing to those produced by the models with 2, 3 and 5 knots.

4.5 Model evaluation

In this section a comparison of the standardized variability for the parameter of interest, GFR, in addition to the Cox-Snell and martingale residuals will be discussed. These comparisons are considered as methods to evaluate each model to obtain the most adequate model that fits the heart transplant data.

4.5.1 Model comparison

Table 4.37 contains the MLE with their sv-values for GFR covariate across the fixed and the time-dependent models. For the fixed continuous case, the sv-values for the log-logistic and the Weibull spline models are less than those obtained from the Cox and the Weibull standard Weibull models. For the fixed categorical case, the log-logistic model has the lowest sv-values for the three covaraites, $GFR1$, $GFR2$ and $GFR3$. According to these results, the log-logistic and the Weibull splines have more significance for the continuous GFR, while the log-logistic produces more efficient estimates of the categorical GFR parameters.

For the time-dependent continuous case, it was found that the sv-value of the Cox, log-logistic, and standard Weibull models were about 0.33, 0.24 and 0.44 but the Weibull spline model has the lowest sv-value (0.19) for that parameter estimate. For the time-dependent categorical case, the sv-values for the $GFR1$, $GFR2$ and $GFR3$ in the Weibull spline model are obviously lower those produced in the Cox , standard Weibull and the log-logistic models. Regarding to GFR continuous and categorical covariate, these results show that the Weibull spline model has the more efficient parameter estimates comparing to the other three competitive models. These results will be examined with residual analysis in the next section and with simulations in chapter seven.

Table 4.37: Standardized variability (sv-values) for the fixed and time-dependent GFR covariates across the four models

Models		Cox		Log-logistic		Weibull		Spline	
		MLE	sv	MLE	sv	MLE	sv	MLE	sv
Fixed	GFR	-0.005	**0.500**	0.558	**0.122**	0.010	**0.431**	0.008	**0.409**
	GFR1	-0.137	**1.675**	1.066	**0.495**	0.255	**1.944**	0.196	**1.927**
	GFR2	-0.278	**0.688**	1.123	**0.400**	0.517	**0.8**	0.424	**0.744**
	GFR3	-0.127	**1.493**	0.896	**0.499**	0.223	**1.836**	-0.181	**1.718**
Time-dependent	GFR	-0.007	**0.333**	0.020	**0.242**	0.009	**0.442**	0.028	**0.19**
	GFR1	-0.418	**0.497**	0.577	**0.822**	0.622	**0.708**	1.740	**0.31**
	GFR2	-0.715	**0.206**	1.342	**0.263**	1.423	**0.22**	2.326	**0.157**
	GFR3	-0.557	**0.220**	1.317	**0.234**	0.604	**0.215**	1.629	**0.185**

4.5.2 Residuals analysis

Two types of residuals were used in model checking.

1. Cox-Snell residuals: This residual is

$$r_{Ci} = \hat{H}_i(t_i),$$

where $\hat{H}_i(t_i)$ is the estimated cumulative hazard function for the ith individual. When the cumulative hazard function of the residuals is plotted against the residuals, a straight line with zero intercept and unity slope indicates that the model fits the data well and then departures from the straight line imply lack of fit. To apply these residuals for observations with multiple records in time-dependent data, the residuals were computed at the last interval for each observation.

2. Martingale residuals: These residuals are computed from the Cox-Snell residuals as

$$r_{Mi} = \delta_i - r_{Ci},$$

where δ_i is the censoring indicator function for the ith observation and r_{Ci} is the Cox-Snell residual. To evaluate the model adequacy, these residuals are plotted against the observations or the survival times and then studying the behavior of these residuals helps to assess satisfaction of the fitted model. For the time-dependent covariates, when each observation has multiple records, the martingale residuals were computed for each record and then were summed for each observation (Therneau and Gambsch, 2000).

4.5.2.1 Fixed covariates residuals

Figure 4.8 shows the plotted cumulative hazard for the Cox-Snell residuals for the four models with the fixed continuous GFR. The plot of the Cox model gives straight line with zero intercept and approximately unity slope while the plot of the Weibull spline model gives some deviations from the straight line affecting the straight line properties. The residual plots of the log-logistic and standard Weibull models are not straight line with unity slope.

Figure 4.9 shows the plotted martingale residuals against the survival times for the different models. The martingale residuals plots are similar for the four models. The plots show some large negative martingale values for the low survival times of patients with age above 45 years and relatively low GFR level.

Figure 4.10 shows the plotted cumulative hazards for the Cox-Snell residuals for the models with GFR as a categorical fixed covariate. As in the previous case, the plots of the Cox and the Weibull spline models. In contrary, many deviations can be noticed in the plots of the log-logistic and the Weibull standard models which refer to less adequacy comparing to other two models.

In Figure 4.11, the martingale residuals are plotted with survival times for the same fixed categorical GFR models. The residuals plots are very similar for the different models appearing some large negative martingale values with the survival times less than 1000 days.

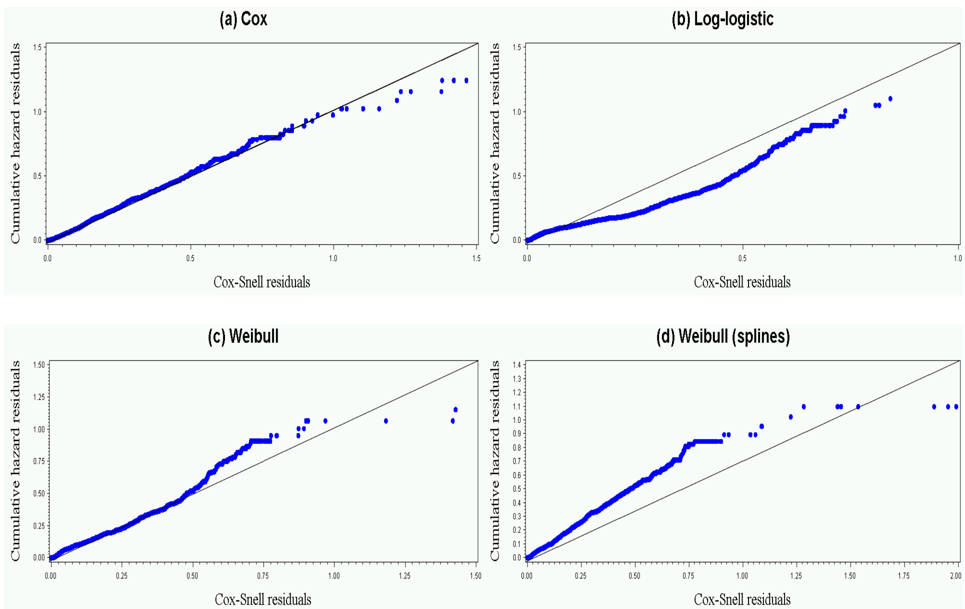

Figure 4.8: Cox-Snell residuals for the models with fixed continuous GFR.

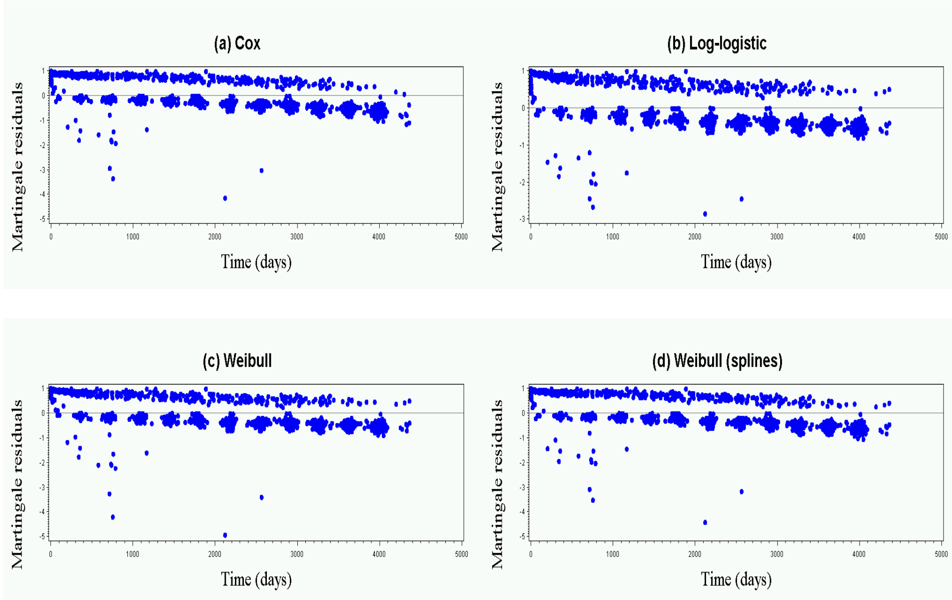

Figure 4.9: Martingale residuals for the models with fixed continuous GFR.

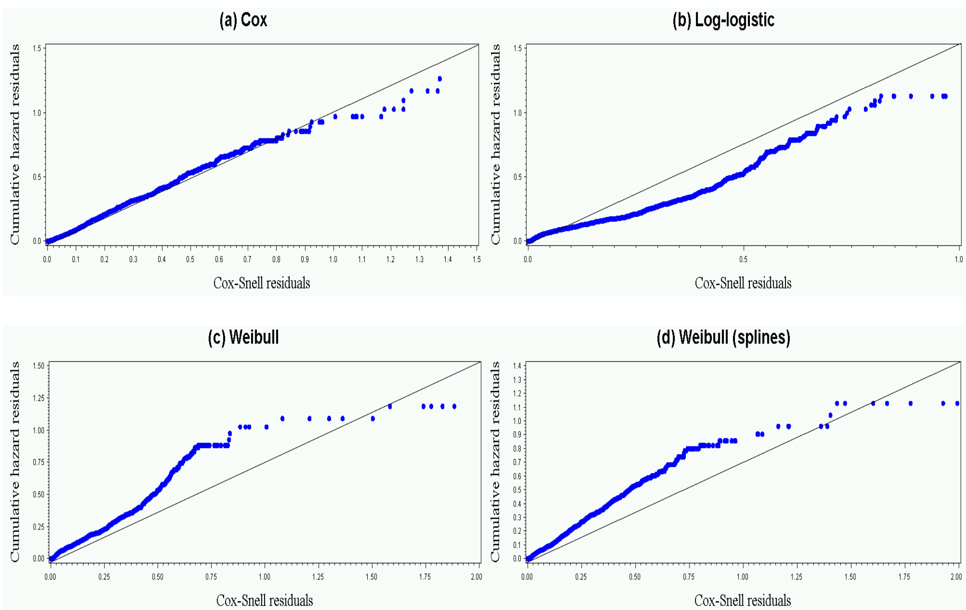

Figure 4.10: Cox-Snell residuals for the models with fixed categorical GFR.

4.5.2.2 Time-dependent covariate residuals

Figure 4.12 presents the plotted cumulative hazard for the Cox-Snell residuals for the models with GFR as a continuous time-dependent. The plot of the Cox model gives straight line with zero intercept and approximately unity slope. The Weibull spline model residuals plot shows some deviations from the straight line. The plots of the log-logistic and the Weibull standard models do not give straight line that indicate to poor fit comparing to the other models.

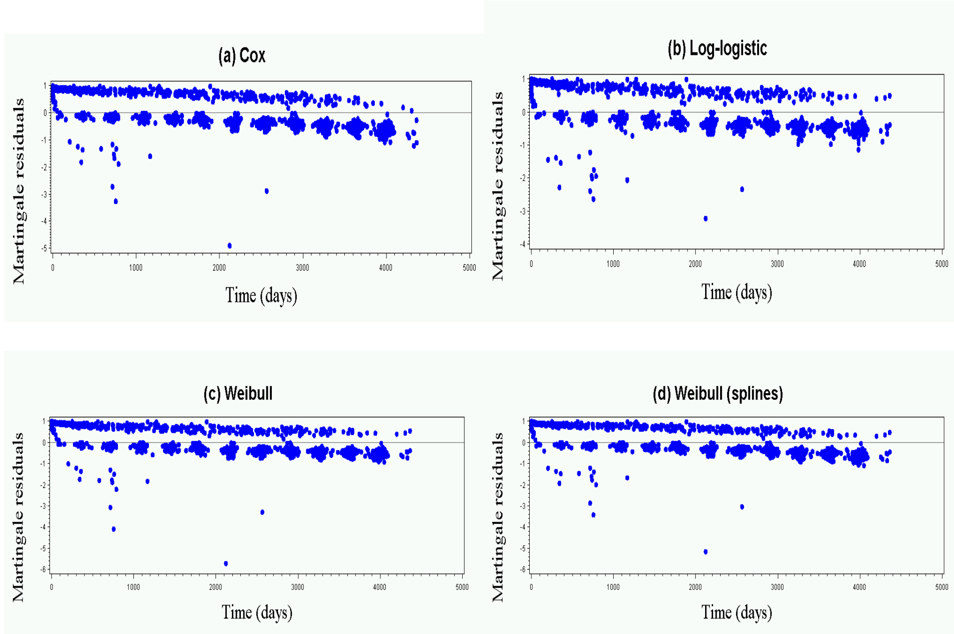

Figure 4.11: Martingale residuals for the models with fixed categorical GFR.

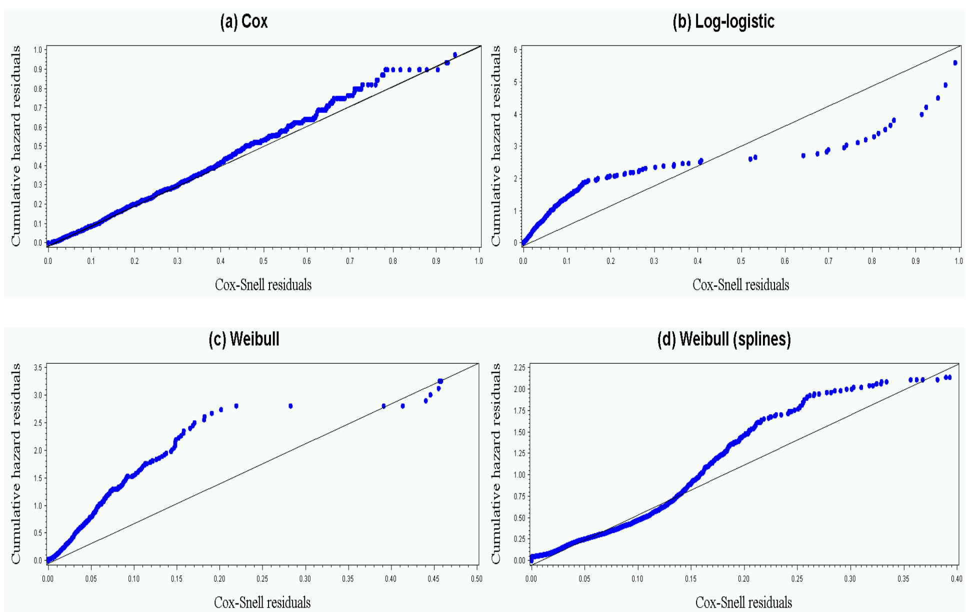

Figure 4.12: Cox-Snell residuals for the models with time-dependent continuous GFR.

Figure 4.13 presents the martingale residuals for the continuous time-dependent GFR models. As the previous cases, there are some large negative martingale values in the times less than 1000 days. Also, it can be noticed many large negative martingale values for the times after the first 1000 days in the standard Weibull model. This plot suggests that the standard Weibull model may not adequately fit the data in comparison to the other three models.

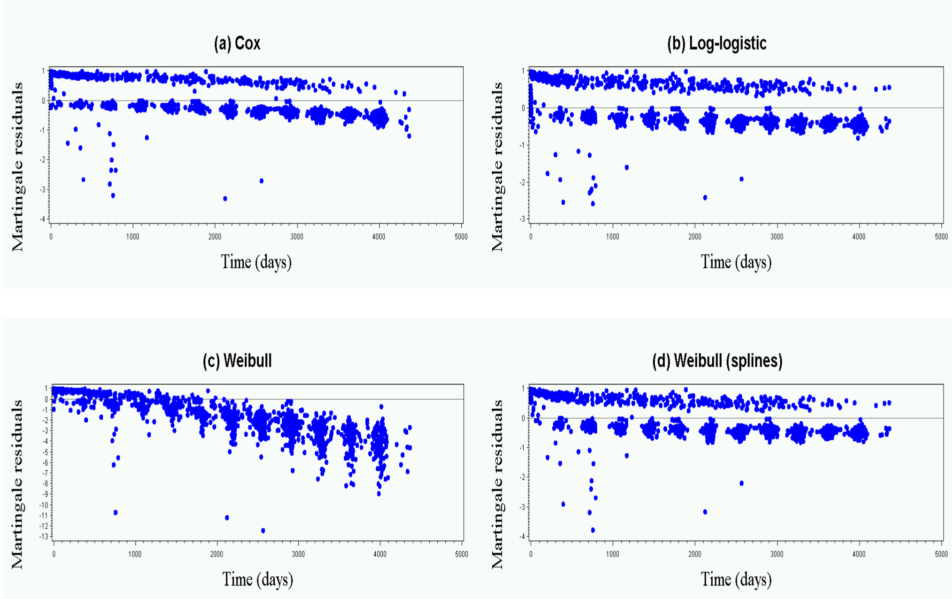

Figure 4.13: Martingale residuals for the models with time-dependent continuous GFR.

Figure 4.14 gives the cumulative hazard plots for the Cox-Snell residuals for the models with categorical time-dependent GFR. The straight line of the Cox model has zero intercept and slop very close to one. However, the plots of the other three models have many deviations affecting the adequacy of these models. Also, it can be noticed that the deviations from the straight line in the Weibull spline plot are less than those found in the log-logistic and the Weibull standard plots.

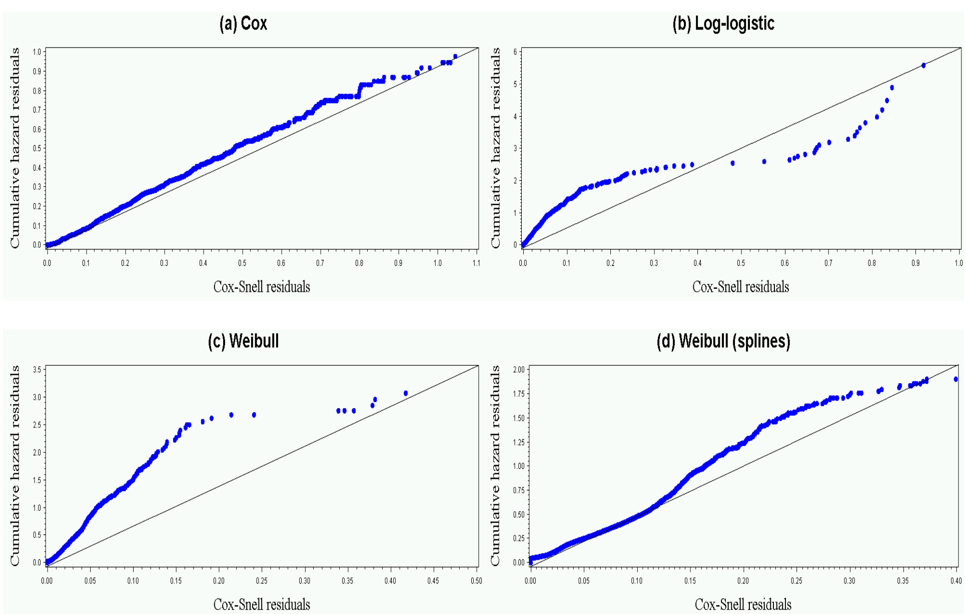

Figure 4.14: Cox-Snell residuals for the models with time-dependent categorical GFR.

In Figure 4.15, the martingale residuals for the models with the categorical time-dependent GFR. For all the models, there some large negative martingales for the low survival times, but there many large negative martingales for the times after 2000 days in the standard Weibull model.

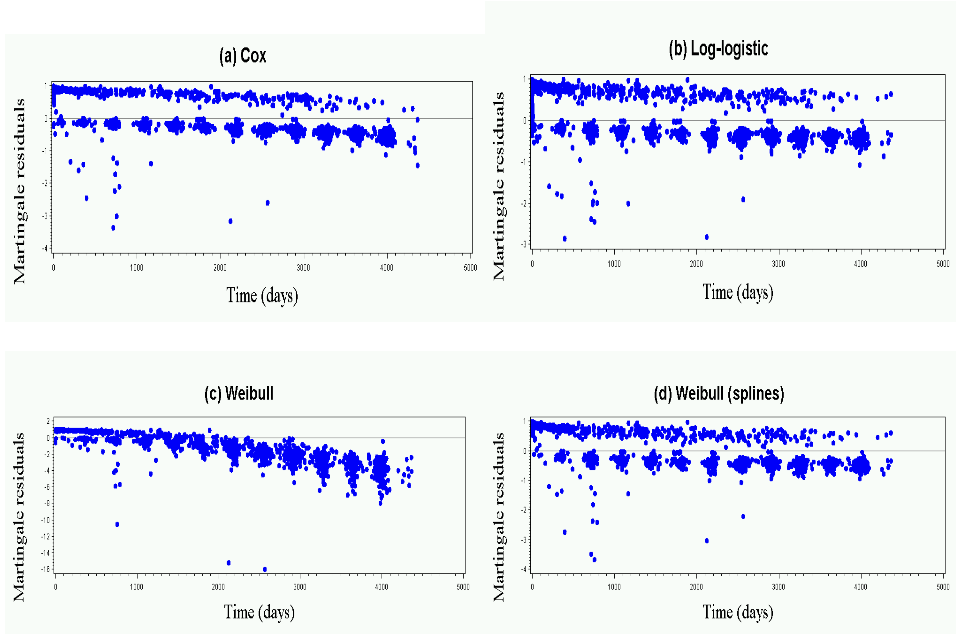

Figure 4.15: Martingale residuals for the models with time-dependent categorical GFR.

4.6 Concluding remarks

The aim of this chapter was to develop an adequate model to fit the heart transplant data. In model building procedures, based on data on hand, it has been found that DAGE, DCMV, PCD and immunosuppressant covariates: CYCLO, FK506 and OTHER are significant. The GFR, as a measure of the kidney functions status, has been transformed to glomerular filtration rate GFR using (4.1). This covariate was treated in the models as a continuous and categorical where baseline values (fixed) and follow-up values (time-dependent) were used.

The levels of the covariates: DCMV and PCD were not significant at the 5% significance level in the fitted models. However, these covariates were retained in the models for two reasons:

- The criteria to retain any categorical covariate is the likelihood ratio test with degree of freedom equals to the number of categories-1. Consequently, the two covariates were significant at the 5% significance level according to the likelihood ratio test.

- In the time-dependent modelling, the effect of treatment difference may be masked when the time-dependent covariate accounts for the levels of that treatment (Collett, 2003), so that the effect of some categories of the $DCMV$ and the PCD may be disappeared when GFR was treated as a time-dependent covariate.

Consequently, these covariates must be retained in the model to study all the factors that possibly affect survival time after heart transplantation.

The first stage to fit the data was executed by applying the competitive models using GFR as a fixed continuous and categorical covariate. For the fixed continuous case, there was no significant difference among the models based on the likelihood ratio tests for the fixed covariates. However, in the categorical case, GFR covariates were not significant at 5% significance level in the Cox, standard Weibull and Weibull spline models. It was found that the effect of GFR covariates are highly significant in the log-logistic model.

Based on the residual analysis, the Cox-Snell residuals plot suggests that the Cox model fits data better than the other three models. For the martingale residuals, it was shown some large negative martingale values with low survival times explaining the high hazards within the first six months after the surgery. In conclusion, for the fixed GFR case, both of residuals types refer to the Cox model as the most suitable model to fit such data and the Weibull spline model that is more adequate than the log-logistic and the Weibull standard models.

Secondly, the alternative four models were fitted using GFR as a continuous and a categorical time-dependent covariate. For the continuous case, GFR was significant in all the models except the log-logistic model. For the categorical case, $GFR2$ and $GFR3$ were significant in all the models. However, $GFR1$ was significant only in the Weibull spline model at the 5% significance level. Based on the sv-values of GFR, the four models have lower values in the continuous case comparing to the categorical case. On the other hand, parameter estimates of the categorical time-dependent covariates GFR2 and GFR3 have lower sv-values than those obtained in the continuous case. The results of the sv-values suggest that the Weibull spline model tends to have more efficient parameter estimates for the continuous and the time-dependent GFR in the fixed and the time-dependent case.

In the residual analysis, the Cox-Snell residual plots showed that the Cox and the Weibull spline models fit the data better than the log-logistic and the standard Weibull models. The martingale residuals were similar for the different models, the plot of the standard Weibull model suggest that the model does not fit the model well particularly with the high survival times.

In conclusion, the results of continuous and categorical GFR in the fixed case show that the log-logistic model has the lowest sv-values while the Weibull spline model has the lowest sv-values in the time-dependent case. On the other hand, the residual analysis suggests that the Cox model is more adequate to fit the heart data than the log-logistic, standard Weibull and the Weibull spline models. Also, the Weibull spline model fits slightly better than the log-logistic and the standard Weibull models. These results will be examined by simulation study with more details in chapter seven in order to assess the relative efficiency of each models to fit such data.

Chapter 5

Cornea transplant survival model

The cornea is the transparent front part of the eye that reflects, with the lens, the light, producing about 65% of the eye's total optical power (Goldstein, 2007). The need for cornea transplant arises for different reasons such as dystrophy, Ectasia and infections. The cornea is damaged when corneal dystrophy occurs and then vision deteriorates. This dystrophy causes a pain which may not be treated by the usual medications. In this case, a corneal transplant becomes an urgent procedure. A corneal transplant is a technique for eradicating a damaged cornea and grafting a healthy donated one, from a suitable donor. This donated cornea is taken after checking the donor's eye in order to verify there is no infection in the new cornea. In the UK, 3,061 patients had corneal transplants during 2010. However, the number of the donated corneas was 4,115 in the same year. Table 5.1 shows the number of grafted corneas and the number of donated corneas from 1999 to 2008.

Table 5.1: The number of grafted and donated corneas in the UK from 2001 to 2010 (NHS Blood and Transplant, 2010).

Year	***Number of grafted corneas***
2001	2320
2002	2060
2003	2301
2004	2364
2005	2377
2006	2505
2007	2407
2008	2491
2009	2734
2010	3061

Table 5.2 shows the graft survivor estimates with confidence intervals for one, two and five years from 1 January 2001 to 31 December 2010 (NHS Blood and Transplant, 2010).

Figure 5.1 shows the survivor function of first eye graft from 1994 to 2001 (NHS Blood and Transplant, 2008).

5.1 Cornea transplant data

In corneal transplantation, the hazard of graft failure is low, especially within the first 10 years after the operation. On the other hand, the risk of failure may increase, particularly

Table 5.2: Cornea graft survival in the UK, 1 January 2001 - 31 December 2010

Year	No. at risk on day 0	% Graft survival (95% confidence interval) One year	Two year	Five year
1999-2001	3343	93 (92-94)	87 (86-88)	77 (75-78)
2002-2004	3667	93 (92-94)	86 (85-87)	74 (72-75)
2005-2008	3757	93 (92-94)		

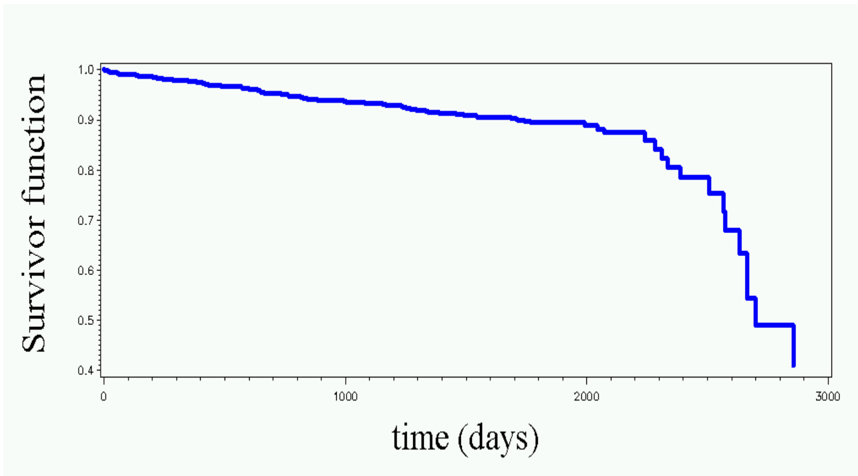

Figure 5.1: Survivor function of first eye graft from 1994 to 2001

in the case of receiving a graft in each eye. Many studies based on the Cox regression model have been done to estimate the survivor function after corneal transplantation and the factors that may affect the survival times (Inoue *et al.*, 2001). The aim of this study is to use all the factors that were used by most of the previous cornea transplant survival studies and the presence of a second eye graft as a binary time-dependent covariate. The analysis is based on NHS Blood and Transplant data for 1571 patients who received corneal transplantation in their first eye between 1 January 1994 and 6 December 2001. Of those, 257 patients had a failure in their first eye graft before receiving the second eye graft. The covariates that may affect the survival time for the grafted cornea were grouped to four categories which are related to recipient, donor, donated organ and the time-dependent covariate.

5.1.1 Recipient variables

The recipient factors that might be related to the cornea survival times are age, sex and sex matching with the donor. There are 11 reasons for needing a cornea graft such as: corneal infection, opacification and corneal dystrophies. These reasons were grouped into 3 categories. Table 5.3 describes the recipient variables.

*See CAUSE codes in the appendix (A2).

5.1.2 Donor variables

In cornea transplant analysis, donor age and sex may be important covariates. Also, the covariate SOLID refers to whether the donor is an ocular donor (corneal donor only) or is a multi-organ donor. Table 5.4 shows the description of the cornea donor variables.

Table 5.3: Description for recipient variables

Variable	***Description***
RSEX	Recipient sex (1=Male, 2=Female)
RMATCH	Donor sex- Recipient sex
RAGE	Recipient age (years)
CAUSE	Cause for transplantation (diagnosis) (groups=1 for diagnosis 1, group=2 for diagnosis 2 and group=3 for diagnoses from 3 to 11)*

Table 5.4: Description of donor variables

Variable	***Description***
DSEX	Donor sex (1=Male, 2=Female)
DAGE	Donor age at donation (years)
SOLID	Donor donation (1=ocular donor only, 2=multi-organ donor)

5.1.3 Description for the donated cornea variables

The properties of the donated cornea may affect the survival times. Firstly, the endothelial cell density, the greater density refers to better quality. Secondly, the time from the death to the removal of the donated cornea. Thirdly, the storage time of the donated cornea. Fourthly, the eye bank, Bristol and Manchester, from which the cornea comes from. Finally, the storage temperature of the donated cornea, and the time between the death and the removal of the eye from the body.

Table 5.5: Description for the donated cornea variables

Variable	***Description***
DE.HRS	The time from death to the removal of the donated cornea (hours)
ENDO.ASS	The quality of the donated cornea (1=excellent, 2=very good, 3=good, 4=poor)
CELSS.MM	The endothelial cell density for the donated cornea (cells)
BANK	Eye banks of Bristol and Manchester (1=the donated cornea from Bristol bank, 2=the donated cornea from Manchester bank)
STORAGE	The storage period of the donated cornea (days)
ST4.34	The storage temperature for the donated cornea (1=4°C, 2=34°C)

5.1.4 The time-dependent covariate

In some circumstances, having had an initial graft in one eye, a patient may subsequently also require a graft in the other eye (a ”second graft”). One possibility is that having the second operation puts pressure on the patient’s system and so reduces the survival time of the first graft. Another possibility is that the presence of the second graft removes stress on the first graft and hence the first graft survival is increased. Hence, the effect of the second eye graft might be important to study the survivor function of the first eye graft. In this study, the second eye graft (SECOND) is studied as a time-dependent covariate with at most one change. This covariate takes the value 0 when the recipient has not had the operation in his second eye, and 1 when the second eye operation has been done.

Figure 5.2 shows the Kaplan-Meier survival curves of the two groups: those that had a second graft during the observation period and those who did not have a second graft during

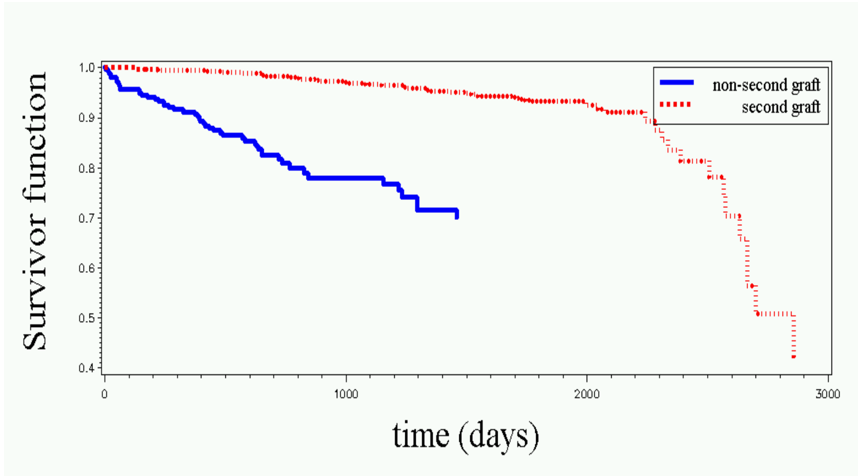

Figure 5.2: Survival curves based on Kaplan-Meier estimates for non-second graft and second graft cornea.

the same period. The survivor of the group with second graft is higher than the survivor of the other group for the data of survival times that are less than about 1600 days.

5.2 Model building

In cornea transplant data, the most appropriate model can be built by determining the lowest number of the explanatory variables that are related to the first eye graft hazard function. As described in section 5.1, the data set includes 13 fixed explanatory variables, and the second eye graft as a time-dependent covariate.

Following the strategy described in section 4.2.1, all the 13 covariates were tested at the 10% significance level using single variable Weibull model. The comparison of each model with the null model determines whether the covariate must be retained in the model. This step was applied through the Weibull model for the 13 fixed explanatory variables. The results are shown in Table 5.6.

Table 5.6: Results of the significant variables for the Weibull model at 10% based on one variable model

Model	Change in -2log$\hat{L}$	*df*	P
RAGE	28.36	1	<0.0001
CAUSE	75.14	2	<0.0001
DAGE	12.11	1	0.0005
SOLID	2.98	1	0.0843
STORAGE	4.56	1	<0.0327

The five significant covariates at the 10% significance level were involved in one model, and then all the covariates were omitted in turn. The covariate that did not increase the $-2\log\hat{L}$ at 5% was discarded from the model. Furthermore, after discarding any covariate, all the other retained covariates were examined in the absence of the discarded covariate. This means that the final model contains the significant covariates with $p \leq 0.05$ not only in the presence of the other covariates, but also in the absence of them. For illustration, the covariate RAGE was dropped from the five covariates model, and it significantly increased the $-2\log\hat{L}$ with ($p \leq 0.0001$). This step was followed by dropping RAGE in the absence of the other four covariates, and it increased the value of $-2\log\hat{L}$ with ($p = 0.027$). Hence, RAGE was retained in the model. The covariates that are significant from this step are RAGE, CAUSE and STORAGE.

In the third step, the three discarded covariates STORAGE, DAGE and SOLID were added to the model that contains RAGE and CAUSE, one at a time. This procedure is performed to check their significance in the presence of the two significant covariates only as a final check. There were no new results from this procedure, so that the model must contain the RAGE and CAUSE only. Table 5.7 summaries the values of $-2\log\hat{L}$ statistic for the 2 variables model and their significance.

Table 5.7: Results of the significant variables in the 2 variables Weibull model

Model	Change in -2log$\hat{L}$	*df*	$P-value$
RAGE	6.16	1	0.0131
CAUSE	14.7	2	0.0021

In this model, RAGE was modelled as a continuous covariate, so that a test of linearity might be necessary. This procedure was performed by adding RAGE as a categorical variable with 4 levels to the model that contains CAUSE, and comparing the result when the model includes CAUSE and RAGE as a qualitative (with values 1, 2, 3 and 4). The change in the value of $-2\log\hat{L}$ for the two models with the two forms of RAGE was 1.23 on 2 df ($p = 0.55$). Hence the effect of RAGE should be modelled with a linear term. Finally, the interaction between the covariates RAGE and CAUSE was examined. The change in $-2\log\hat{L}$ when the interaction between RAGE and the levels of CAUSE was 4.12 on 2 df ($p = 0.1275$). Consequently, there is no interaction term between the two covariates and then the model includes the two fixed covariates RAGE and CAUSE in addition to the time-dependent covariate second eye graft (SECOND). In order to add the SECOND as a time-dependent covariate, a counting process input style has been used with two records for patients who have done a second graft. The original survival time was divided to two intervals according to the time of second eye graft. The time in the first interval starts from 0 to the time of the second eye graft, and the second interval starts from the time of the second eye graft to the original survival time (see Table 3.2 for more details).

5.3 Time-dependent covariates models

The SECOND covariate was treated as a binary time-dependent covariate, and then the four models were applied to the data in this case. In this section, the results of fitting the four models are presented to investigate the performance of each model to present such data when it is allowed for SECOND values to change over time.

5.3.1 Cox model

The Cox model was fitted to the data that includes SECOND as a time-dependent covariate. Table 5.8 presents the results of MLE and tests for the four covariates. All the covariates are significant at the 5% significance level. Also, it is noticed that the relative hazard of the SECOND is 1.667 which means that the second eye graft increases the first graft failure by 0.667 where the other covariates are held fixed. The effect of second graft on the hazard of the first graft failure was positive when the time-dependent values of the SECOND were used.

Table 5.8: Cox model estimates and tests including $SECOND$ as a time-dependent covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
RAGE(β_1)	0.0115	0.0060	3.6479	0.0561	3.8950	0.0484
CAUSE1(β_2)	-1.3148	0.3288	15.9935	0.0001	17.3590	<0.0001
CAUSE2(β_3)	-1.1961	0.2324	26.4812	<0.0001	30.5490	<0.0001
SECOND(β_4)	0.5109	0.2513	4.1323	0.0421	4.2320	0.0397

Figure 5.3 shows the estimated survival function for patient with non-second graft against who has done a second graft in the time-dependent Cox model when the average values of the other fixed covariates were used. It can be seen that the patient with second graft has a lower survivor function. This means that the second graft as a time-dependent covariate may increase the hazard of failure for the first eye graft.

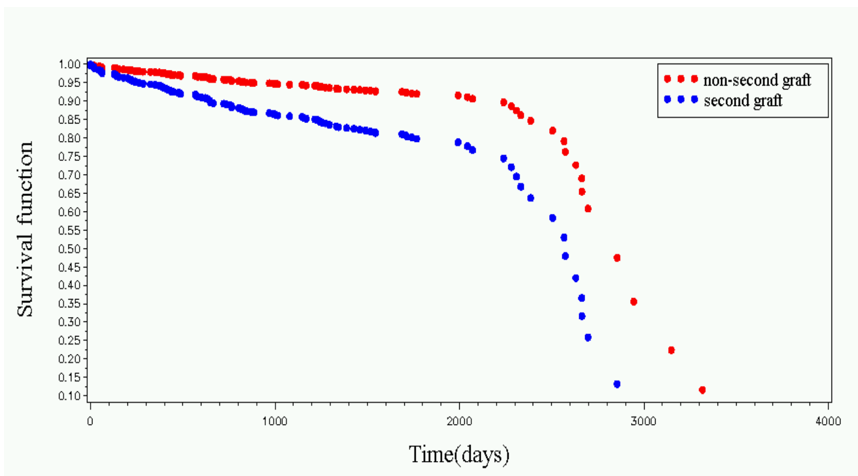

Figure 5.3: Estimated survival function for patients with non-second and second graft in the Cox model based on the average values of the other fixed covariates.

5.3.2 Log-logistic model

The log-logistic AFT model with time-dependent SECOND, as described in section 3.3.2 was fitted using Proc Nlp in SAS. The results in table 5.9 show that the RAGE is not significant at the 5% level. Also, as in the time-dependent Cox model, the effect of SECOND on hazard of failure for the first eye graft increased using the changing values of SECOND from 0 before the second operation to 1 after that.

5.3.3 Standard Weibull model

The standard Weibull AFT model with the SECOND as time-dependent covariate, as described in section 3.3.1, was applied using Proc Nlp in SAS. The results are similar to the

Table 5.9: Log-logistic model estimates and tests including $SECOND$ as a time-dependent covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept(β_0)	9.9241	0.6034	-	-	-	-
RAGE(β_1)	-0.0099	0.0068	2.1020	0.1472	2.6180	0.1057
CAUSE1(β_2)	1.5180	0.4081	13.8345	0.0002	16.1920	0.0001
CAUSE2(β_3)	1.3047	0.3043	18.3777	<0.0001	24.8340	<0.0001
SECOND(β_4)	-0.9024	0.3492	6.6786	0.0098	10.2640	0.0014
Shape(ρ)	0.9203	0.1239	-	-	-	-

results of the time-dependent log-logistic model. The p-value of the RAGE is 0.1373 indicating that the recipient age is not significant in that model at the 5% level. What is more, the effect of SECOND was found similar to that obtained in the Cox and log-logistic models.

Table 5.10: Standard Weibull model estimates and tests including $SECOND$ as a time-dependent covariate

Covariate	MLE	SE	Wald		Likelihood ratio	
			χ^2	P	χ^2	P
Intercept	8.133	0.729	-	-	-	-
RAGE(β_1)	-0.008	0.0051	2.489	0.115	2.208	0.137
CAUSE1(β_2)	1.105	0.2850	15.027	0.000	18.058	<0.0001
CAUSE2(β_3)	0.947	0.2022	21.934	<0.0001	26.376	<0.0001
SECOND(β_4)	-0.647	0.2064	9.815	0.002	11.200	0.001
Shape(ρ)	0.897	0.127	-	-	-	-

Figure 5.4 shows estimated log hazard functions for patients with non-second and second graft in the standard Weibull model. As in the previous two models, it can be seen that the first graft hazard increased when the second graft was done.

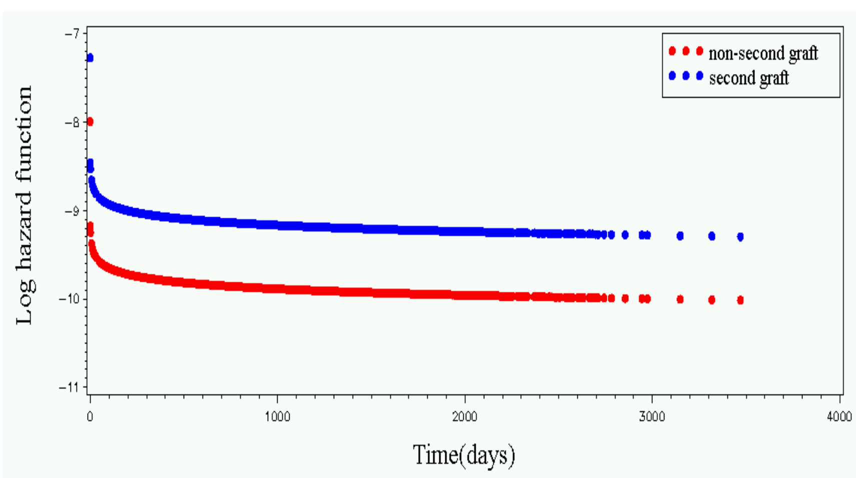

Figure 5.4: Estimated log hazard functions for patients with non-second and second graft in the standard Weibull model.

5.3.4 Weibull spline model

The Weibull spline models with 0, 1, 2, 3, 4 and 5 knots were applied based on the knot positions in Table 5.11. The results in table 5.11 show the AIC criterion for each spline model. It is noticed that the best choice is the 5 knots model. Consequently, the results of the Weibull spline with 5 knots model are presented in Table 5.12. The four covariates are significant at the 5% level including RAGE which was non-significant through the time-dependent Cox, log-logistic and standard Weibull models. The parameter estimate of SECOND was dramatically increased to 17.745 with 0.001 acceleration factor which refers to substantially acceleration for survival time of first eye graft when the second eye graft is not taken place. However, this results need to be checked to determine the appropriateness of the spline model that includes a binary time-dependent covariate.

Table 5.11: Knot positions of survival times and the AIC values for the six estimated spline models including $SECOND$ as a time-dependent covariate

No. of knots	Centile positions	Heart transplant survival times (days)	AIC
0	-	-	2423.42
1	50	766	2423.58
2	33, 67	487, 1254	2359.58
3	25, 50, 75	361, 766, 1461	2341.36
4	20, 40, 60, 80	264, 637, 1015, 1709	2294.58
5	17, 33, 50, 67, 83	224, 487, 766, 1254, 1769	2265.72

Table 5.12: Weibull spline (5 knots) estimates and Wald tests including $SECOND$ as a time-dependent covariate

Covariate	MLE	SE	Wald	
			χ^2	P
Intercept	57.447	4.4951	-	-
RAGE(β_1)	-0.036	0.0155	5.368	0.021
CAUSE1(β_2)	3.404	0.8303	16.810	<0.0001
CAUSE2(β_3)	3.148	0.5996	27.558	<0.0001
SECOND(β_4)	17.745	1.9224	85.201	<0.0001
First knot (γ_1)	1.422	0.207	47.3468	<0.0001
Second knot (γ_2)	-4.6841	1.2662	13.6848	0.0002
Third knot (γ_3)	4.711	2.641	3.1819	0.0745
Fourth knot (γ_4)	0.0586	3.9067	0.0002	0.988
Fifth knot (γ_5)	-2.4379	3.0149	0.6538	0.4188
Shape(ρ)	2.6567	0.0317	-	-

Table 5.13 presents the MLE and their standard errors through the six spline models. Even though there was no important change in the parameter estimates for the RAFE, CAUSE1 and CAUSE2 across the six models. For the SECOND, the parameter estimate considerably changed from 0.707 in the 0 knots model to -6.6792 in the 5 knots model. The shape parameter changed from 0.8971 in the 0 knots model to 2.6567 in the 5 knots model. This means that increasing the knots number changes the shape of the hazard function in the model with higher. Furthermore, treating the SECOND as a time-dependent covariate affected the hazard shape through the different knots models.

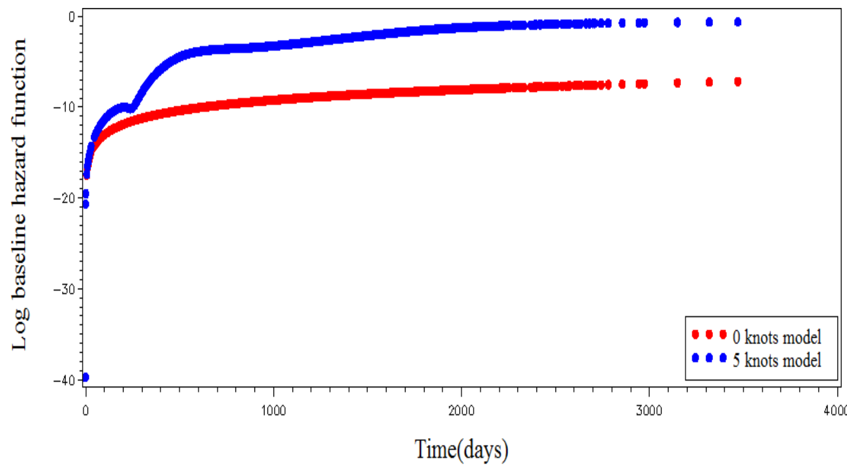

Figure 5.5: Estimated log baseline hazard functions for the Weibull models with 0 and 5 knots.

Figure 5.5 shows the estimated log baseline hazard functions for the Weibull models with 0 and 5 knots. Notice that the baseline hazard of the 5 knots spline model behaves strangely at around 220 days. This is because there are seventeen patients who did not have a second eye graft and who experienced graft failure between 180 and 280 days. This is picked up by the first knot, which is 224 days. After this time point, the hazard in spline model increases slightly faster than the hazard in the standard model.

The sv-values of parameter estimates across the six models are presented in Table 5.14. The 1 knot model has the highest sv-value for the parameter estimate of SECOND. Also, it is noticed that the 5 knots model has the lowest sv-values comparing to the other models. This result means that the 5 knots model has more efficient parameter estimates than those obtained from the other competitive spline models indicating to possibly better in fitting the data that contain the time-dependent SECOND.

Table 5.13: MLE estimates and standard errors for the Weibull spline models from 0 to 5 knots including $SECOND$ as a time-dependent covariate

Covariate	0 Knots		1 Knot		2 Knots		3 Knots		4 Knots		5 Knots	
	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE	MLE	SE
Intercept	8.133	0.729	13.413	1.819	19.572	2.101	29.81	2.952	52.608	4.418	57.447	4.496
RAGE(β_1)	-0.008	0.005	-0.012	0.007	-0.016	0.009	-0.021	0.011	-0.032	0.015	-0.036	0.016
CAUSE1(β_2)	1.105	0.285	1.507	0.380	1.944	0.473	2.495	0.594	3.35	0.797	3.404	0.832
CAUSE2(β_3)	0.947	0.202	1.316	0.272	1.708	0.336	2.211	0.424	3.057	0.574	3.148	0.600
SECOND(β_4)	-0.647	0.206	0.166	0.698	3.159	0.961	6.92	1.355	15.954	1.922	17.745	1.924
Shape(ρ)	0.897	0.127	1.2	0.144	1.486	0.087	1.874	0.061	2.539	0.036	2.657	0.032
First knot (γ_1)	-	-	0.011	0.007	0.658	0.106	1.036	0.201	1.153	0.159	1.422	0.207
Second knot (γ_2)	-	-	-	-	-1.199	0.199	-1.921	0.633	-3.623	0.771	-4.684	1.266
Third knot (γ_3)	-	-	-	-	-	-	0.876	0.657	2.248	0.666	4.711	2.641
Fourth knot (γ_4)	-	-	-	-	-	-	-	-	0.867	0.659	0.059	3.907
Fifth knot (γ_5)	-	-	-	-	-	-	-	-	-	-	-2.438	3.015

Table 5.14: Standardized variability of parameter estimates for the Weibull spline models from 0 to 5 knots $SECOND$ as a time-dependent covariate

Covariate	0 Knots	1 Knot	2 Knots	3 Knots	4 Knots	5 Knots
Intercept	0.100	0.113	0.072	0.053	0.033	0.029
RAGE(β_1)	0.750	0.500	0.375	0.286	0.188	0.167
CAUSE1(β_2)	0.288	0.210	0.164	0.127	0.094	0.092
CAUSE2(β_3)	0.238	0.172	0.132	0.102	0.074	0.072
SECOND(β_4)	0.355	3.506	0.205	0.104	0.047	0.041
Shape(ρ)	0.142	0.120	0.059	0.033	0.014	0.012

5.4 Model evaluation

Evaluation the alternative models is initially performed by comparing the sv-values for the parameter of interest, SECOND in the cornea model. Following this stage, analysis of the Cox-Snell and martingale residuals for the applied models may reflect the adequacy of each model to fit such data.

5.4.1 Model comparisons

Modelling second eye graft as a fixed covariate using the last status of SECOND leads to a negative effect on hazard of the first graft. The reason that may cause this effect is the survival times of the patients who have not done second eye graft, group 1, are less than the other patients in group 2 with second eye graft, and then second graft takes the value 1 in group 2 that has higher survival times. In this case, the second eye graft leads to have decreasing effect on hazard of failure of the first eye graft. However, this covariate is not sensible because the second graft was not performed for all the patients at the beginning of the study in addition to the time of the second operation has important impact on the first graft recovery and then SECOND should be treated as a time-dependent covariate only. In the time-dependent models, the effect of the second eye graft on hazard of the first eye graft failure was positive in the Cox, log-logistic and standard Weibull models. When the time-dependent values are considered, the values were 0 in the low survival times and 1 for the higher survival times. This reflects the decrease in the survival function when second eye operation is performed. Consequently, it is preferable to adopt the model that allow for second eye graft to change over time. For the Weibull spline (5 knots) model with the SECOND as time-dependent covariate, the SECOND acceleration factor was .0013 which is different from the three standard time-dependent models. The parameter of that covariate was overestimated in the spline model. These results must be checked with more procedures to evaluate the time-dependent Weibull spline model to fit the cornea data.

In Table 5.15, the MLE with their sv-values for the SECOND as a time-dependent covariate are supplied across the four models. The sv-values of the time-dependent SECOND are close in the Cox, log-logistic and Weibull models while the spline model produced considerably lower sv-value comparing to these three model.

5.4.2 Residual analysis

To check adequacy of the applied models, the Cox-Snell and martingale residuals as described in section 4.5.2. Figure 5.6 shows the Cox-Snell residuals for the models with time-dependent SECOND. The four plots do not give straight lines with unity slope. However, the plots of

Table 5.15: Standardized variability (sv-values) for $SECOND$ as a time-dependent covariate across the four models

Models	Cox		Log-logistic		Weibull		Spline	
	MLE	**sv**	MLE	**sv**	MLE	**sv**	MLE	**sv**
Time-dependent-SECOND	0.511	**0.492**	-0.902	**0.387**	-0.647	**0.355**	17.745	**0.041**

the Cox and the Weibull spline models show slightly better fit than the other two models.

In Figure 5.7, martingale residuals for the four models were plotted against survival times. There were negative martingales in all the models for the times between 1300 and 2700 days. However, for the plots of the log-logistic and the standard Weibull models, the number of the negative martingale values is higher than the Cox and the Weibull spline models and start from times before 1000 days.

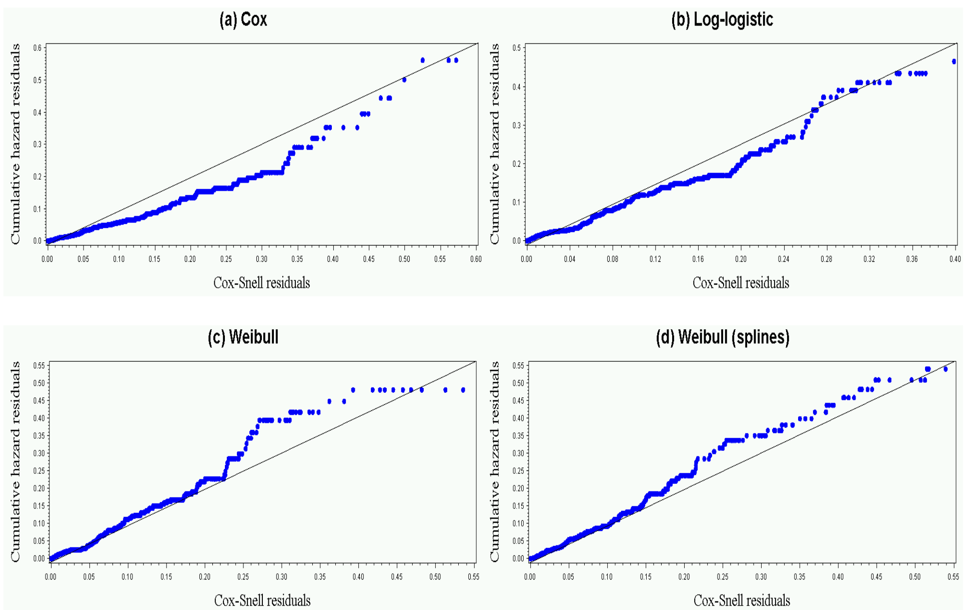

Figure 5.6: Cox-Snell residuals for the models with time-dependent $SECOND$.

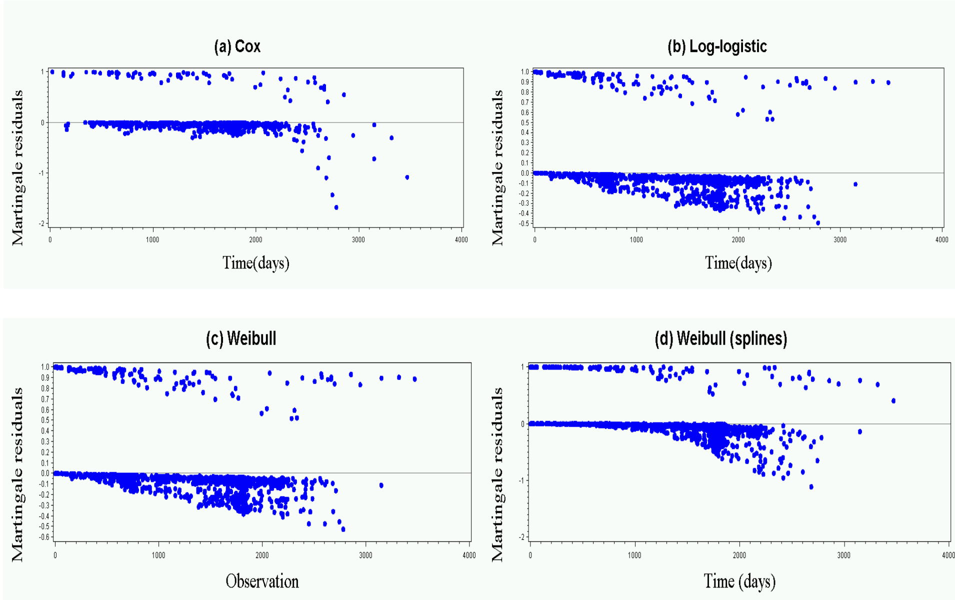

Figure 5.7: Martingale residuals for the models with time-dependent $SECOND$.

5.5 Concluding remarks

Selecting the best model that fits cornea transplant data was the main aim of this chapter. Using the data set introduced by NHS Blood and Transplant of the grafted cornea between 1994 and 2001 in the UK, it was found three important covariates: RAGE, CAUSE1 and CAUSE2. The covariate SECOND was added as a time-dependent covariate with one change to the model that contains the three significant covariates representing the effect of the second eye graft on the survival time of the first eye graft.

It was noticed that the effect of the second graft on the hazard of the first graft failure was positive as a result of using the changing nature of the covariate over time while this effect was negative in the Weibull spline model. Based on the sv-values of the covariates, the Weibull spline model produced the most efficient SECOND parameter estimate relative to the other three models. Also, the Cox-Snell plots of the Cox and the Weibull spline models had slightly better fit comparing to the log-logistic and the standard Weibull models. Also, the deviations of the martingale residuals were less in the Cox and the Weibull spline models comparing to the other two models.

To sum up, it is recommended to adopt the model with incorporated second eye graft as a time-dependent covariate. This procedure will help to reflect the effect of changing the second graft status during the first graft survival times. Moreover, to evaluate the time-dependent Weibull spline model against the time-dependent standard models based on cornea transplantation data, simulations will be run with results that explains the relative efficiency of each model through different scenarios that may arise in reality.

Chapter 6

Weibull splines simulation

This chapter introduces a method to simulate observations from the Weibull spline model. The standard Weibull AFT model can be simulated using the inversion method for the survivor function that is defined as

$$S_i(t) = \exp\left\{-\left(\frac{1}{\alpha_i}\right)^{\rho} t^{\rho}\right\},$$

where $\alpha_i = \exp(\theta + \beta' x_i)$. Based on the inversion of this survivor function, the survival times can be generated as

$$T = [-\log(U)]^{\frac{1}{\rho}} [\alpha_i], \tag{6.1}$$

where $U \sim Uni[0, 1]$.

Now consider the Weibull spline model with m knots. For simplicity we shall initially consider the case with no covariates. The survivor function is defined based on the cumulative hazard function given in (3.20) but we restate it for 1-knot model here as

$$\begin{aligned} S(t) \;=\; & \exp\Big[-\Big\{\exp\Big(-\rho\theta + \rho\log t + \gamma_1[(\log t - \kappa_1)_+^3 - \lambda_1(\log t - \kappa_{min})_+^3 \\ & -(1-\lambda_1)(\log t - \kappa_{max})_+^3]\Big)\Big\}\Big]. \end{aligned} \tag{6.2}$$

The cubic terms in (6.2) make analytical inversion impossible. Thus other approaches are needed to generate observations from Weibull splines models. Two methods are discussed in section 6.2 and the results of a simulation study based on Weibull splines models with 0 and 1 knot are presented in the no covariate case in section 6.3. However, first, in section 6.1, the parameters of the model are investigated.

6.1 The Weibull spline parameters

In the paper by Royston and Parmar (2002), it was not discussed how to determine the spline parameters in simulation of the Weibull spline model. However, as an example, consider the Weibull spline model with 1 knot, the cumulative hazard function for which is

$$\begin{aligned} H(t) \;=\; & \Big\{\exp\Big(-\rho\theta + \rho\log t + \gamma_1[(\log t - \kappa_1)_+^3 - \lambda_1(\log t - \kappa_{min})_+^3 \\ & -(1-\lambda_1)(\log t - \kappa_{max})_+^3]\Big)\Big\}. \end{aligned} \tag{6.3}$$

Consider the cases where (a)Weibull scale, shape and spline parameters are $\theta = 0.5$, $\rho = 0.1$ and $\gamma_1 = 0.02$ respectively, (b)the same Weibull parameters with spline parameter $\gamma_1 = 0.008$. Also, κ_1 is the internal knot while κ_{min} and κ_{max} are the external knots. Then Figure 6.1 shows plots of (6.3) in these two cases. While $H(t)$ behaves satisfactorily in case (b), case (a) yields a cumulative hazard that is not increasing. Thus the particular combination of parameters in case (a) cannot be used.

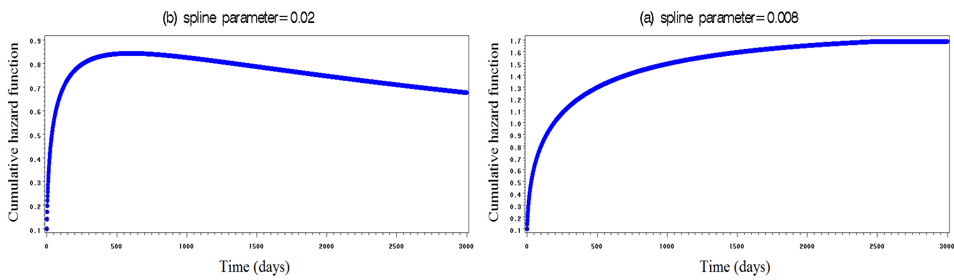

Figure 6.1: Cumulative hazard functions: (a)γ_1=0.02, (b)γ_1=0.008.

We now examine the 1-knot model in detail. If $\log t < \kappa_{min}$, the (6.3) is simply a Weibull cumulative hazard and hence is always increasing for $\rho > 0$. Suppose now $\kappa_{min} \le \log t \le \kappa_1$. Then

$$H(t) = \exp\left\{\rho(-\theta) + \rho \log t + \gamma_1 \left[-\lambda_1(\log t - \kappa_{min})^3\right]\right\}. \tag{6.4}$$

This function is monotone increasing if $\frac{dH(t)}{dt} \ge 0$. Differentiating (6.4) we require

$$\frac{\rho}{t} - \frac{3\gamma_1\lambda_1}{t}(\log t - \kappa_{min})^2 \quad \ge \quad 0.$$

That is

$$3\gamma_1\lambda_1(\log t - \kappa_{min})^2 \quad \le \quad \rho.$$

Since t >0, $\rho > 0$ and $\lambda_1 > 0$, we require

$$\gamma_1 \le \frac{\rho}{3\lambda_1(\log t - \kappa_{min})^2},$$

to hold for all $\kappa_{min} \le \log t \le \kappa_{max}$. Thus, we require

$$\gamma_1 \le \frac{\rho}{3\lambda_1(\kappa_1 - \kappa_{min})^2}. \tag{6.5}$$

$$= \quad \frac{\rho(\kappa_{max} - \kappa_{min})}{3(\kappa_{max} - \kappa_1)(\kappa_1 - \kappa_{min})^2}.$$

Now suppose that $\kappa_1 \le \log t < \kappa_{max}$. Then

$$H(t) = \exp\left\{\rho(-\theta) + \rho \log t + \gamma_1 \left[(\log t - \kappa_1)^3 - \lambda_1(\log t - \kappa_{min})^3\right]\right\}.$$

This function is monotone increasing if

$$\gamma_1 \le \frac{\rho}{3\lambda_1(\kappa_1 - \kappa_{min})^2}. \tag{6.6}$$

Consider the term in square brackets. It is easy to show that this term is a maximum when $\log t = \kappa_{max}$. In this case the term in square brackets becomes

$$\begin{aligned} & (\kappa_{max} - \kappa_1)^2 - \frac{(\kappa_{max} - \kappa_1)(\kappa_{max} - \kappa_{min})^2}{(\kappa_{max} - \kappa_{min})} \\ = \; & (\kappa_{max} - \kappa_{min})(\kappa_{min} - \kappa_1). \end{aligned}$$

Hence we require

$$\gamma_1 \leq \frac{\rho}{3(\kappa_{max} - \kappa_1)(\kappa_1 - \kappa_{min})}. \tag{6.7}$$

This is stronger inequality than (6.5).

Now consider the case with $\log t \geq \kappa_{max}$. Hence

$$H(t) = \exp\left\{\rho(-\theta) + \rho \log t + \gamma_1 \left[(\log t - \kappa_1)^3 - \lambda_1(\log t - \kappa_{min})^3 - (1 - \lambda_1)(\log t - \kappa_{max})^3\right]\right\}.$$

By letting $\log t \longrightarrow \infty$, we see that eventually $H(t)$ will no longer be increasing. In a practical data analysis context this is not a problem because κ_{max} is chosen so that no data point is greater than κ_{max}. So provided (6.7) holds there is no difficulty. However, for simulations we choose κ_{max} to be large enough so that it is extremely rare that an observation will be generated and ensure that

$$\gamma_1 < \frac{\rho}{3(\kappa_{max} - \kappa_1)(\kappa_1 - \kappa_{min})}.$$

The problem is more complex when number of knots exceeds 1. However for simulations from the other Weibull splines with higher number of knots, feasible splines parameters were specified graphically by assuming a certain parameters. These parameters were examined to ensure that the obtained cumulative hazard functions in each case are monotone increasing. Graphical method was sufficient to assume these splines parameters when Weibull spline model with 2 and 3 knots were simulated.

6.2 Spline model simulation

In order to generate survival times from the Weibull spline model, two methods were investigated, rejection sampling and numerical inversion. The rejection sampling with its difficulties will be discussed and then the numerical inversion method is supplied as an alternative method to simulate data from the model.

6.2.1 Rejection sampling algorithm

The survivor function of the Weibull splines model in (6.2) cannot be inverted analytically. The first investigated approach to generate survival times from such model is the rejection sampling method. This method is a theoretical probabilistic method that enables to generate random variables from distributions in which analytical inversion is not available (Murray, 2007). To clarify the idea of this technique, suppose that generation of x values from density function $\pi(x)$ is not possible using the analytical inversion method. In this case, an auxiliary density function $q(x)$ is employed to generate from. This method is started by multiplying the function $q(x)$ by a positive constant C to make $Cq(x) \geq \pi(x)$ for all x. The next step is to draw values of x from the function $Cq(x)$ and $u \sim U[0, 1]$ and then x is accepted as a value from $\pi(x)$ if $Cuq(x) \leq \pi(x)$ (Gamerman and Lopes, 2006).

Following this technique, generating survival times from the Weibull spline model (1 knot) can be executed using the following algorithm:

1. Assume that the survival times between 0 and 5000 days, generate survival times (t) from U(0, 5000) in order to mimic heart data case.

2. Assume values for the median (κ_1), the minimum (κ_{min}) and the maximum (κ_{max}) of the log survival times that have been generated uniformly.

3. Calculate λ_1 as $\lambda_1 = \frac{\kappa_{max}-\kappa_1}{\kappa_{max}-\kappa_{min}}$

4. Calculate the terms $(\log t-\kappa_1)_+^3$, $(\log t-\kappa_{min})_+^3$ and $(\log t-\kappa_{max})_+^3$ where $(\log t-\kappa_j)_+^3 = max\{0, (\log t - \kappa_j)^3\}$

5. Calculate the one knot basis function as
$\upsilon_1(t) = (logt - \kappa_1)_+^3 - \lambda_1(logt - \kappa_{min})_+^3 - (1 - \lambda_1)(logt - \kappa_{max})_+^3$

6. Calculate the values of the survivor function $S(t)$ of the Weibull splines (1 knot) model using the assumed splines parameter γ_1 and the basis function in (5) as
$S(t) = \exp\{-\exp[-\rho\theta + \rho \log t + \gamma_1 \upsilon_1(t)]\}$.

7. Compare the density function value $S(t)$ for each time (t) with $C \cdot U(0, 1)$ (C is an assumed constant based on the maximum value of the density function), if $S(t) \geq C \cdot U(0, 1)$ then accept (t) as survival time from the Weibull splines with 1 knot model, otherwise go to step 1.

This algorithm was applied using the basis functions of the Weibull splines models with 1, 2 and 3 knots to generate survival times from the model with 1, 2 and 3 knots. Different scenarios were followed using multiple sample sizes 50, 100, 200, 300 and 500 observations with no censoring, 30%, 50% and 70% censoring ratios.

The efficiency of this technique depends on the rejection rate. To decrease the rejection rate, the distance between the envelope function, $U(0, 1)$ in our algorithm, and the aimed function, $S(t)$, should be small as possible (Fishman, 2006). This condition was not achieved because the distance between the $U(0, 1)$ and the survivor function $S(t)$ for the splines models was not small enough. For this reason, the rejection rate for this algorithm was higher than 50%, and then this method was not efficient enough to be adopted. In the next section, a suggested numerical algorithm will be discussed as an alternative approach. The results that have been obtained from the two methods were similar, so that the results of the rejection sampling will not be supplied.

6.2.2 Numerical inversion algorithm

The survivor function in (6.2) shows that analytic inversion for the Weibull spline models is impossible. A simple numerical inversion using Newton-Raphson method is employed to generate solutions for the non-linear survivor function of the Weibull spline model. The Newton-Raphson method is a numerical technique to solve non-linear equations by using iterative process to specify one root x_{n+1} depending on the assuming initial value x_n for that root. The value of x_{n+1} is determined by (Kaw *et al.*, 2010)

$$x_{n+1} = x_n - \frac{f(x_n)}{f\prime(x_n)},$$

where $f(x_n)$ is a defined function over all the values of x_n and $f\prime(x_n)$ is the first derivative of this function.

This numerical inversion may yield multiple solutions so that a modification for the Newton-Raphson inversion will be applied. The idea of the suggested method depends on selecting number of x-values, $0 < x_1 < x_2 < x_3 < \ldots < x_n$, and then the values of $F(y_1), F(y_2), F(y_3), \ldots, F(y_n)$ are calculated using the function that must be inverted. When a value of u^* is generated from $U(0,1)$ with $F(y_1) < F(u^*) < F(y_2)$, the value of y^* is obtained from the inversion of $F(u^*)$. In this case, the generated value y^* is accepted if $y_1 < y^* < y_2$.

Based on this method, the following algorithm was followed to generate survival times from the Weibull spline model with 1 knot:

1. Select the values of κ_{min}, κ_1 and κ_{max} at assumed locations for the data that are generated.

2. Calculate λ_1 as $\lambda_1 = \frac{\kappa_{max}-\kappa_1}{\kappa_{max}-\kappa_{min}}$.

3. Assume the Weibull scale, shape and Weibull spline (1 knot) parameters θ, ρ and γ_1 respectively.

4. Calculate the log cumulative hazards for generated t values as

$$\begin{aligned}\log H(t) &= \rho(-\theta) + \rho \log t + \gamma_1 \Big[(\log t - \kappa_1)^3_+ - \lambda_1(\log t - \kappa_{min})^3_+ \\ &\quad -(1-\lambda_1)(\log t - \kappa_{max})^3_+\Big], \end{aligned} \tag{6.8}$$

5. From the relationship between the cumulative hazard and survivor functions, calculate the survival probabilities for the generated t values using (6.8) as

$$S(t) = \exp\{-\exp[\log H(t)]\}.$$

6. Select the survivor probabilities $S_1(t)$, $S_2(t)$ and $S_3(t)$ at $\log t = \kappa_{min}$, $\log t = \kappa_1$ and $\log t = \kappa_{max}$ respectively.

7. Determine the function that can be inverted to generate the survival time t depending on the time interval. For the first interval $\kappa_{min} \leq \log t < \kappa_1$, the function is defined as

$$\log H(t) = \rho(-\theta) + \rho \log t + \gamma_1 \left[-\lambda_1(logt - \kappa_{min})^3_+\right],$$

where $\log H(t) = \log\{-\log S(t)\}$ and $\kappa_{min} = \log 1 = 0$, the function becomes

$$\log\{-\log S(t)\} = -\theta\rho + \rho \log t - \gamma_1 \lambda_1 (\log t)^3. \tag{6.9}$$

For the second interval $\kappa_1 \leq \log t < \kappa_{max}$, the function is defined as

$$\log H(t) = \rho(-\theta) + \rho \log t + \gamma_1 \left[(\log t - \kappa_1)^3_+ - \lambda_1(\log t - \kappa_{min})^3_+\right],$$

where $\log H(t) = \log\{-\log S(t)\}$ and $\kappa_{min} = \log 1 = 0$, the function becomes

$$\log\{-\log S(t)\} = \rho(-\theta) + \rho \log t + \gamma_1 \left[(logt - \kappa_1)^3_+ - \lambda_1(logt - \kappa_{min})^3_+\right].$$

Hence,

$$\log\{-\log S(t)\} = -\rho\theta+\gamma_1(1-\lambda)(\log t)^3-3\gamma_1\kappa_1(\log t)^2+(3\gamma_1\kappa_1^2+\rho)(\log t)-\gamma_1\kappa_1^3 \quad (6.10)$$

For the third interval, $\log t \geq \kappa_{max}$, the function is defined as

$$\begin{aligned}\log H(t) &= \rho(-\theta)+\rho\log t+\gamma_1\Big[(logt-\kappa_1)_+^3-\lambda_1(\log t-\kappa_{min})_+^3 \\ &\quad -(1-\lambda_1)(\log t-\kappa_{max})_+^3\Big],\end{aligned}$$

where $\log H(t) = \log\{-\log S(t)\}$ and $\kappa_{min} = \log 1 = 0$, the function becomes

$$\begin{aligned}\log\{-\log S(t)\} &= \rho(-\theta)+\rho\log t+\gamma_1\Big[(\log t-\kappa_1)_+^3-\lambda_1(\log t-\kappa_{min})_+^3 \\ &\quad -(1-\lambda_1)(\log t-\kappa_{max})_+^3\Big],\end{aligned}$$

and then,

$$\begin{aligned}\log\{-\log S(t)\} &= -\rho\theta+3\gamma_1\{(1-\lambda_1)\kappa_{max}+\lambda_1\kappa_{min}-\kappa_1\}(\log t)^2 \\ &\quad +\left\{\rho+\gamma_1\left[3\kappa_1^2-3\lambda_1\kappa_{min}^2-3(1-\lambda_1)\kappa_{max}^2\right]\right\}\log t \\ &\quad +3\gamma_1\left\{\lambda_1\kappa_{min}^3+(1-\lambda_1)\kappa_{max}^3-\kappa_1^3\right\} \qquad (6.11)\end{aligned}$$

8. Generate $S^*(t)$ from $U \sim [0,1]$. If $S_1(t) \leq S^*(t) < S_2(t)$, generate the survival times from the inversion of (6.9). Also, if $S_2(t) \leq S^*(t) < S_3(t)$, generate the survival times from the inversion of (6.10). Finally, if $S^*(t) \geq S_3(t)$, generate the survival times from the inversion of (6.11)

9. Check each generated time to ensure that the inversion provides the right value based on the time intervals in 7.

6.3 Simulation results

The numerical method has been used to generate survival times from different Weibull models with 0 (standard) and 1 knot. These simulations were performed using 60 scenarios. It was assumed four shape parameters 0.5, 1, 2 and 4 with sample sizes of 50, 100, 200, 300 and 500. In the 1-knot spline model, spline parameter γ_1 was specified using (6.7) and the assumed values of κ_{min}, κ_1 and κ_{max}. The different combinations of shapes and sample sizes were applied with no censoring, 30% and 50% censoring proportions for 5000 replications. After implementing each simulation, the Weibull spline models with 0, 1, 2, 3, 4 and 5 knots were fitted and then the empirical power of the Likelihood test for each fitted model was calculated to select the best model within each scenario. This power was calculated using three criteria: -2 Log L, AIC and BIC.

Table 6.1 presents the empirical power of models based on data that are simulated from the Weibull spline model where there is no censoring. The BIC results show that the power of test in the fitted 0 knot model is about 95% of the number of replications. These results were found for the different shapes, ρ=0.5, 1, 2 and 4, and sample of n=50. For the other samples of n=100, 200, 300 and 500 observations, the power slightly increased by about 3%.

The results of the simulated 0 knots model with 30% and 50% censoring are presented in Tables 6.2 and 6.3. In Table 6.2, it can be noticed that the power decreased by about 2% for the samples of n=50 when 30% censoring proportion was used. However, there was no change in the power for the other sample sizes. Similarly, the obtained power in Table 6.3 decrease by about 4%, compared to the no censoring case, for the samples of n=50 while there was no noticeable change for the other sample sizes. These results mean that the robustness of the model is slightly affected by the censoring proportions as a result to the change in the computation of the likelihood function for the censored observations.

Figure 6.2 compares the empirical power of the fitted 0 knot model with no, 30% and 50% censoring ratios through different samples sizes. The survival times were generated from 0 knots model with shapes $\rho = 0.5$, $\rho = 1$, $\rho = 2$ and $\rho = 4$. The estimated power in the three censoring scenarios are shown for the shape parameters, $\rho = 0.5$, $\rho = 1$, $\rho = 2$ and $\rho = 4$, in Figures 6.2(a), 6.2(b), 6.3(c) and 6.4 (d) respectively. The four figures show that the power in the 50% censoring case is lower by about 3% compared to the no censoring case when sample size is less than 100 observations.

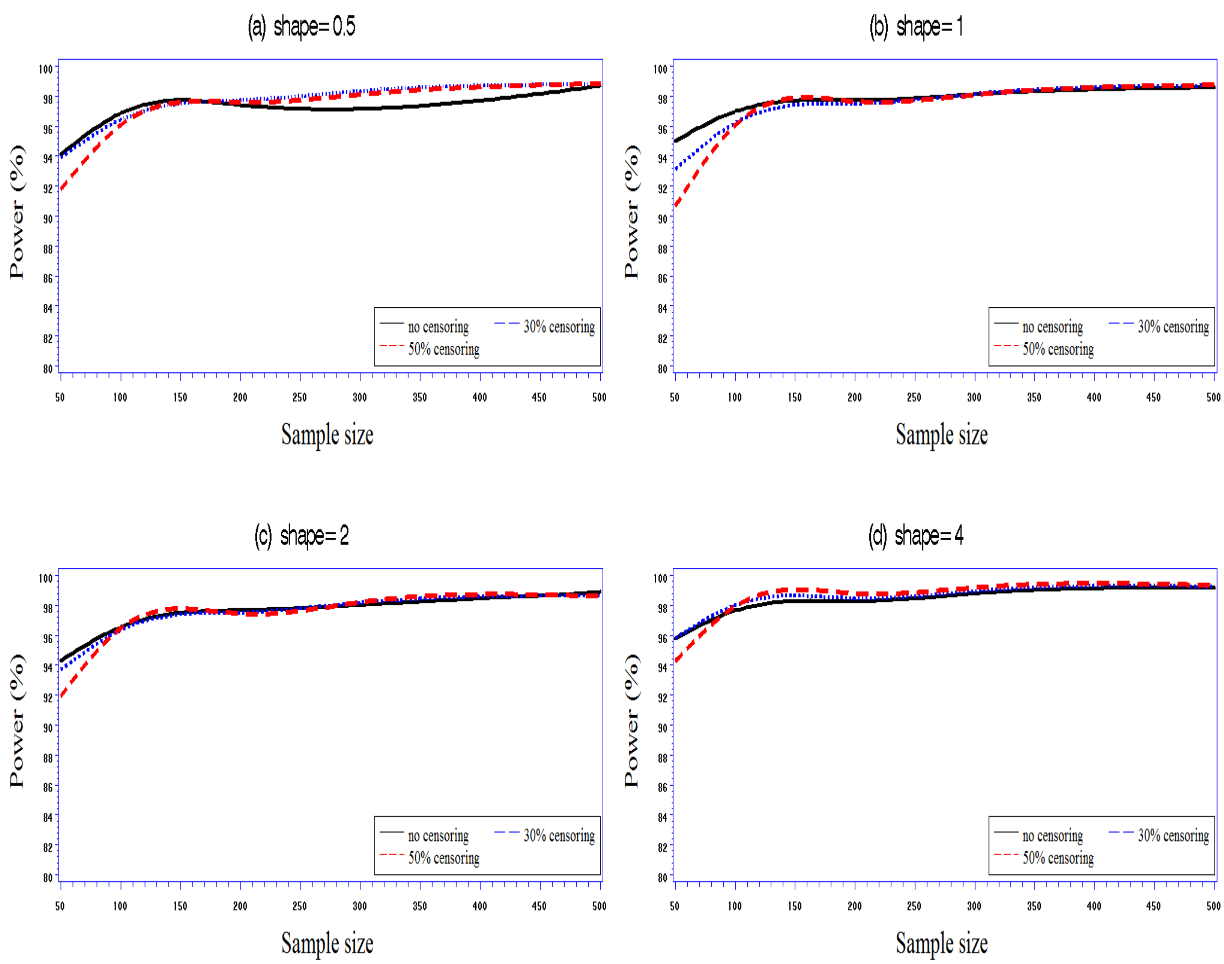

Figure 6.2: Empirical power of the Likelihood test at $\alpha = 0.05$ for the Weibull model (0-knot model) based on generated survival times from the same model using $\rho = 0.5$, $\rho = 1$, $\rho = 2$ and $\rho = 4$ with no, 30% and 50% censoring.

Table 6.1: Empirical power of the Likelihood test at $\alpha = 0.05$ for spline models based on generated survival times from ***the Weibull model (0-knot model*** with no censoring

Sample	Shape	-2LogL						AIC						BIC					
		0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
n=50	ρ=.5	89.07	3.47	2.17	1.69	1.71	1.88	73.98	11.50	6.31	3.66	2.43	2.12	94.10	4.08	1.34	0.27	0.13	0.08
	ρ=1	89.15	2.81	2.55	1.56	1.67	2.24	75.70	9.73	6.09	3.37	2.27	2.82	95.02	3.37	1.17	0.20	0.11	0.12
	ρ=2	88.32	3.20	2.46	1.68	1.86	2.47	73.92	10.45	6.65	3.45	2.57	2.96	94.32	3.77	1.23	0.35	0.16	0.17
	ρ=4	90.90	2.75	1.61	1.53	1.28	1.92	77.42	10.29	4.66	3.26	2.02	2.34	95.80	3.13	0.64	0.27	0.08	0.08
n=100	ρ=.5	90.68	3.31	2.43	1.62	1.18	0.77	76.14	11.44	6.37	3.35	1.74	0.96	96.87	2.47	0.56	0.08	0.01	0.01
	ρ=1	90.05	3.07	2.32	1.46	1.38	1.70	76.36	10.52	5.57	3.30	2.13	2.10	96.99	2.38	0.52	0.10	0.00	0.00
	ρ=2	88.41	3.48	2.49	1.91	1.50	2.20	73.93	10.79	6.37	3.84	2.39	2.68	96.54	2.80	0.46	0.18	0.02	0.00
	ρ=4	91.91	2.80	1.42	1.17	1.18	1.51	78.46	10.50	4.20	2.88	2.02	1.93	97.65	1.94	0.32	0.08	0.01	0.00
n=200	ρ=.5	91.33	4.29	2.28	1.18	0.65	0.26	77.60	13.15	5.57	2.32	1.02	0.33	97.40	2.29	0.25	0.06	0.00	0.00
	ρ=1	89.24	3.46	2.16	1.70	1.56	1.87	74.70	11.18	5.77	3.61	2.48	2.25	97.70	2.00	0.20	0.09	0.01	0.00
	ρ=2	88.80	3.65	2.28	1.57	1.70	1.99	74.68	11.07	5.93	3.46	2.47	2.38	97.65	1.95	0.34	0.05	0.01	0.00
	ρ=4	91.95	2.79	1.30	1.15	1.20	1.60	79.34	9.85	4.26	2.68	1.88	1.98	98.26	1.60	0.12	0.02	0.00	0.00
n=300	ρ=.5	91.01	3.80	2.36	1.40	0.92	0.52	76.87	12.29	5.97	2.84	1.38	0.65	97.13	2.38	0.41	0.07	0.01	0.01
	ρ=1	88.19	3.80	2.59	1.81	1.73	1.87	72.71	11.80	6.60	3.95	2.59	2.35	98.10	1.61	0.25	0.03	0.01	0.00
	ρ=2	88.52	3.65	2.51	1.79	1.78	1.74	74.03	11.42	6.22	3.72	2.56	2.04	98.01	1.75	0.19	0.05	0.00	0.00
	ρ=4	92.37	2.67	1.33	1.13	1.19	1.30	80.62	9.56	3.68	2.61	1.76	1.76	98.78	1.11	0.11	0.00	0.00	0.00
n=500	ρ=.5	93.16	4.54	1.62	0.48	0.16	0.03	81.11	13.92	3.98	0.77	0.19	0.02	98.68	1.27	0.04	0.01	0.00	0.00
	ρ=1	87.90	4.19	2.34	1.75	1.95	1.86	72.70	11.92	6.31	3.94	2.87	2.26	98.57	1.34	0.09	0.00	0.00	0.00
	ρ=2	89.00	3.60	2.26	1.72	1.72	1.69	73.46	12.15	6.02	3.76	2.48	2.12	98.87	1.06	0.07	0.00	0.00	0.00
	ρ=4	92.96	2.28	1.21	1.16	1.22	1.16	82.41	8.15	3.45	2.53	1.87	1.59	99.15	0.74	0.08	0.03	0.00	0.00

Table 6.2: Empirical power of the Likelihood test at $\alpha = 0.05$ for spline models based on generated survival times from ***the Weibull model (0-knot model*** with 30% censoring

Sample	Shape	-2LogL						AIC						BIC					
		0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
n=50	ρ=.5	87.73	3.18	2.73	1.89	1.80	2.66	72.89	10.64	6.91	3.96	2.56	3.04	93.90	3.69	1.28	0.46	0.15	0.52
	ρ=1	85.92	3.27	2.79	1.67	2.26	4.08	70.39	10.86	7.01	3.82	3.17	4.75	93.10	4.19	1.36	0.32	0.30	0.72
	ρ=2	86.81	3.04	2.50	1.63	2.13	3.88	71.23	11.24	6.38	3.62	2.98	4.55	93.68	3.76	1.27	0.33	0.28	0.67
	ρ=4	89.72	2.04	1.63	1.45	1.61	3.54	76.90	8.68	4.47	3.26	2.57	4.11	95.80	2.47	0.74	0.24	0.23	0.52
n=100	ρ=.5	89.57	3.98	2.56	1.50	1.35	1.03	75.48	12.07	6.44	2.98	1.79	1.24	96.41	2.88	0.60	0.07	0.02	0.02
	ρ=1	87.96	3.38	2.51	1.80	1.73	2.61	72.75	11.30	6.43	3.91	2.69	2.92	96.22	2.87	0.61	0.17	0.11	0.02
	ρ=2	88.05	3.66	2.36	1.84	1.86	2.22	73.26	11.72	5.91	3.64	2.63	2.83	96.35	2.88	0.59	0.11	0.05	0.02
	ρ=4	91.97	2.27	1.45	1.23	1.52	1.55	80.01	8.41	4.53	2.76	2.23	2.05	98.01	1.65	0.25	0.06	0.01	0.02
n=200	ρ=.5	91.29	4.13	2.31	1.35	0.61	0.30	77.97	12.66	5.68	2.57	0.78	0.33	97.71	2.04	0.21	0.03	0.01	0.00
	ρ=1	88.11	3.74	2.51	1.72	1.97	1.94	73.27	11.48	6.40	3.64	2.83	2.38	97.49	2.23	0.25	0.02	0.00	0.01
	ρ=2	88.78	3.78	2.17	1.62	1.70	1.94	73.04	12.06	6.18	3.52	2.69	2.50	97.50	2.15	0.32	0.02	0.01	0.00
	ρ=4	92.17	2.42	1.32	1.12	1.59	1.37	80.18	9.03	4.17	2.71	2.16	1.74	98.45	1.33	0.19	0.02	0.01	0.00
n=300	ρ=.5	92.24	4.27	2.08	0.83	0.48	0.09	79.09	13.38	5.34	1.45	0.63	0.10	98.32	1.58	0.09	0.00	0.01	0.00
	ρ=1	88.45	3.76	2.26	1.81	1.83	1.88	73.44	11.59	6.46	3.57	2.75	2.19	98.13	1.63	0.18	0.05	0.01	0.00
	ρ=2	88.31	3.68	2.58	1.66	1.81	1.95	73.61	11.39	6.30	3.85	2.56	2.29	98.16	1.68	0.14	0.02	0.00	0.00
	ρ=4	92.81	2.08	1.43	1.15	1.20	1.32	81.46	8.13	3.83	2.72	1.97	1.89	98.93	0.95	0.12	0.00	0.00	0.00
n=500	ρ=.5	93.35	4.36	1.85	0.31	0.11	0.01	81.39	13.58	4.28	0.59	0.15	0.01	98.77	1.15	0.08	0.00	0.00	0.00
	ρ=1	88.36	4.05	2.45	1.72	1.56	1.85	73.85	11.86	6.12	3.50	2.42	2.24	98.68	1.25	0.06	0.01	0.00	0.00
	ρ=2	88.52	3.62	2.22	1.88	1.80	1.95	73.76	11.21	6.13	3.87	2.74	2.28	98.62	1.23	0.11	0.04	0.00	0.00
	ρ=4	92.37	2.43	1.38	1.20	1.25	1.36	82.33	7.96	3.71	2.44	1.95	1.61	99.24	0.72	0.04	0.00	0.00	0.00

Table 6.3: Empirical power of the Likelihood test at $\alpha = 0.05$ for spline models based on generated survival times from ***the Weibull model (0-knot model*** with 50% censoring

Sample	Shape	-2LogL						AIC						BIC					
		0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
n=50	ρ=.5	84.52	3.12	2.94	1.67	2.31	5.43	69.24	10.75	6.94	3.71	3.47	5.89	91.80	3.82	1.42	0.39	0.76	1.80
	ρ=1	81.65	3.20	2.81	1.66	2.85	7.83	67.07	10.02	6.92	3.78	3.88	8.33	90.68	4.13	1.48	0.38	0.84	2.48
	ρ=2	83.85	3.07	2.12	1.55	2.24	7.17	68.47	10.79	5.80	3.67	3.21	8.05	91.94	3.87	0.89	0.33	0.72	2.24
	ρ=4	87.11	1.50	1.38	1.19	1.95	6.87	75.09	6.97	4.11	2.89	3.05	7.89	94.28	1.94	0.74	0.22	0.46	2.36
n=100	ρ=.5	89.19	3.67	2.89	1.68	1.50	1.06	74.58	11.63	7.00	3.21	2.34	1.24	96.08	2.94	0.77	0.06	0.08	0.07
	ρ=1	87.48	3.49	2.38	1.73	2.11	2.80	71.84	11.87	6.02	3.82	3.20	3.24	96.08	2.96	0.66	0.10	0.08	0.12
	ρ=2	88.07	3.69	2.14	1.49	1.81	2.79	73.14	11.66	5.88	3.34	2.78	3.19	96.47	2.79	0.49	0.08	0.08	0.09
	ρ=4	91.33	2.08	1.45	1.48	1.38	2.27	79.80	8.07	3.97	3.08	2.21	2.86	97.94	1.44	0.38	0.09	0.08	0.07
n=200	ρ=.5	90.68	4.09	2.94	1.22	0.78	0.28	76.08	12.66	7.48	2.39	1.05	0.34	97.59	2.08	0.26	0.05	0.01	0.01
	ρ=1	88.15	3.89	2.29	1.89	1.83	1.94	72.43	11.91	6.75	3.89	2.65	2.37	97.66	2.08	0.18	0.05	0.02	0.01
	ρ=2	87.59	4.01	2.58	1.64	1.83	2.34	72.77	11.91	6.51	3.49	2.74	2.58	97.44	2.18	0.34	0.03	0.01	0.00
	ρ=4	92.49	2.26	1.41	1.07	1.31	1.45	81.29	8.07	3.87	2.67	2.03	2.07	98.80	0.99	0.16	0.03	0.01	0.01
n=300	ρ=.5	91.68	4.29	2.84	0.76	0.32	0.10	77.43	13.22	7.21	1.57	0.47	0.10	98.12	1.69	0.17	0.01	0.00	0.01
	ρ=1	88.53	3.74	2.27	2.02	1.60	1.83	72.79	11.94	6.35	4.12	2.45	2.35	98.10	1.74	0.15	0.01	0.00	0.00
	ρ=2	88.37	3.90	2.34	1.75	1.68	1.95	73.59	11.56	6.24	3.63	2.52	2.45	98.21	1.53	0.17	0.06	0.02	0.01
	ρ=4	92.83	1.83	1.35	1.15	1.34	1.49	82.29	7.16	3.98	2.63	2.03	1.91	99.19	0.71	0.09	0.00	0.01	0.00
n=500	ρ=.5	92.21	3.82	3.36	0.47	0.12	0.01	78.59	12.37	8.11	0.75	0.17	0.01	98.84	1.02	0.13	0.00	0.00	0.01
	ρ=1	88.45	3.55	2.46	1.79	1.89	1.85	73.06	11.73	5.99	3.98	2.83	2.40	98.75	1.15	0.08	0.02	0.00	0.00
	ρ=2	88.48	3.77	2.23	1.72	1.94	1.85	73.21	11.80	5.86	3.89	3.07	2.16	98.61	1.34	0.04	0.00	0.01	0.00
	ρ=4	93.15	1.87	1.56	1.06	1.01	1.34	83.53	6.72	3.80	2.39	1.93	1.63	99.35	0.54	0.10	0.01	0.00	0.00

Table 6.4 presents the power of the fitted spline models based on simulation from the 1 knot model with no censoring. The parameter values of γ_1 were specified as 0.007, 0.014, 0.028 and 0.056 for the shape parameters $\rho = 0.5, 1, 2$ and 4 respectively. For n=50, the power was 87%, 94%, 93% and 85% for the models with shape parameters 0.5, 1, 2 and 4 respectively. This power increased to about 97% for the model with $\rho = 0.5$ while decreased to about 70% for the model with $\rho = 4$ when n=500. There were no considerable change in power of the models when data were simulated from the 1 knot model with $\rho = 1$ and $\rho = 2$ in the larger sample size cases. Tables 6.5 and 6.6 show the results of 30% and 50% censoring respectively. These results are close to those obtained from the no censoring case. However, it can be noticed a small decrease in power when censoring ratios were increased to 30% and 50%. On the other hand, the power of the model with $\rho = 4$ increased with the increase of the censoring proportion for the sample of n=500. Generally, the model with $\rho = 4$ has the lowest power indicating that the models with higher number of knots were selected as the best models in some cases. This result means that the model robustness may be affected when shape parameter is higher than 2.

The power of the 1 knot model with no, 30% and 50% censoring ratios are compared for the model with different shape parameters and sample sizes from n=50 to n=500 in the figure below. In Figures 6.3(a), 6.3(b) and 6.3(c), it is shown that the power decreased as the censoring ratios increased from 0% (no censoring) to 50%. In contrast, Figure 6.3(d) shows increase in the power when censoring proportion increases to 50%. The reason for that is the tendency of the model to be significant as a higher number of knots are included when $\rho = 4$ and no censoring is used. When the censoring proportion increases, the model with lower number of knots tends to has higher power and then the power of the 1 knot model increased against the 2, 3, 4 and 5 knots models in the 30% and 50% cases.

Table 6.4: Empirical power of the Likelihood test at $\alpha = 0.05$ for spline models based on generated survival times from ***the 1-knot spline Weibull model*** with no censoring

Sample	Shape	-2LogL						AIC						BIC					
		0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
n=50	ρ=.5	4.98	86.67	8.13	0	0.06	0.16	4.6	86.89	8.27	0.02	0.1	0.12	5.23	87.03	7.71	0	0.02	0.02
	ρ=1	1.9	94.65	3.26	0.08	0.08	0.02	1.72	94.83	3.26	0.08	0.08	0.02	1.9	94.67	3.26	0.1	0.06	0
	ρ=2	3.46	93.57	2.66	0.3	0	0	3.24	93.79	2.66	0.3	0	0	3.48	93.57	2.64	0.3	0	0
	ρ=4	0.88	62.54	16.62	5.39	5.87	8.71	0.3	62.98	18.92	6.05	5.17	6.59	1.12	85.87	9.43	1.94	1	0.64
n=100	ρ=.5	3.62	94.99	1.38	0	0	0	3.54	95.08	1.38	0	0	0	3.72	95.04	1.24	0	0	0
	ρ=1	2.22	97.46	0.32	0	0	0	2.1	97.58	0.32	0	0	0	2.24	97.44	0.32	0	0	0
	ρ=2	3.9	95.96	0.14	0	0	0	3.8	96.06	0.14	0	0	0	3.96	95.9	0.14	0	0	0
	ρ=4	0	54.01	21.66	5.91	6.75	11.67	0	53.79	24.2	6.67	6.29	9.05	0.04	83.76	11.99	2.96	0.62	0.62
n=200	ρ=.5	2.98	96.94	0.08	0	0	0	2.88	97.04	0.08	0	0	0	3.1	96.82	0.08	0	0	0
	ρ=1	2.72	96.44	0.84	0	0	0	2.66	96.5	0.84	0	0	0	2.78	96.38	0.84	0	0	0
	ρ=2	4.9	95.1	0	0	0	0	4.78	95.22	0	0	0	0	4.96	95.04	0	0	0	0
	ρ=4	0	50.97	19.3	6.81	5.81	17.12	0	51.25	20.98	8.05	5.37	14.35	0	78.6	12.95	6.83	0.66	0.96
n=300	ρ=.5	2.72	97.28	0	0	0	0	2.66	97.34	0	0	0	0	2.78	97.22	0	0	0	0
	ρ=1	4.3	95.68	0.02	0	0	0	4.26	95.72	0.02	0	0	0	4.32	95.66	0.02	0	0	0
	ρ=2	5.37	94.63	0	0	0	0	5.33	94.67	0	0	0	0	5.43	94.57	0	0	0	0
	ρ=4	0	51.53	12.95	7.45	4.8	23.26	0	52.07	13.95	8.87	4.6	20.5	0	74.93	10.63	11.85	0.56	2.02
n=500	ρ=.5	2.34	97.66	0	0	0	0	2.32	97.68	0	0	0	0	2.36	97.64	0	0	0	0
	ρ=1	5.43	94.55	0.02	0	0	0	5.37	94.61	0.02	0	0	0	5.49	94.49	0.02	0	0	0
	ρ=2	7.23	92.77	0	0	0	0	7.11	92.89	0	0	0	0	7.45	92.55	0	0	0	0
	ρ=4	0	52.81	5.69	4	3.02	34.47	0	53.69	6.15	5.29	2.84	32.03	0	70.65	5.81	16.88	0.86	5.81

Table 6.5: Empirical power of the Likelihood test at $\alpha = 0.05$ for spline models based on generated survival times from ***the 1-knot spline Weibull model*** with 30% censoring

Sample	Shape	-2LogL						AIC						BIC					
		0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
n=50	ρ=.5	6.53	86.57	6.65	0.06	0.04	0.16	5.63	87.37	6.73	0.06	0.06	0.16	6.73	87.13	6.09	0	0.02	0.04
	ρ=1	3.12	93.71	3	0.12	0.04	0	2.7	94.11	3.02	0.12	0.04	0	3.14	93.83	2.88	0.1	0.04	0
	ρ=2	3.9	93.15	2.58	0.36	0	0	3.64	93.41	2.58	0.36	0	0	3.94	93.17	2.52	0.36	0	0
	ρ=4	2.64	64.16	14.13	5.17	5.31	8.59	0.68	65.33	16.76	5.55	4.84	6.85	3.56	86.11	7.33	0.94	0.88	1.18
n=100	ρ=.5	5.25	93.67	1.06	0.02	0	0	4.84	94.05	1.08	0.02	0	0	5.43	93.53	1.04	0	0	0
	ρ=1	4.38	95.4	0.22	0	0	0	4.16	95.62	0.22	0	0	0	4.44	95.36	0.2	0	0	0
	ρ=2	5.79	94.17	0.04	0	0	0	5.53	94.43	0.04	0	0	0	5.91	94.05	0.04	0	0	0
	ρ=4	0.04	61.16	17.52	6.31	5.95	9.03	0.02	61.02	19.98	6.83	5.17	6.99	0.08	88.25	8.79	2.08	0.44	0.36
n=200	ρ=.5	4.96	94.97	0.06	0	0	0	4.82	95.12	0.06	0	0	0	5.11	94.83	0.06	0	0	0
	ρ=1	4.3	94.97	0.72	0	0	0	4.1	95.18	0.72	0	0	0	4.5	94.77	0.72	0	0	0
	ρ=2	7.03	92.97	0	0	0	0	6.87	93.13	0	0	0	0	7.15	92.85	0	0	0	0
	ρ=4	0	56.2	17.22	7.97	5.41	13.21	0	56.82	18.34	8.85	4.86	11.13	0	84.72	9.39	5.11	0.38	0.4
n=300	ρ=.5	4.9	95.1	0	0	0	0	4.74	95.26	0	0	0	0	5.07	94.93	0	0	0	0
	ρ=1	7.23	92.77	0	0	0	0	6.97	93.03	0	0	0	0	7.43	92.57	0	0	0	0
	ρ=2	8.79	91.21	0	0	0	0	8.57	91.43	0	0	0	0	9.01	90.99	0	0	0	0
	ρ=4	0	55.24	14.35	8.45	5.03	16.94	0	56.16	15.42	9.73	4.4	14.29	0	81.46	8.69	8.55	0.4	0.9
n=500	ρ=.5	4.06	95.94	0	0	0	0	3.96	96.04	0	0	0	0	4.16	95.84	0	0	0	0
	ρ=1	8.67	91.33	0	0	0	0	8.63	91.37	0	0	0	0	8.75	91.25	0	0	0	0
	ρ=2	11.11	88.89	0	0	0	0	11.03	88.97	0	0	0	0	11.25	88.75	0	0	0	0
	ρ=4	0	55.24	6.77	8.17	3.48	26.35	0	56.1	7.21	9.99	3.2	23.5	0	75.86	5.11	16.06	0.62	2.36

Table 6.6: Empirical power of the Likelihood test at $\alpha = 0.05$ for spline models based on generated survival times from ***the 1-knot spline Weibull model*** with 50% censoring

Sample	Shape	-2LogL						AIC						BIC					
		0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
n=50	ρ=.5	6.45	87.25	6.09	0.02	0.1	0.1	5.33	88.23	6.21	0.04	0.08	0.12	6.67	88.25	5.03	0.02	0.02	0.02
	ρ=1	4.28	93.11	2.4	0.1	0.08	0.02	3.64	93.75	2.4	0.1	0.08	0.02	4.28	93.21	2.32	0.1	0.08	0
	ρ=2	6.27	91.63	1.92	0.18	0	0	5.57	92.31	1.94	0.18	0	0	6.31	91.65	1.86	0.18	0	0
	ρ=4	6.07	60.4	10.45	4.16	5.91	13.01	1.92	63.8	12.71	4.94	5.21	11.41	8.53	79.86	5.23	1.2	1.46	3.72
n=100	ρ=.5	7.89	91.27	0.84	0	0	0	7.23	91.91	0.86	0	0	0	8.17	91.05	0.78	0	0	0
	ρ=1	5.09	94.61	0.3	0	0	0	4.76	94.93	0.3	0	0	0	5.29	94.41	0.3	0	0	0
	ρ=2	6.79	93.17	0.04	0	0	0	6.57	93.39	0.04	0	0	0	6.93	93.03	0.04	0	0	0
	ρ=4	0.2	66.81	14.01	5.27	5.13	8.59	0.04	67.11	15.72	5.85	4.7	6.59	0.66	90.69	6.49	1.12	0.64	0.4
n=200	ρ=.5	7.29	92.69	0.02	0	0	0	6.85	93.13	0.02	0	0	0	7.59	92.39	0.02	0	0	0
	ρ=1	5.93	93.33	0.74	0	0	0	5.63	93.63	0.74	0	0	0	6.17	93.09	0.74	0	0	0
	ρ=2	8.51	91.49	0	0	0	0	8.27	91.73	0	0	0	0	8.67	91.33	0	0	0	0
	ρ=4	0	62.28	12.93	7.77	5.79	11.23	0	62.64	14.51	9.19	5.15	8.51	0.02	89.27	6.41	3.64	0.32	0.34
n=300	ρ=.5	6.75	93.25	0	0	0	0	6.51	93.49	0	0	0	0	6.95	93.05	0	0	0	0
	ρ=1	8.51	91.49	0	0	0	0	8.33	91.67	0	0	0	0	8.87	91.13	0	0	0	0
	ρ=2	10.57	89.43	0	0	0	0	10.29	89.71	0	0	0	0	10.81	89.19	0	0	0	0
	ρ=4	0	59.84	9.93	9.75	5.35	15.14	0	60.6	10.87	10.99	4.92	12.61	0	85.85	5.89	7.47	0.48	0.32
n=500	ρ=.5	4.68	95.32	0	0	0	0	4.52	95.48	0	0	0	0	4.82	95.18	0	0	0	0
	ρ=1	9.69	90.31	0	0	0	0	9.55	90.45	0	0	0	0	10.07	89.93	0	0	0	0
	ρ=2	13.63	86.37	0	0	0	0	13.53	86.47	0	0	0	0	13.89	86.11	0	0	0	0
	ρ=4	0	57.3	4.58	10.49	4.72	22.9	0	58.26	4.86	12.47	4.46	19.94	0	80.14	3.08	15.14	0.6	1.04

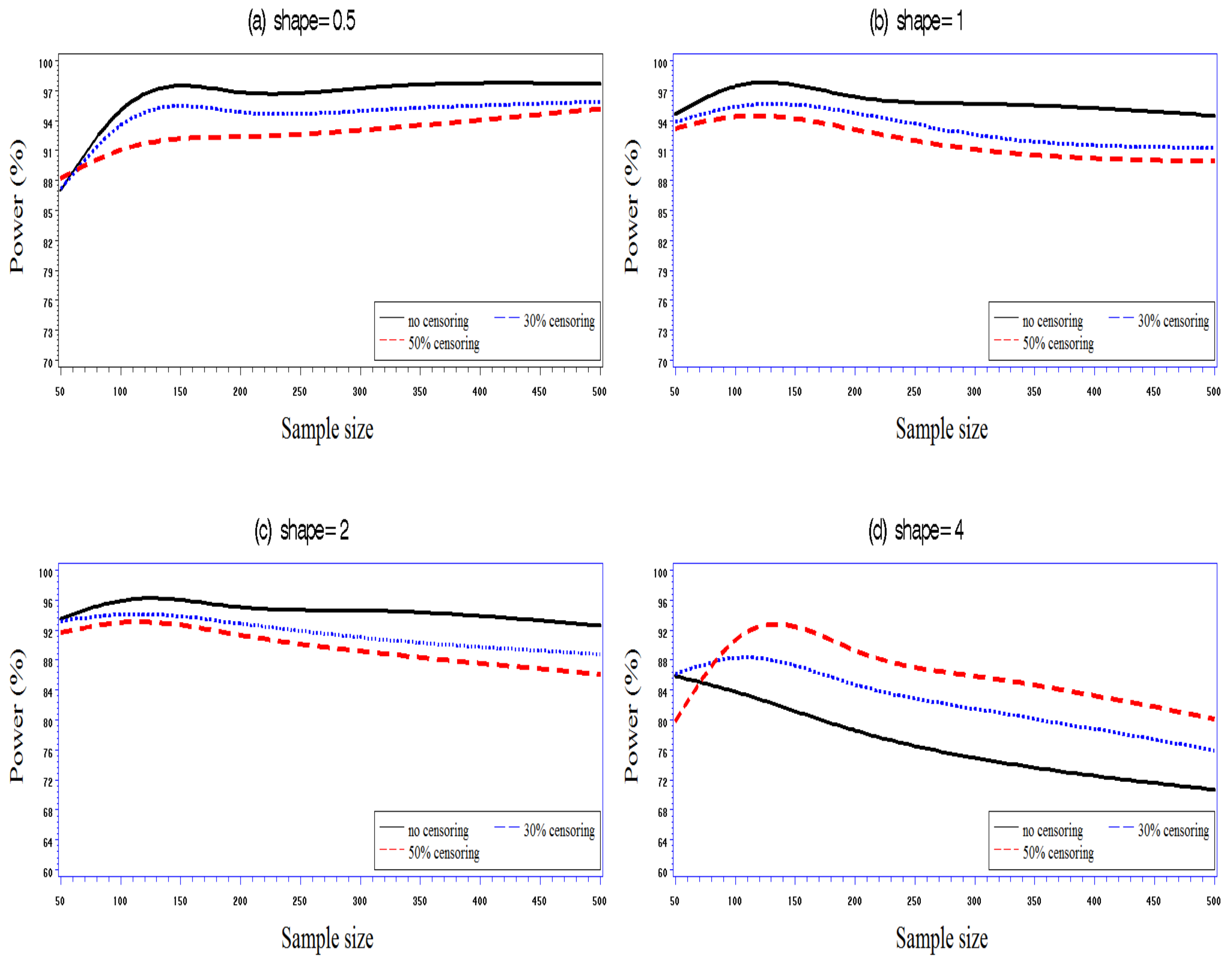

Figure 6.3: Empirical power of the Likelihood test at $\alpha = 0.05$ for the 1-knot spline model based on generated survival times from the same model using $\rho = 0.5$, $\rho = 1$, $\rho = 2$ and $\rho = 4$ with no, 30% and 50% censoring.

6.4 Concluding remarks

In this chapter, it was discussed how to select feasible spline parameters that ensure the cumulative hazard function to be increasing with time when simulation is done from one of the spline models. To simulate data from the Weibull spline models, analytical inversion is not available and then it was suggested rejection sampling method as a first choice. However, some difficulties were found in applying this method to generate survival times from spline models. Consequently, a numerical method was suggested as a possibly more efficient alternative. This method depends on assuming Weibull shape and scale parameters in addition to feasible spline parameters that yield correct cumulative hazard function (i.e., monotone increasing). Furthermore, a number of knots is assumed at ceratin positions to simulate the desired model. However, assuming these positions may be an issue when the produced knots positions (i.e., based on generated data) are very different from the assumed positions. This may lead to confusing results. For example, when spline model with $\rho = 4$ is simulated based on 1 knot at the median of survival times, the generated data at each replication may have completely different median from the assumed value. In this case, the produced data may lead to select another spline model as the best one. Hence, doubts about the robustness of the spline models, particularly for models with shape parameters that are greater than 2, may be found.

Generally, it was found that simulation of the Weibull spline models may be slightly affected by factors as censoring ratio, sample size and shape parameters. It was noticed that increasing the censoring proportion may lead to select a lower degree model as the best choice based on the BIC. Also, the shape parameter may be a factor in selecting the best spline model. The suggested numerical method yielded reasonable results and had a higher efficiency compared to the rejection sampling method. In chapter seven, the suggested method will be used to generate survival data from the Weibull spline models with 1, 2 and 3 knots based on the two real data sets that have supplied in chapters four and five in order to evaluate the Weibull spline model in different situations in survival data modelling.

Chapter 7

Simulation results

The first aim of this chapter is to simulate the Weibull spline model when no time-dependent covariates are included in the model. This simulation helps to evaluate the competitive models when their performance measures are compared. The second aim is to simulate the Weibull standard model to compare the Weibull model with the Cox and the log-logistic models with time-dependent covariates. Thirdly, the Weibull spline model with time-dependent covariates is simulated to investigate the properties of estimators in the Weibull spline models when one or more covariates change over time.

Simulation procedures in this chapter are based on the two real data sets of heart and cornea transplantation. Then specifications of parameter values and dependence relationships of the covariates will be employed to mimic the real data on hand. Right censoring data will be generated following the method that was described in section 2.5. Further, survival times will be generated from the Weibull spline models with fixed covariates using the numerical method that was described in chapter 6. Survival times in the standard Weibull model with time-dependent covariates will be generated using an algorithm that depends on generating survival times conditional on the updated values of such covariates. A combination of the numerical method and the time-dependent model algorithm will be used to generate survival times from the Weibull spline model that allows for covariates to change over time. The survival data sets help to specify the scenarios that are adopted to investigate the performance of the alternative models in different situations. For example, in the heart transplant data set the number of patients was about 1500 with 70% right censoring, so that the scenarios that mimic theses specifications will combine between samples of n = 500, 1000 and 1500 observations with 60%, 70% and 80% censoring. Output from the fitted models includes bias percentages, mean square error, empirical power, coverage probabilities and average confidence interval length for likelihood-based parameter estimates.

Section 7.1 will include simulations of the Weibull spline model based on the heart transplant data when all covariates are fixed and then the results that help to compare properties of tests and estimators within the spline models are presented. In section 7.2, simulation of the Weibull model will be performed when the time-dependent GFR in heart model and the time-dependent SECOND in the cornea model are included. Then the results of fitting the Cox, Weibull and the log-logistic models will help to compare such models. Finally, section 7.3 will include simulations of the Weibull spline models with 0, 1, 2 and 3 knots when the previous time-dependent covariates are included in the model. The results of these simulations will be presented in the case where time-dependent covariates are present.

7.1 Simulation of Weibull spline models with fixed covariates

The flexibility of the Weibull spline model depends on the number of knots in the model. In this section, simulation of the spline models when all covariates are held fixed will be discussed. This simulation is based on the heart and cornea transplant data.

7.1.1 Model based on the heart transplant data

In the heart transplant data, seven important covariates were found. DAGE was the only continuous covariate while the other covariates, DCMV, PCD, CYCLO, FK506 and OTHER were treated as categorical. The kidney function, GFR, was treated as continuous and as categorical to investigate the optimal form to measure its effect on survival time of patients after heart transplantation. In this data set, about 70% of the patients are right censored so that censoring data have to be generated to mimic this specification.

7.1.1.1 Covariate generation

A multivariate log normal distribution, as described in section 2.4.1, was applied to generate correlated covariates. Based on the real data, the explanatory covariates are divided into 3 groups: donor covariates, recipient covariates and immunosuppressant covariates.

7.1.1.1.1 Donor covariates A multivariate log normal distribution was used to generate values of DAGE and DCMV with correlation matrix

$$\begin{pmatrix} 1 & 0.0868 \\ 0.0868 & 1 \end{pmatrix}.$$

The generated values of DCMV were categorised based on the proportion of each category in the original data and using (7.1) as

$$CrV(\mu, \sigma, p_i) = \exp\{\mu + \sigma.NORMINV(p_i)\}, \tag{7.1}$$

where μ and σ are the mean and the standard deviation that have been used to generate the covariate while $NORMINV(p_i)$ is the inverse normal probability for the proportion p_i (see 2.4.1). In the original data, $\mu = 35.38$, $\sigma = 12.27$ for DAGE and $\mu = 1.45$, $\sigma = 0.52$ with $p_i = 56\%, 43\%$ and 1% for DCMV.

7.1.1.1.2 Recipient covariates Similarly PCD and GFR were generated from a multivariate log normal distribution with correlation matrix

$$\begin{pmatrix} 1 & 0.0821 \\ 0.0821 & 1 \end{pmatrix}.$$

Using (7.1), PCD is categorised to PCD1, PCD2, PCD3 and PCD4 while the categorical form of GFR was transformed to GFR1, GFR2, GFR3 and GFR4. The measures of PCD were $\mu = 2.45$, $\sigma = 1.23$ with $p_i = 36\%, 10\%$, 26% and 28%, while for GFR were $\mu = 64.18$, $\sigma = 20.67$ with $p_i = 9\%, 45\%$, 43% and 3%.

7.1.1.1.3 Immunosuppressant covariates The three immunosuppressant covariates, CYCLO, FK506 and OTHER were generated using a multivariate log normal distribution with correlation matrix

$$\begin{pmatrix} 1 & -0.4682 & -0.0236 \\ -0.4682 & 1 & -0.0067 \\ -0.0236 & -0.0067 & 1 \end{pmatrix}.$$

The three covariates are binary so their generated values were categorised to two levels based on the proportion in each level using (7.1). The measures of CYCLO were $\mu = 1.93$, $\sigma = 0.25$ with $p_i = 7\%$ and 93%, for FK506 were $\mu = 1.05$, $\sigma = 0.21$ with $p_i = 95\%$ and 5% and for OTHER were $\mu = 1.25$, $\sigma = 0.43$ with $p_i = 75\%$ and 25%.

7.1.1.1.4 Censoring data The censoring data were generated using an algorithm that enables different censoring proportions in order to reflect different simulation scenarios as follows

1. Generate survival times C from an exponential model that represents the censoring mechanism.
2. Generate survival times T from a Weibull model depending on the set of covariates that have a specific relationship with survival times.
3. If T$\leq$C then censor=1 (event), otherwise censor=0 (censoring).
4. Different censoring proportions can be produced by changing the specified scale parameter of the exponential model (censoring distribution).

In heart transplant data, the censoring proportion was 70% so the simulation of this model was performed with censoring proportions 60%, 70% and 80% to mimic the heart transplant data characteristics.

7.1.1.2 Survival time generation

7.1.1.2.1 Weibull AFT model The heart transplant data were modelled using Weibull and Weibull spline models. For each simulated model, 9 scenarios were adopted using sample sizes of 500, 1000 and 1500 patients with 60%, 70% and 80% censoring proportions. The standard Weibull model was simulated including its significant covariates. Based on this model, survival times were generated as follows.

1. Specify the parameter function α_i for the covariates that were included in the model and using the parameters that have been obtained from the heart model.

$$\alpha_i = \exp(\theta + \beta' x_i).$$

2. generating survival times T_i for the *ith* subject using (6.1) as

$$T_i = [-\log(U)]^{1/\rho} [\alpha_i]$$

7.1.1.2.2 Weibull spline models The Weibull spline models with 1, 2 and 3 knots were simulated including the generated covariates as with the standard model. The Weibull spline model with 1 knot was simulated using the numerical algorithm as described in section 6.2.2.

1. According to the minimum and the maximum survival times in the heart transplant data, assume that the generated uncensored survival times between 1 day and 5000 days.

2. Select the values of κ_{min}, κ_1 and κ_{max} at the minimum, median and the maximum of the log uncensored survival times of the heart transplant data set.

3. Calculate λ_1 as $\lambda_1 = \frac{\kappa_{max}-\kappa_1}{\kappa_{max}-\kappa_{min}}$.

4. Assume the Weibull scale, shape and Weibull spline (1 knot) parameters θ, ρ and γ_1 respectively based on the obtained estimates of these parameter from the estimated 1 knot model in chapter four. The values of these parameters were $\theta = 8.335$, $\rho = 0.405$ in addition to $\gamma_1 = -0.006$ which is a feasible parameter in accordance with the specification that was explained in section 6.1.

5. Calculate the log cumulative hazard function including the covariates using the generated t values as

$$\begin{aligned}\log H(t) &= \rho(-\theta - \beta' x) + \rho \log t + \gamma_1 \Big[(\log t - \kappa_1)^3_+ - \lambda_1(\log t - \kappa_{min})^3_+ \\ &\quad -(1-\lambda_1)(\log t - \kappa_{max})^3_+\Big], \end{aligned} \tag{7.2}$$

6. From the relationship between the cumulative hazard and the survivor functions, calculate the survival probabilities for the generated t values using (6.3) as

$$S(t) = \exp\{-\exp[\log H(t)]\}.$$

7. Select the survivor probabilities S_1, S_2 and S_3 where $S_1 = S(e^{\kappa_{min}})$, $S_2 = S(e^{\kappa_1})$ and $S_3 = S(e^{\kappa_{max}})$.

8. Determine the function that can be inverted to generate the survival time t depending on the time interval. For the first interval $\kappa_{min} \le \log t < \kappa_1$, the function is defined as

$$\log H(t) = \rho(-\theta - \beta' x) + \rho \log t + \gamma_1 \left[-\lambda_1(\log t - \kappa_{min})^3_+\right],$$

where $\log H(t) = \log\{-\log S(t)\}$ and $\kappa_{min} = \log 1 = 0$, the function becomes

$$\log\{-\log S(t)\} = \rho(-\theta - \beta' x) + \rho \log t - \gamma_1 \lambda_1 (\log t)^3. \tag{7.3}$$

For the second interval $\kappa_1 \le \log t \le \kappa_{max}$, the function is defined as

$$\log H(t) = \rho(-\theta - \beta' x) + \rho \log t + \gamma_1 \left[(\log t - \kappa_1)^3_+ - \lambda_1(\log t - \kappa_{min})^3_+\right], \tag{7.4}$$

where $\log H(t) = \log\{-\log S(t)\}$ and $\kappa_{min} = \log 1 = 0$, the function becomes

$$\log\{-\log S(t)\} = \rho(-\theta - \beta' x) + \rho \log t + \gamma_1 \left[(\log t - \kappa_1)^3_+ - \lambda_1(\log t - \kappa_{min})^3_+\right]. \tag{7.5}$$

Hence,

$$\log\{-\log S(t)\} = \rho(-\theta-\beta' x)+\gamma_1(1-\lambda_1)(\log t)^3-3\gamma_1\kappa_1(\log t)^2+(3\gamma_1\kappa_1^2+\rho)(\log t)-\gamma_1\kappa_1^3 \tag{7.6}$$

9. Generate $S^*(t)$ from $U \sim [0,1]$. If $S_1 \le S^*(t) < S_2$, generate the survival times from the inversion of (7.3). Otherwise, if $S_2 \le S^*(t) \le S_3$, generate the survival times from the inversion of (7.6).

10. Check each generated time to ensure that the inversion provides the right value based on the time intervals in 8.

7.1.1.3 Heart simulation results

The heart transplant data were simulated using the covariates DAGE, DCMV1, DCMV2, PCD1, PCD2, PCD3, CYCLO, FK506, OTHER and GFR as a continuous and a categorical fixed covariate. These simulations have been done from the Weibull spline models with 0, 1, 2 and 3 knots where 60%, 70% and 80% censoring proportions were used with 10000 replications. For each simulation, four measures were calculated: bias percentage, mean square error (MSE), empirical power and average confidence interval length. These measures were calculated for each covariate at 5% significance level in each model to investigate the properties of the obtained estimators based on the different methods. The simulation of data from heart model was executed firstly when GFR is treated as a continuous covariate and secondly when GFR is treated as a categorical covariate.

The empirical power of the Wald test was calculated for each covariate across the different models. In the two cases (continuous and categorical GFR), results of the two covariates DCMV and PCD were neglected because it is not relevant to evaluate the power of their test. In the results of chapter four, the covariates that represent the DCMV and the PCD categories were found non-significant at 5% significance level and then the empirical power of their test was not considered. Hence, the results will be presented for the other covariates focusing on empirical power, bias percentages, MSE and average confidence interval length for these covariates, particularly in the 70% censoring case which reflects the censoring proportion in the real data on hand.

7.1.2 Simulation results of heart model with GFR as a continuous covariate

Table 7.1 presents the powers of covariate tests when data were generated from the Weibull model with samples of $n = 500$, 1000 and 1500 observations and 70% censoring. For DAGE, the power was 79% in the 0 knots model while it was slightly lower in the other spline models (with 1 to 5 knots) when $n = 500$. The power of this covariate increased to about 97% when $n = 1000$ and about 99% when $n = 1500$ with no noticeable difference in power among all the models. For CYCLO, the power was about 98% when $n = 500$ and increased to 100% when $n = 1500$. There was no difference among the six models in the power of CYCLO. FK506 has given very close results to those obtained for CYCLO. However, the power of OTHER was slightly low compared to CYCLO and FK506 when $n = 500$. These results mean that the null hypothesis of no effect for those covariates was not rejected at the 5% significance level in about 40% and 21% of the small simulated samples ($n = 500$) for the two covariates respectively while their power increased as the sample size increases to 1000 and 1500. For the GFR, the power was about 40% in the 0 knots model when $n = 500$ and increased to about 83% when $n = 1500$. For the same covariate in the other knots models, the power was slightly lower comparing to the 0 knots model. However, the powers in the models with 3, 4 and knots were close to those obtained in the 0 knots model. When the model was simulated with 60% and 80% censoring, it was noticed that the power for each covariate decreased as the censoring proportion increased.

Table 7.1: The empirical power at α=0.05 in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	79.79	69.85	71.69	73.61	73.86	72.83
CYCLO	98.88	99.29	99.45	94.93	99.48	99.05
FK506	99.65	99.57	99.63	99.44	99.53	99.08
OTHER	60.77	49.48	49.18	54.07	53.17	50.87
GFR	40.92	35.65	34.54	36.01	36.32	36.20
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	97.67	94.42	94.87	95.58	95.80	95.34
CYCLO	99.99	100.00	100.00	98.70	100.00	99.72
FK506	100.00	100.00	100.00	100.00	100.00	99.72
OTHER	89.16	81.46	79.26	83.66	83.36	81.86
GFR	66.34	58.87	56.95	58.46	60.00	59.15
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	99.92	99.18	99.32	99.47	99.58	99.44
CYCLO	100.00	100.00	100.00	99.45	100.00	99.85
FK506	100.00	100.00	100.00	100.00	100.00	99.83
OTHER	98.15	94.15	93.35	95.65	95.35	94.75
GFR	83.23	76.69	74.68	76.15	77.86	77.04

In Tables 7.2, 7.3 and 7.4, the power of tests for the same covariates are presented based on generated data from the 1, 2 and 3 knot models with 70% censoring. The results in these three tables are very close to those obtained from the simulated 0 knots model. However, the powers of the tests for CYCLO and FK506 in the fitted 3 knot model were slightly lower than those obtained in the other spline models in the three tables when $n = 500$. The power of all covariate tests was calculated when the the three spline models were simulated based on 60% and 80% censoring proportions. It was found that the power decreased as the censoring proportion increased. In general, the powers of covariate tests were similar to the results based on simulating from the four models, while slight changes in power were noticed when censoring proportion changed from 70% to 60% and 80% as previously explained. The power for some covariates was low, as DAGE, OTHER and GFR, particularly when $n = 500$ which indicates to have low effect on survival times comparing to CYCLO and FK506. To compare the six models, it was found that the power of all covariate tests in the 0 knots model were slightly higher than those calculated in the other spline models.

Figure 7.1 shows the power for GFR in the Weibull and the 5-knot spline models when simulations were performed from the 0, 1, 2 and the 3 knots models in Figures 7.1(a), 7.1(b), 7.1(c) and 7.1(d) respectively. Figure 7.1(a) shows that the power in the 0 knots model was about 35% when $n = 500$ and increased to about 72% when $n = 1500$, while the power in

Table 7.2: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	77.90	65.21	64.91	64.17	65.30	65.67
CYCLO	94.96	96.73	97.36	89.53	97.77	97.69
FK506	63.87	65.07	65.37	55.07	65.27	63.87
OTHER	45.98	53.07	51.87	42.08	47.88	46.68
GFR	36.82	31.80	30.17	30.32	30.79	30.96
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	96.85	91.40	90.92	90.43	91.15	91.39
CYCLO	99.83	99.94	99.97	98.52	99.97	99.90
FK506	99.65	90.25	90.05	78.86	89.46	88.36
OTHER	71.36	80.06	70.76	72.86	74.86	74.16
GFR	59.37	53.71	50.80	51.03	52.14	52.43
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	99.62	98.28	98.06	97.66	98.12	98.18
CYCLO	99.99	99.99	100.00	98.68	100.00	99.94
FK506	99.95	98.45	97.95	92.15	98.05	97.45
OTHER	84.86	93.25	85.26	86.56	88.66	88.26
GFR	73.35	68.00	64.91	64.99	65.91	66.27

the 5 knots model was lower by about 5% when $n = 500$ to 1500 compared to the 0 knots model. The results in the other three figures when the 1, 2 and the 3 knots were simulated were very close to the results of the simulated 0 knots model in Figure 7.1(a).

In order to evaluate the Weibull spline models with 1 to 5 knots against the standard model (0 knots), the results of bias percentages of parameter estimates are presented in Tables C.1, C.2, C.3 and C.4 when simulations were done from the 0, 1, 2 and 3 knot models respectively with 70% censoring. Through the four tables, it was found that the bias percentages were lower in the spline models with 1 to 5 knots compared to the 0 knot model. The MSE of parameter estimates are presented in tables C.5, C.6, C.7 and C.8 when simulations were done from the 0, 1, 2 and the 3 knot models with 70% censoring respectively. In the four tables, it was found that the MSE in the spline models with 1 to 5 knot were lower than those calculated in the 0 knot model. These results reflect higher accuracy for parameter estimates in the spline models comparing to the 0 knots model. The average confidence interval length of parameter estimates were calculated from the simulated 0, 1, 2 and the 3 knot models in Tables C. 9, C.10, C.11 and C.12 with 70% censoring respectively. The results in the four tables show very close average confidence interval lengths among the six models for all parameters indicating that there is no difference among the average confidence interval lengths of the fitted models based across the different simulations.

In conclusion, the empirical power of the covariate tests was slightly higher in the 0 knot model. Using the criteria of the bias percentage and the MSE, the parameter estimates in the fitted spline models (1 to 5 knot) are less biased and have smaller MSE compared to the parameter estimates in the fitted 0 knot model. The AIC criterion was calculated for each fitted model within the four simulation cases with 70% censoring over the 10000 replications. In the simulation of the 0 knot model, the 5 knot model had the lowest AIC value in 38%,

Table 7.3: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	81.97	67.49	69.86	68.16	69.28	69.28
CYCLO	96.23	97.20	97.77	89.32	98.24	98.11
FK506	95.75	62.67	73.66	62.97	67.17	67.37
OTHER	48.48	47.58	38.38	39.48	41.68	40.58
GFR	38.36	32.46	31.54	31.09	31.81	31.98
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	98.23	92.86	93.95	92.51	93.61	93.63
CYCLO	99.92	99.93	99.96	98.72	99.97	99.90
FK506	99.95	89.46	92.85	85.86	90.35	89.86
OTHER	74.16	76.66	68.27	69.47	71.36	71.06
GFR	60.92	53.42	51.85	51.27	52.45	52.63
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	99.87	98.76	98.94	98.67	98.90	98.90
CYCLO	100.00	100.00	100.00	91.1	100.00	99.93
FK506	99.95	97.75	98.85	95.05	97.85	97.85
OTHER	89.76	91.25	84.16	85.76	87.26	86.36
GFR	77.50	69.73	67.97	67.07	68.52	68.84

76% and 91% of the replications when $n = 500$, 1000 and 1500 respectively. When simulation was done from the 1 knot model, the 3 knot model had the lowest AIC value in 78%, 75% and 67% of the replications with $n = 500$, 1000 and 1500 respectively. A close results to those obtained in the simulation of the 1 knot model have been found when simulations were done from the 2 and 3 knot models. Although, the model with lower AIC value may be preferred, this criterion should not be used regardless of other criteria (Royston and Parmar, 2002). The models with lower number of knots are not generally nested within those with higher knots number and then outcomes of statistical inferences should be considered in this case. Also, it was noticed that the obtained test power from the fitted spline model when simulation was done from the same model was slightly lower than that obtained form the Weibull model as in Tables 7.2, 7.3 and 7.4, particularly for sample sizes of $n = 500$. This may occur as a result of the mismatching that sometimes found between the assumed and the real locations of the knots while the data are generating from one of the spline models.

7.1.3 Simulation results of heart model with GFR as a categorical covariate

In this section data were generated from the heart model including all the previous covariates and the covariates GFR1, GFR2 and GFR3. Table 7.5 presents the empirical powers for the three covariate tests based on simulation from the Weibull model with 70% censoring. In the sample of $n = 500$, the powers for GFR1, GFR2 and GFR3 in the 0 knots model were 16%, 29% and 18% respectively, and very close power results were obtained in the fitted spline models at the same sample size. In the simulations with sample of $n = 1000$ and

Table 7.4: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	74.68	57.51	60.95	59.96	60.41	60.15
CYCLO	94.85	96.49	97.32	82.53	97.20	97.31
FK506	97.45	69.77	83.96	75.46	73.96	75.56
OTHER	51.67	46.78	37.28	38.98	41.88	39.88
GFR	35.07	28.80	28.16	27.95	28.80	28.62
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	95.55	86.15	87.91	86.99	87.86	87.45
CYCLO	99.81	99.92	99.95	92.34	99.94	99.95
FK506	99.95	93.45	98.05	95.55	94.95	95.55
OTHER	77.76	73.26	61.37	63.87	67.07	64.87
GFR	56.52	46.75	45.71	45.04	46.77	46.40
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	99.34	96.61	97.20	96.56	97.09	97.03
CYCLO	100.00	100.00	100.00	97.2	100.00	100.00
FK506	99.02	82.65	96.24	87.61	90.02	91.47
OTHER	99.95	99.05	99.75	99.55	99.25	99.35
GFR	91.55	90.35	81.56	84.06	85.56	83.66

1500, there was no noticeable increase in the power with no difference among the models comparing to the results when $n = 500$. The powers for the the three covariate tests was generally low reflecting the low effect of the three covariates when they included in the heart model instead of using GFR as a continuous covariate. As in the previous cases, the powers were determined when simulation was done based on 60% and 80% censoring proportions. The power increases as the censoring proportion decreases as shown in the previous result.

To investigate the effect when data were generated from the spline models, Tables 7.6, 7.7 and 7.8 present the powers for the three covariate tests when simulations were done from the 1, 2 and 3 knot models with 70% censoring. The powers across the fitted models were low as in the previous case for the same reason. Also, the results in the three tables show that the powers in the fitted Weibull model (0 knot) was slightly higher than in the fitted spline models with 1 to 5 knots. This result means that the algorithm fails to generate from the correct model in some simulated samples where knot locations are specified very far from the correct places. As in the 0 knot model, simulations of the three spline models with 60% censoring proportion conducted general increase in the powers of all covariate tests by about 10%.

Figure 7.2 compares the power for GFR1 between the fitted Weibull (0 knot) model and the 5 knot model when simulation was done from the 0 knot model in Figure 7.2(a), 1 knot model in Figure 7.2(b), 2 knot model in Figure 7.2(c) and 3 knot model in Figure 7.2(d). In the four figures, the power for GFR1 in the 0 knot model was about 20% when $n = 500$ and increased to about 57% when $n = 1500$. In Figure 7.2(a), there was no difference between the powers in the two models. However, in Figures 7.2(b), 7.2(c) and 7.2(d), the power in the 0 knot model was higher by about 7% across the different samples.

Figure 7.3 compares the power for GFR2 between the fitted 0 and 5 knot models when

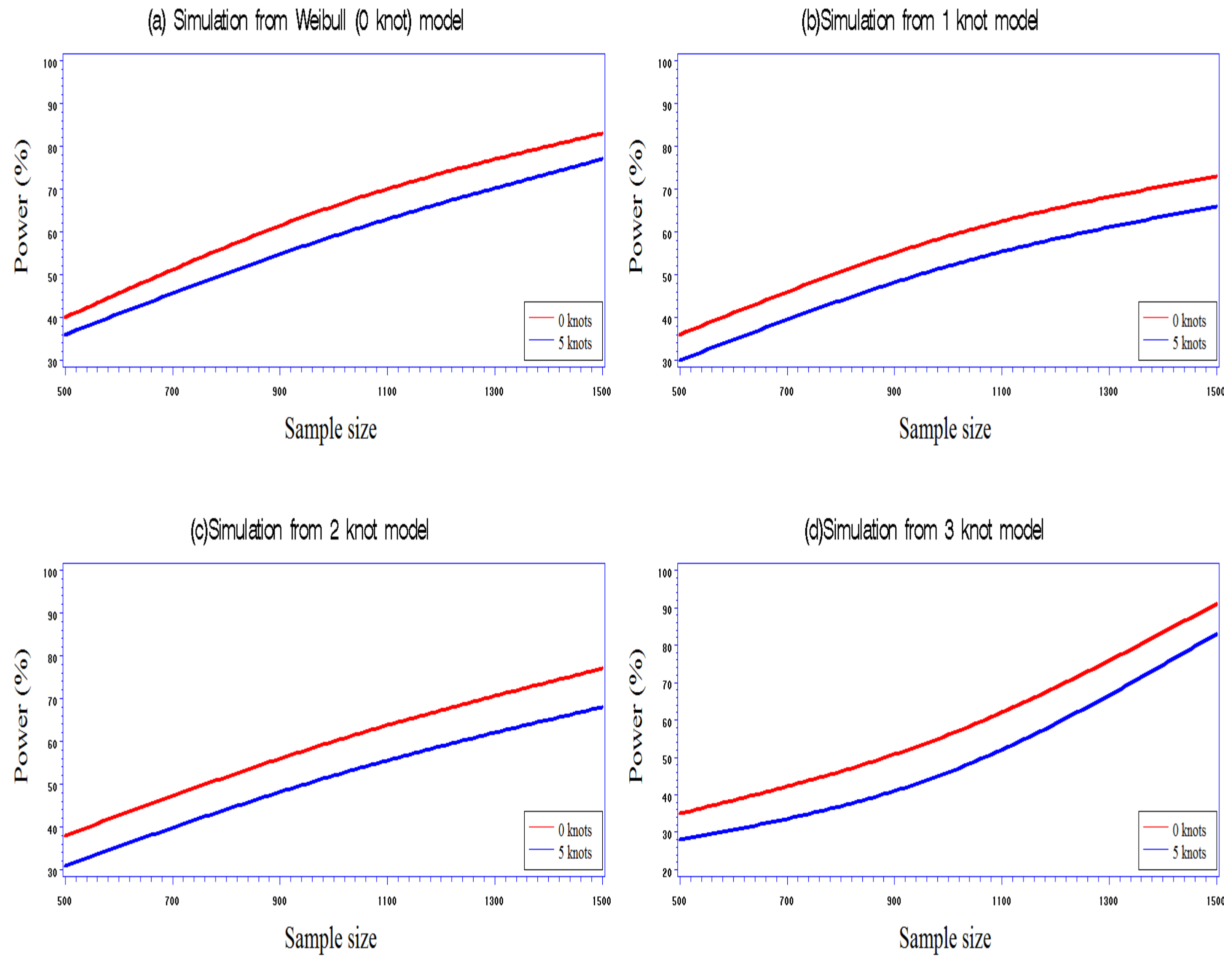

Figure 7.1: Power of GFR test in the fitted Weibull (0 knot) and the 5-knot models based on simulations from the Weibull (0 knot), 1, 2 and 3 knot models with 70% censoring.

simulations were done from the 0, 1, 2 and the 3 knot models in Figures 7.3(a), 7.3(b), 7.3(c) and 7.3(d) respectively. The powers for this covariate tests in the fitted 0 knot model started at about 30% when $n = 500$ and increased to about 85% when $n = 1500$. There was no difference between the power in the two models in Figure 7.3(a), while the power in the fitted 0 knot model was higher than that obtained in the fitted 5 knot model as shown in the other three figures.

Figure 7.4 shows the powers of for GFR3 tests in the same previous cases. The results that are shown in Figures of 7.4(a), 7.4(b), 7.4(c) and 7.4(d) were very close to those shown in Figures of 7.2.

In the 70% censoring case, the bias percentage of parameter estimates through simulations from the four models (0, 1, 2, and 3 knots) are presented in Tables C13, C14, C15 and C16. The bias percentages across the fitted spline models from 1 to 5 knot were considerably less than those calculated in the 0 knot model. The same result has been found in the four simulated models. Tables C17, C18, C19 and C20 present the MSE for parameter estimates that have been calculated when the model with 0, 1, 2 and 3 knot were simulated. The MSE of all parameter estimates in the spline models with 1 to 5 models were noticeably smaller than that obtained in the 0 knots model in the samples of $n = 500$, 1000 and 1500 . Also, the lowest MSE in the spline models have been found for all the simulated models.

Table 7.5: The empirical power at α=0.05 in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
	$n = 500$					
GFR1	16.59	13.03	18.41	18.31	19.46	19.54
GFR2	29.54	21.74	31.21	30.50	31.69	31.97
GFR3	18.11	13.11	20.22	19.66	20.92	21.30
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	39.71	29.86	42.77	38.99	39.37	40.35
GFR2	63.71	52.80	65.11	62.65	62.63	63.63
GFR3	46.34	35.07	49.06	45.64	46.06	46.90
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	58.83	47.07	62.18	58.15	58.44	59.41
GFR2	83.96	74.90	84.59	82.96	82.93	83.83
GFR3	67.31	54.09	69.98	66.46	66.62	67.66

Table 7.6: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
	$n = 500$					
GFR1	19.25	10.35	13.28	12.14	12.66	12.56
GFR2	31.32	17.10	20.99	19.76	20.39	20.20
GFR3	20.94	9.86	13.32	12.06	12.57	12.39
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	40.86	23.83	29.63	27.57	28.22	27.98
GFR2	63.43	42.72	49.30	47.49	47.95	47.87
GFR3	46.56	26.78	33.75	31.63	32.25	32.08
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	57.84	36.86	43.95	41.58	42.22	42.09
GFR2	81.49	63.53	69.24	67.85	68.09	68.04
GFR3	64.73	42.77	50.45	47.94	48.63	48.50

Tables C21, C22, C23 and C24 present the average confidence interval length of the parameter estimates when simulations were performed based on models with 0,1,2 and 3 knot and 70% censoring respectively. The results through the four tables show small differences for the average confidence interval lengths for all parameter estimates among the six fitted models with all the samples size. This means that this criterion is not very helpful in this case to compare the fitted models.

In general, to compare the 0 knots model with the other spline models, it was found that the power in the fitted 0 knot model is slightly higher than the other models. On the other hand, the percentage bias and the MSE results refer to the possibility of the spline models to yield less biased parameter estimates with more accuracy comparing to the 0 knot model.

Table 7.7: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	21.31	11.69	15.88	14.28	15.15	14.87
GFR2	36.85	20.78	27.22	24.76	25.99	25.72
GFR3	25.54	12.41	18.49	15.99	17.30	16.97
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	47.90	28.75	38.13	34.72	35.76	35.32
GFR2	70.96	50.61	60.18	57.22	58.23	57.90
GFR3	54.82	33.72	43.67	39.99	41.44	40.94
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	65.43	44.01	54.62	50.81	52.13	51.57
GFR2	87.21	71.00	78.73	76.48	77.12	77.04
GFR3	72.78	51.56	62.45	58.93	60.10	59.83

Table 7.8: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	18.93	9.70	14.45	12.22	13.68	13.18
GFR2	30.23	15.13	22.82	19.50	20.94	20.46
GFR3	20.97	9.45	15.89	12.99	14.31	13.70
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	41.69	23.42	34.19	28.50	30.12	29.42
GFR2	62.21	39.75	52.62	47.62	49.08	48.48
GFR3	47.10	25.70	39.01	32.51	34.23	33.79
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	57.85	35.08	48.57	42.07	44.05	43.22
GFR2	79.35	59.12	71.16	66.08	67.43	66.93
GFR3	64.67	40.69	54.90	48.52	50.47	49.63

The AIC values of the fitted models from each simulation were very close to those found in the heart model with the continuous GFR.

7.1.4 Simulation from the cornea model

In the cornea transplant data, it was found that there are two important covariates, RAGE as a continuous and CAUSE as a categorical covariate in addition to SECOND. RAGE, CAUSE and the second graft time (the number of days between first and second graft) were generated using a multivariate log normal distribution with correlation matrix

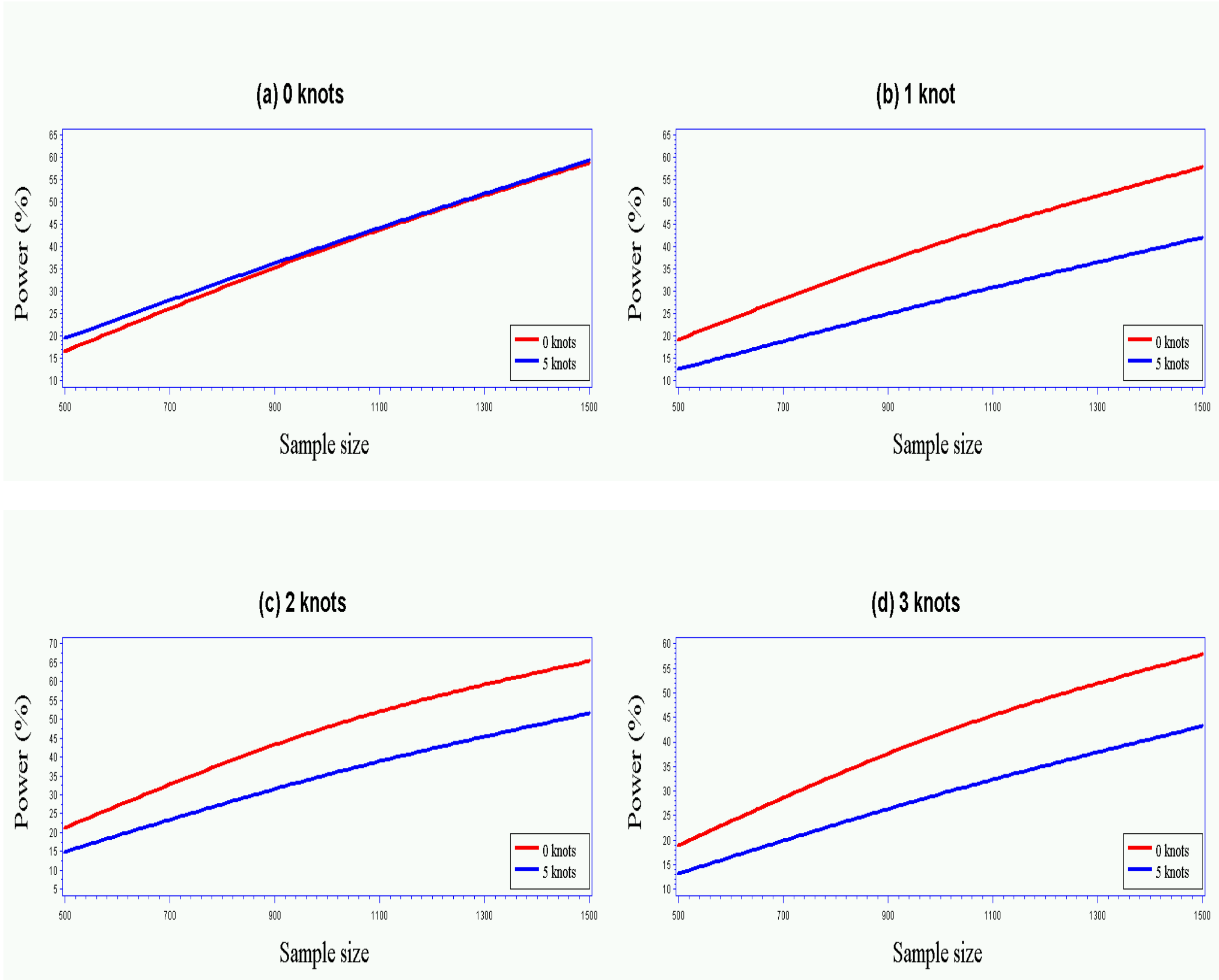

Figure 7.2: Power of GFR1 test in the fitted Weibull (0 knot) and the 5-knot models based on simulations from the Weibull (0 knot), 1, 2 and 3 knot models with 70% censoring.

$$\begin{pmatrix} 1 & 0.62698 & -0.07257 \\ 0.62698 & 1 & -0.08770 \\ -0.07257 & -0.08770 & 1 \end{pmatrix}.$$

Categorisation of CAUSE was performed according the proportion of each level using (7.1). The value of SECOND is set as 1 when the first graft survival time exceeds the generated second graft time and 0 otherwise. Based on the cornea data set, RAGE has $\mu = 48.21$, $\sigma = 1.69$, CAUSE has $\mu = 1.8$, $\sigma = 1.57$ with $p_i = 34.1\%$, 33.4% and 32.5%, and SECOND has $\mu = 1.73$, $\sigma = 1.33$ with $p_i = 79.1\%$ and 20.9%.

Generating survival times from both of the standard and the spline models can be performed following the algorithm that has been described for the heart model. However, these specifications will be used to generate survival times from the Weibull and spline models with SECOND as a time-dependent covariate only in section 7.2.3 and 7.3.3. Censoring proportion in the cornea data was 90% for about 1200 patients so that simulation based on the real data was performed including 9 scenarios with censoring proportions 70%, 80% and 90% and $n = 400$, 800 and 1200 with 10000 replications per scenario.

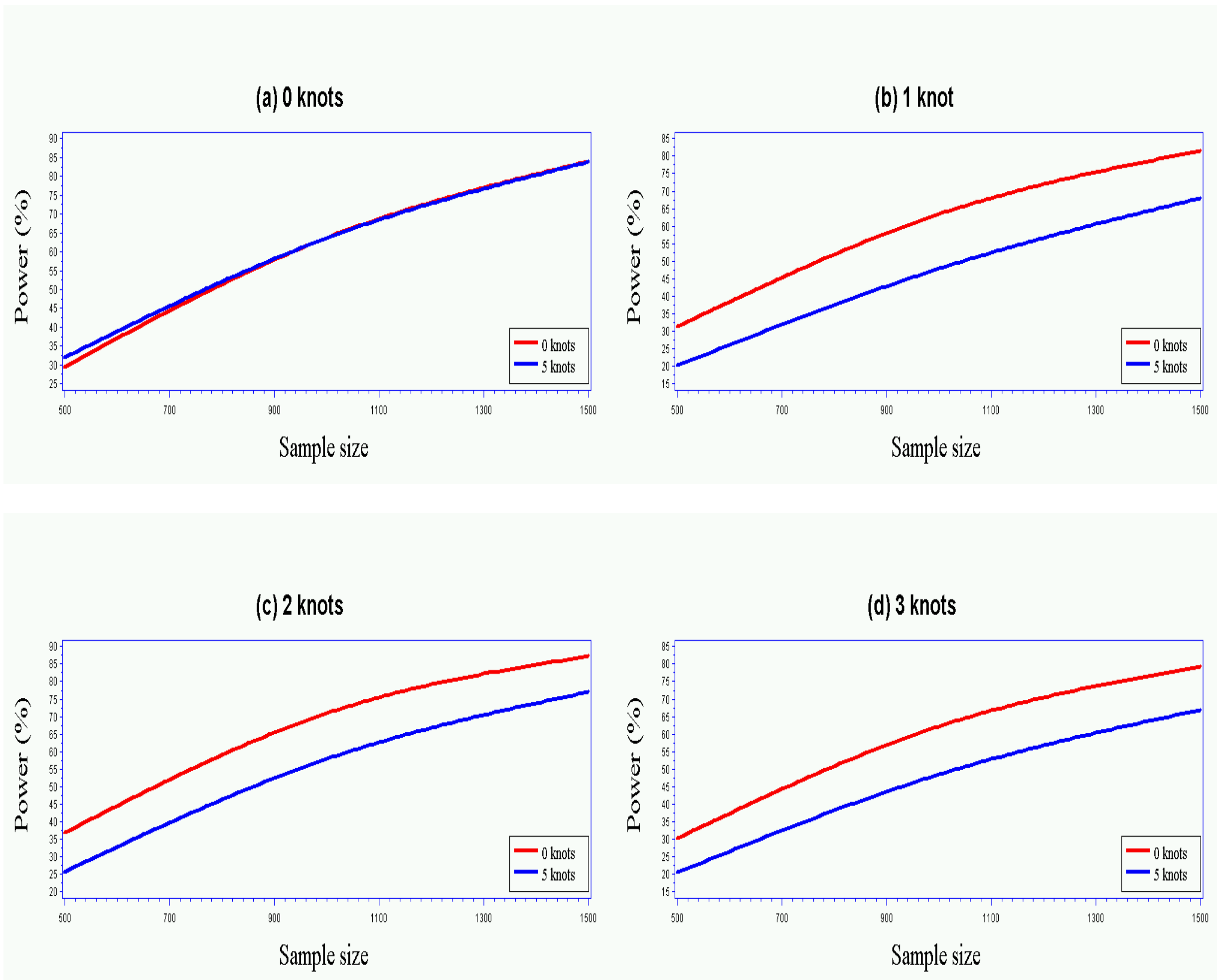

Figure 7.3: Power of GFR2 test in the fitted Weibull (0 knot) and the 5-knot models based on simulations from the Weibull (0 knot), 1, 2 and 3 knot models with 70% censoring.

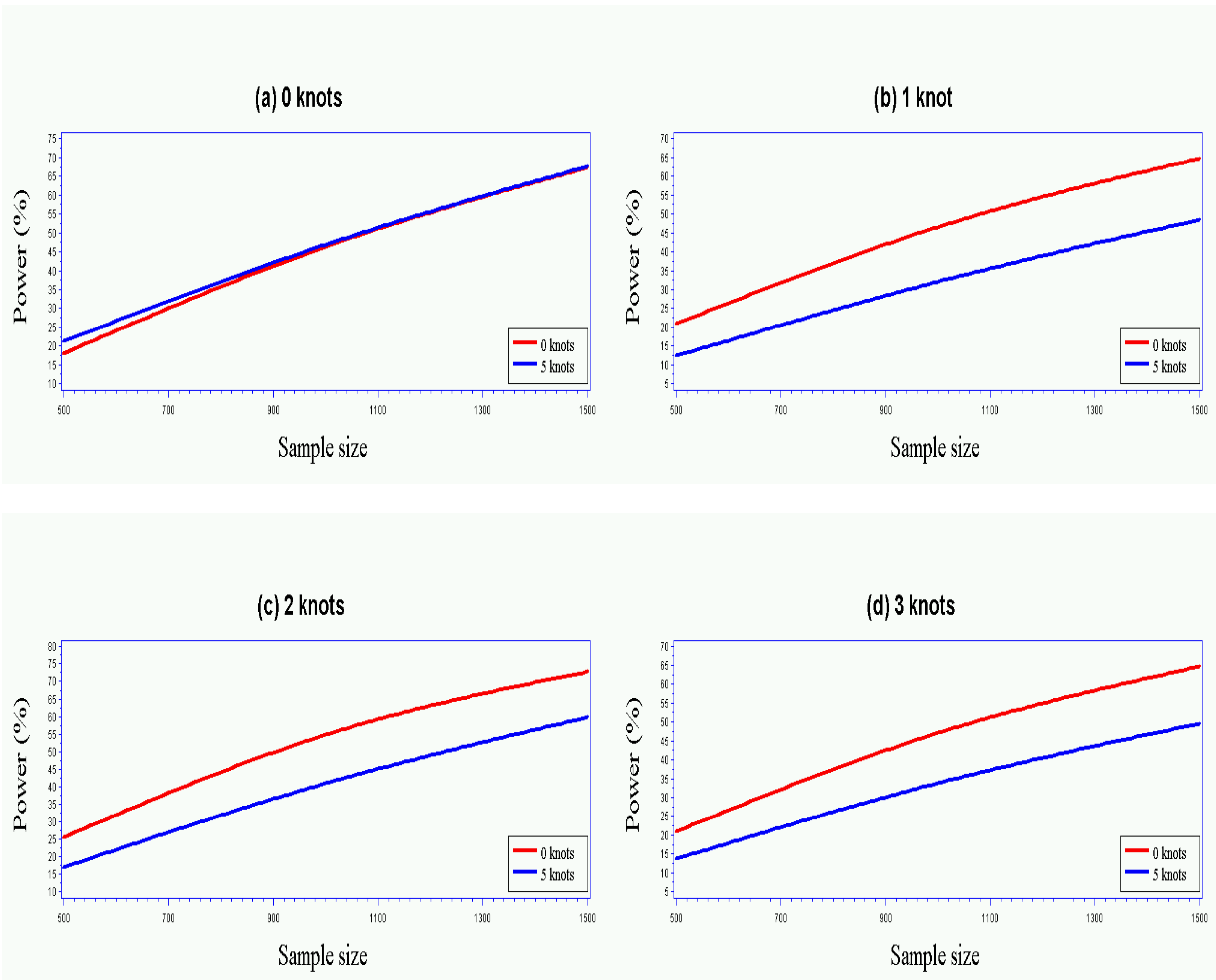

Figure 7.4: Power of GFR3 test in the fitted Weibull (0 knot) and the 5-knot models based on simulations from the Weibull (0 knot), 1, 2 and 3 knot models with 70% censoring.

7.2 Simulation of Weibull model with time-dependent covariates

In this section, the results of fitting the Cox, standard Weibull and the log-logistic models will be discussed. The data were generated from the standard Weibull model using the algorithm that will be described in section 7.2.1.

7.2.1 Simulation results of heart model with GFR as a continuous time-dependent covariate

Liu and Craig (2006) introduced a method for generating vectors of time-dependent covariates. Based on this method, the time-dependent values of GFR were generated using the baseline values that have been generated in the fixed model simulations in addition to the updated values that are available. There were only 31 subjects whose GFR values were completed and then the information of those subjects were used to generate the time varying values of GFR. A time-dependent process for GFR values $y_i(t)$ was considered using a combination of time trend and autoregressive models as

$$y_i(t) = \beta_0 + \beta_1 t + \Omega_t + A_i, \tag{7.7}$$

where β_0 and β_1 are the line trend parameters, A_i is a subject random effect where $A_i \sim N(0, \sigma^2)$ and Ω_t is the AR(1) autoregressive model with parameter a_1 and error term ε_t that defined as

$$\Omega_t = a_1 \Omega_{t-1} + \varepsilon_t, \tag{7.8}$$

In this model, trend and autoregressive parameters were calculated from the data of the 31 subjects with complete vectors of GFR values while the σ_A^2 was calculated based on the baseline values of GFR.

Generating survival times from survival model including time-dependent covariates was described by Leemis and Reynertson (1989). Following their algorithm, generating survival times from the Weibull AFT model was done where GFR was incorporated as a time-dependent covariate. The cumulative hazard function of the Weibull AFT model with time-dependent covariates can be defined as

$$H_i(t) = \begin{cases} \left(\frac{1}{\alpha_{i1}}\right)^{\rho} t^{\rho}, & 0 \leq t < \tau_{i1}, \\ \left(\frac{1}{\alpha_{i1}}\right)^{\rho} \tau_{i1}^{\rho} + \left[\left(\frac{1}{\alpha_{i2}}\right)^{\rho} (\tau_{i2} - \tau_{i1})^{\rho}\right], & \tau_{i1} \leq t < \tau_{i2}, \\ \vdots & \vdots \\ \vdots & \vdots \\ \left(\frac{1}{\alpha_{ij}}\right)^{\rho} \tau_{ij}^{\rho} + \left[\left(\frac{1}{\alpha_{i(j+1)}}\right)^{\rho} (\tau_{i(j+1)} - \tau_{ij})^{\rho}\right], & \tau_{ij} \leq t < \tau_{i(j+1)}, \end{cases} \tag{7.9}$$

where α_{ij} is parameter function of fixed and time-dependent covariates for the ith individual at time τ_{ij} and ρ is the Weibull shape parameter. Thus, the survival times can be generated using the condition hazard that changes with the updated value for the time-dependent GFR as

$$
T_i = \begin{cases} [-\log(1-u)]^{\frac{1}{\rho}}\left[\alpha_{i1}\right], \\ \qquad\qquad 0 \le u < 1 - e^{-\left\{\left(\frac{1}{\alpha_{i1}}\right)^{\rho} t^{\rho}\right\}}, \\ \left[\frac{-\log(1-u)-\left(\frac{1}{\alpha_{i1}}\right)^{\rho}\tau_{i1}^{\rho}}{\frac{1}{\alpha_{i2}}}\right]^{\frac{1}{\rho}} + T_{i1}, \\ \qquad\qquad 1 - e^{-\left\{\left(\frac{1}{\alpha_{i1}}\right)^{\rho}\tau_{i1}^{\rho}\right\}} \le u < 1 - e^{-\left\{\left(\frac{1}{\alpha_{i1}}\right)^{\rho}\tau_{ij}^{\rho}+\left(\frac{1}{\alpha_{i2}}\right)^{\rho}(\tau_{i2}-\tau_{i1})^{\rho}\right\}}, \\ \qquad \vdots \qquad\qquad\qquad \vdots \\ \qquad \vdots \qquad\qquad\qquad \vdots \\ \left[\frac{-\log(1-u)-\left(\frac{1}{\alpha_{ij}}\right)^{\rho}\tau_{ij}^{\rho}}{\frac{1}{\alpha_{i(j+1)}}}\right]^{\frac{1}{\rho}} + T_{ij}, \qquad \vdots \\ \qquad\qquad\qquad\qquad \vdots \\ \qquad\qquad 1 - e^{-\left\{\left(\frac{1}{\alpha_{ij}}\right)^{\rho}\tau_{ij}^{\rho}\right\}} \le u \le 1 - e^{-\left(\frac{1}{\alpha_{ij}}\right)^{\rho}\tau_{ij}^{\rho}+\left(\frac{1}{\alpha_{i(j+1)}}\right)^{\rho}(\tau_{i(j+1)}-\tau_{ij})^{\rho}}. \end{cases} \tag{7.10}
$$

The fixed covariates were generated as described in section 7.1.1 in addition to the vectors of GFR. The parameter values were specified based on the parameter values of the fitted Weibull AFT model with continuous time-dependent GFR as presented in chapter four. Hence, survival time from that model were generated using the following algorithm.

1. Evaluate the cumulative hazard function in each interval using (7.9), based on the intervals in which GFR values are updated. The follow-up times in days are $t = 1, 90, 360, 720, \ldots, 4320$ (i.e., the follow-up times after heart transplant in the real data).

2. Generate N survival times T_i, $i = 1, \ldots, N$ using (7.10) with starting by generating u from uniform distribution $U \sim Uni[0, 1]$. If $0 \le u < 1 - e^{-H_{i1}(t)}$ generate survival time from T_{i1}. Otherwise if $u = 0$ then assign $T_{i1} = 1$ and stop follow up for this subject. If the generated $T_{i1} \ge 1$ generate a new value for u, if $1 - e^{-H_{i1}(t)} \le u < 1 - e^{-H_{i2}(t)}$ then generate the second time from T_{i2}. If $T_{i2} \le 90$ assign T_{12} as generated. Otherwise go to the third interval and so on.

3. Generate N censored times C_i, $i = 1, \ldots, N$ from an exponential distribution as described in section 7.1.1. For each subject i, if $T_i \le C_i$ then the subject is uncensored with censoring indicator $\delta_i = 1$, otherwise $\delta_i = 0$.

The heart model was simulated including the significant covariates as described in the previous section in two stages: continuous time-dependent GFR, and categorical time-dependent GFR. In the heart model with GFR as a continuous time-dependent covariate, the results that compare the three models are presented. In Table 7.9, the powers for covariate tests with 70% censoring are presented for n = 500, 1000 and 1500. For DAGE, the power in the Cox model increased from about 88% when n = 500 to about 99% when n = 1500. The Weibull model has slightly higher power than in the Cox and the log-logistic models for DAGE, OTHER and GFR, particularly when $n = 500$. For the other covariates, it was found that the powers in the Weibull model were lower than those obtained in the Cox model, while the powers in the log-logistic model were lower compared to those obtained for all covariates in the two models.

Table 7.9: The empirical power at α=0.05 in the heart model based on generated survival times from ***the Weibull model*** with 70% censoring

	$n = 500$			$n = 1000$			$n = 1500$		
Parameter	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
DAGE	88.92	91.94	83.24	99.03	99.63	97.73	99.83	99.93	99.73
CYCLO	82.87	74.65	67.75	96.33	85.54	89.84	99.03	94.53	96.63
FK506	96.65	93.44	91.25	99.40	99.60	99.00	99.40	99.78	99.20
OTHER	83.57	87.26	73.88	98.44	99.44	95.84	99.84	99.84	99.24
GFR	92.88	93.98	87.46	98.73	98.83	98.04	98.83	98.83	98.63

The powers for covariate tests in the three models were calculated when simulations were performed with 60% and 80% censoring. This powers across the three models in the two censoring cases was close to those obtained when the model was simulated with 70% censoring case, particularly for = 1500.

Figure 7.5 shows the powers for GFR in the three fitted models when simulation was done with 70% censoring from the Weibull model. The figure shows that the power in the Weibull model was slightly higher than that obtained in the other two models, particularly with $n < 1000$.

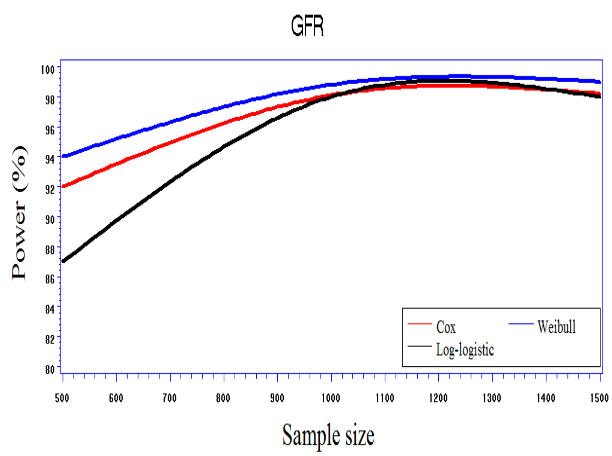

Figure 7.5: Power for GFR test in the fitted Cox, Weibull and log-logistic models based on simulation from the Weibull model with 70% censoring.

To compare the three models, percentage bias, MSE and average of confidence interval length were calculated for the parameter estimates in the three models with 70% censoring in Tables D.1, D.2 and D.3 respectively. The percentage bias in Table D.1 shows that the bias percentage for most of parameter estimates are higher in the Cox model than the Weibull and the log-logistic models. Also, the Weibull model has lower bias percentages than the log-logistic model. The MSE of parameter estimates in the three models in Table D.2 shows that the Weibull model has smaller MSE for all the parameter estimates compared to the other two models. The average confidence interval length of parameter estimates in Table D.3 was close to each other in the three models. However, the Weibull model has slightly smaller averages confidence interval length for all parameters comparing to the other two models. In conclusion, the simulation results of the heart model with a continuous time-dependent GFR show higher power for covariate tests of the Weibull model compared to the log-logistic model with less difference in power when it is compared with the Cox model. Also, the Weibull model has parameter estimates with less bias and smaller MSE compared to those obtained in the other two models.

7.2.2 Simulation results of heart model with GFR as a categorical time-dependent covariate

The heart survival data using the GFR as a categorical covariate were simulated from the Weibull model. Table 7.10 presents the powers for the three GFR categorical covariate tests in the Cox, Weibull and log-logistic models. The powers for GFR1 and GFR3 were mildly higher in the Cox model when $n = 500$ compared to the other two models. However, there was no difference in powers among the the three models when $n = 1000$ and 1500. When the same simulation was done with 60% and 80%, the Weibull model had relatively higher powers comparing to the other two models in the 60% censoring case.

Table 7.10: The empirical power at α=0.05 in the heart model based on generated survival times from ***the Weibull model*** with 70% censoring

	$n = 500$			$n = 1000$			$n = 1500$		
Parameter	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
GFR1	88.76	85.46	80.46	99.35	98.95	97.25	99.95	99.95	99.65
GFR2	99.95	99.95	99.95	99.95	99.95	99.95	99.45	99.95	99.10
GFR3	92.85	89.66	85.16	99.65	99.55	98.15	98.35	99.95	98.12

Figure 7.6 compares the powers for GFR1, GFR2 and GFR3 in the three models with 70% censoring. Figure 7.7(a) shows that the power for GFR1 in the Cox model is slightly higher than that obtained in the other two models. Figure 7.6(b) shows that the power for GFR3 in the Weibull model is slightly higher than that obtained in the other two models for $n \geq 1000$. Figure 7.6(c) shows approximately the same results as shown in Figure 7.6(a).

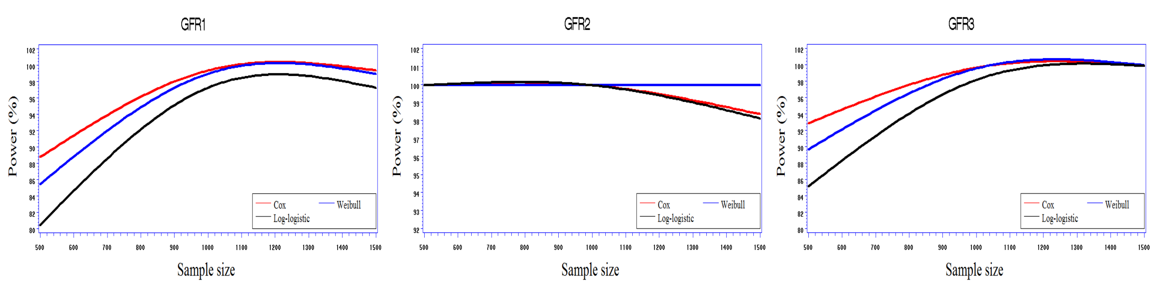

Figure 7.6: Powers for GFR1, GFR2 and GFR3 tests in the fitted Cox, Weibull and log-logistic models based on simulation from the Weibull model with 70% censoring.

Tables D.4, D.5 and D.6 present the bias percentage, MSE and average of confidence interval length respectively when simulation was performed with 70% censoring. There was no specific model can be selected as the model with less bais percentage. However, the Weibull model had the smallest MSE comparing to the other two models for all the parameter estimates except for GFR3. Further, the average of confidence interval length for the Weibull model was noticeably less than those obtained in the other two models. These results reflect a slight better performance for the Weibull model against the other two models.

The simulation results in the heart model with the continuous time-dependent GFR show a lightly higher power values, particularly when compared to the log-logistic model. However, the powers for GFR1, GFR2 and GFR3 in the second model simulation was higher in the cox model for $n = 500$ and equivalent across the three models when $n = 1000$ and 1500. This result changed only when the censoring proportion decreased to 60%, since the powers for the three covariate tests were higher in the fitted Weibull model, particularly when compared to the log-logistic model.

7.2.3 Cornea model simulation results

The time-dependent values of SECOND were generated based on the obtained second graft time. This time was generated with RAGE and CAUSE from a multivariate log normal distribution (see section 7.1.4). The survival times of the first eye graft is generated using RAGE and CAUSE only. If the second eye graft time exceeds the first graft time, it means that the second eye graft has not been done during the life time of the first eye graft and the value of SECOND is zero. Otherwise, the second eye graft was done and the survival time of the first eye graft is generating depending on the value of SECOND which changes from zero before the second graft operation and one thereafter. In this case, the algorithm that described in section 7.2.1 was employed to generate such survival times through two intervals only per each subject. This simulation was done based on the cornea data so that parameter values of the Weibull model with SECOND as a time-dependent covariate as described in chapter five were employed. Also, right censoring data were generated and assigned for the survival times following the algorithm of the heart model simulations.

Data from the cornea model were simulated including RAGE, CAUSE1, CAUSE2 and SECOND as a time-dependent covariate. This simulation has been done based on the Weibull model with 70%, 80% and 90% censoring with 10000 replications per scenario. Table 7.11 presents the powers for the four covariate tests when the model was simulated with 90% censoring. The Weibull model had a higher power for DAGE and SECOND while approximately the same powers were obtained for CAUSE1 and CAUSE2 across the three fitted models when $n = 400$. It was noticed that the powers tends to be the same when the sample size increases from $n = 400$ to 1200. The results when the model was simulated with 70% and 80% censoring show general increase in the power when as the censoring proportion decreased to 70% and 80%.

Table 7.11: The empirical power at α=0.05 in the cornea model based on generated survival times from ***the Weibull model*** with 90% censoring

	$n = 400$			$n = 800$			$n = 1200$		
Parameter	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
RAGE	68.85	76.46	69.64	91.74	95.22	91.91	98.13	99.29	98.15
CAUSE1	75.05	75.36	76.38	94.99	95.90	95.23	99.25	99.62	99.33
CAUSE2	70.50	71.75	71.73	93.89	93.97	94.00	99.06	99.03	99.05
SECOND	75.72	89.31	68.45	97.17	99.23	98.06	99.14	99.97	99.27

Figure 7.7 compares the power for SECOND test among the three fitted models when simulation was done form the Weibull model with 90% censoring. The figure shows that the power in the Weibull model was higher than the other two models when $n = 400$. However, there was no obvious difference in power among the three models when $n > 400$.

The percentage bias, MSE and average confidence interval length of parameter estimates are presented in Tables D.7, D.8 and D.9 when the model was simulated with 90% censoring. The percentage of bias in Table D.7 shows that the lower bias for DAGE was in the Cox model

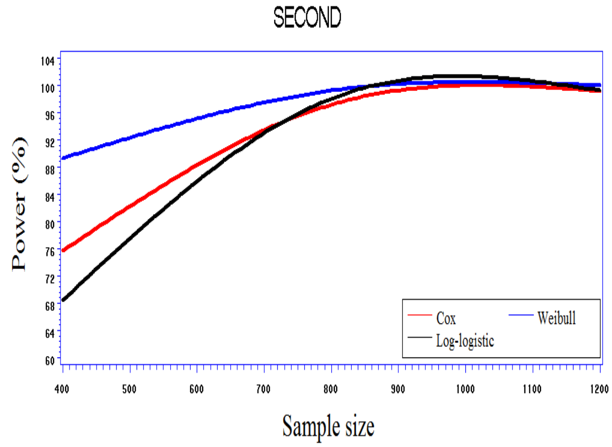

Figure 7.7: Power for SECOND test in the fitted Cox, Weibull and log-logistic models based on simulation from the Weibull model with 90% censoring.

while bias of CAUSE1, CASUE2 and SECOND was lower in the Weibull model compared to the other two models. The MSE results in Table D.8 show that the Cox model had the smallest MSE for RAGE and CAUSE1, while the Weibull model had the smallest MSE for CAUSE2 and SECOND. The results of average confidence interval length were similar to the results of the percentage bias and MSE across the three fitted models. Generally, the comparison of performance measures among the three fitted models concludes that the Weibull model can be considered as a reasonable alternative to the Cox model when the cornea data include second eye graft as a time-dependent covariate.

7.3 Simulation study of Weibull spline model with time-dependent covariates

In this section generating survival times has been performed by a combination of the numerical algorithm to generate survival times from the Weibull spline models and the algorithm that was described to generate survival times from the Weibull AFT model with time-dependent covariates in section 7.2. The results of the simulations from the spline models with time-dependent covariates will be discussed. Data from the heart model were simulated with the fixed covariates and GFR as a continuous and a categorical time-dependent covariate. Further, simulations from the cornea model were done using the fixed covariates and SECOND as a binary time-dependent covariate. These simulations were run using samples of n = 500, 1000 and 1500 observations for the heart model with 60%, 70% and 80% censoring proportions. For the cornea model, simulations were run with a combination of n = 400, 800 and 1200 observations with 70%, 80% and 90% censoring proportions. In the two models, simulations from the 0, 1, 2 and 3 knot models were performed for 2000 replications.

7.3.1 Simulation results of heart model with GFR as a continuous time-dependent covariate

Table 7.12 presents the powers for covariate tests when simulation was done from the Weibull model including GFR as a continuous covariate for n = 500, 1000 and 1500 with 70% censoring. For DAGE, the power was about 94% in the 0 knot model, and then decreased to about 92% in the 4 knot model when $n = 500$. In the sample of $n = 1500$, the powers of the same covariate were about 99% in the two models. There was no noticeable difference in power of GFR in all sample sizes. However, the powers of CYCLO, FK506 and OTHER in the 4 knot model were lower than those obtained for the same covariates in the 0 knot model. The powers of all the covariate tests considerably increased as n increased from 500 to 1500. The results in this table are based on generating from the Weibull model as was done in Table 7.9. Hence, power values of the fitted 0 knot model are close to those obtained for the fitted Weibull model in Table 7.9, particularly when $n = 1000$ and 1500.

Table 7.12: The empirical power at α=0.05 in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	93.80	91.95	92.35	92.65	92.35	91.15
CYCLO	91.30	89.20	95.45	97.95	89.70	90.95
FK506	99.85	99.80	99.75	99.80	88.80	91.00
OTHER	97.25	94.70	95.60	96.70	85.90	84.45
GFR	99.85	99.80	99.80	99.85	99.15	99.75
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	96.75	94.35	95.35	97.00	97.00	97.05
CYCLO	99.20	98.60	99.40	99.55	95.85	99.15
FK506	99.60	99.45	99.55	99.60	94.00	97.75
OTHER	99.60	99.45	99.55	99.60	94.00	96.15
GFR	99.60	99.45	99.55	99.60	99.25	99.60
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	98.95	98.30	98.55	99.00	99.50	98.95
CYCLO	99.25	99.20	99.10	99.25	98.35	99.25
FK506	99.25	99.20	99.10	99.25	97.50	98.85
OTHER	99.25	99.20	99.10	99.25	97.50	98.40
GFR	99.75	99.20	99.20	99.25	99.27	99.25

In Tables 7.13, 7.14 and 7.15, the results for power of the same covariate tests when simulation was done from the 1, 2 and 3 knot models respectively, are presented. The powers for all covariates are less than those obtained in the simulated 0 knot model particularly for DAGE in the samples of n = 500. For the other covariates, the power were slightly less than the powers for the same covariates when n= 500, while equivalent powers had been obtained for $n = 1500$. The reason for the difference in power when simulation is done from one of the spline models is the error in data generation that might have happened when a considerable difference between the assumed knot locations and the locations that are found in the generated data. For the time-dependent covariate GFR, it was noticed that its power was about 99% across the different fitted models in the three simulation cases which is considerably higher than that obtained in the same scenarios for fixed covariate mode. This explains the increase in effect of GFR on survival times when it is treated as a time-dependent covariate. Generally, the power of covariate tests decreased as the proportion of censoring increased. For GFR, the power was about 99% in the results of the three simulated models with the two censoring scenarios. Two remarks can be concluded from these results:

1. The calculated power in the the 0 knot model simulations was slightly higher than that obtained from simulations of the spline models.

2. GFR had the same power (>98%) through the different scenarios.

Table 7.13: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	90.70	88.65	86.55	86.55	86.85	86.10
CYCLO	88.80	88.05	88.35	88.05	90.25	88.15
FK506	90.40	89.10	88.30	88.25	92.25	87.85
OTHER	99.05	99.30	99.05	99.10	99.10	96.45
GFR	98.15	99.20	99.05	98.85	99.50	98.60
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	98.55	98.45	98.10	97.95	98.85	99.10
CYCLO	91.25	90.50	91.25	91.45	91.10	87.25
FK506	92.60	91.90	91.20	91.50	93.15	89.30
OTHER	99.05	99.15	99.05	98.80	99.65	97.85
GFR	99.05	99.70	99.35	98.85	99.60	98.80
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	99.05	99.25	98.80	98.85	99.05	98.75
CYCLO	93.55	92.80	93.10	92.80	93.80	90.85
FK506	94.10	93.75	92.85	91.60	94.85	91.45
OTHER	99.55	99.55	99.50	99.55	99.85	98.10
GFR	99.50	99.70	99.45	99.50	99.80	98.80

Figure 7.8 compares the power of GFR in the fitted 0 knot and 4 knot models when simulation was done from 0, 1, 2 and 3 knot models with 70% censoring. In the four Figures, the power of the GFR was about 99% at all scenarios with small difference between the two fitted models as shown in Figures 7.8(a) and 7.8(b).

To achieve complete comparisons between the Weibull model (0 knots) and the spline models, the three criteria, bias percentage, MSE and average confidence interval length were employed. Tables E.1, E.2, E.3 and E.4 include the bias percentage of parameter estimates of the fitted models based on simulation of models with 0, 1, 2 and 3 knots. The results in the four tables show that the bias percentages of CYCLO, FK506 and OTHER in the 4 knot model were lower than those obtained in the 0 knot model. DAGE had lower bias percentage in the 4 knot model when n = 500 and 1000. For GFR, there was no noticeable difference between the 0 and the 4 knot model when the percentage of bias for this covariate estimate is compared within the two fitted models. Tables E.5, E.6, E.7 and E.8 present the MSE of the parameter estimates when the simulation was performed from 0, 1, 2 and 3 knot respectively. The difference between the MSE in the 0 knot and the 4 knot model did not change when the results were calculated based on different simulated models. The same MSE had been found for DAGE and GFR. For the other parameter estimates, the 0 knot model had slightly smaller MSE than the 4 knot model when simulation was done from 1, 2 and 3 knot models. Tables E.9, E.10, E.11 and E.12 include the average confidence interval length for the same

Table 7.14: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

Parameter	$n = 500$					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	75.85	70.10	66.55	67.10	67.50	69.30
CYCLO	99.45	99.60	99.45	99.45	99.45	96.25
FK506	88.80	87.85	88.70	88.50	91.25	84.20
OTHER	89.65	87.40	84.65	84.65	85.50	82.65
GFR	98.85	98.45	98.25	98.65	99.25	98.25
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	92.65	92.10	90.45	91.25	90.85	91.45
CYCLO	98.65	98.80	98.65	98.65	98.45	97.05
FK506	89.05	87.65	89.10	89.30	90.90	87.70
OTHER	97.80	97.85	97.10	97.65	97.25	93.45
GFR	99.30	99.60	99.35	99.25	99.45	98.50
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	95.80	95.60	95.05	95.10	95.35	96.40
CYCLO	99.60	99.45	99.45	99.65	99.65	97.20
FK506	94.05	92.65	93.45	93.85	92.85	90.25
OTHER	98.60	98.80	98.50	98.45	98.10	96.45
GFR	98.55	98.85	98.60	98.55	99.25	98.20

scenarios. The results in the four tables show approximately same average confidence interval length across the six fitted models.

To compare the performance of the 0 knot model with the 4 knot model, the power of covariate tests in the fitted 0 knot model was slightly higher than that obtained in the fitted 4 knot model in the results of the 1, 2 and 3 knot model simulations while equivalent power has been found for GFR. The bias percentages of parameter estimates were lower in the fitted 0 knot model for the continuous covariates, while the parameter estimates of the categorical covariates in the 4 knot model had lower bias percentages. The MSE were generally smaller in the 0 knot model, but in some scenarios, the MSE were equivalent. The average confidence interval length was approximately the same in the two compared models. Finally, when the AIC values were calculated over the 2000 replication based on simulation from the 0 knot model, the 5 knot model had the lowest AIC values in 67%, 89% and 95% for n = 500, 1000 and 1500 respectively. However, in the simulation from the 1 knot model, the 4 knot model had the lowest AIC values in 47%, 53% and 72% for n = 500, 1000 and 1500 respectively. The AIC results based on simulations from the 2 and 3 knot models were close to those obtained in the 1 knot model simulation.

7.3.2 Simulation results from the heart model with GFR as a categorical time-dependent covariate

Table 7.16 present the power of test for the time-dependent covariates GFR1, GFR2 and GFR3 when simulation was done from the Weibull model with 70% censoring. For GFR1, the power in the fitted 0 knot model was about 95% and then decreased to about 81% in

Table 7.15: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	88.95	88.45	82.45	83.45	82.60	81.90
CYCLO	99.95	99.35	99.35	99.90	99.75	94.90
FK506	95.35	95.15	94.25	94.95	94.45	85.95
OTHER	94.65	93.75	91.45	90.95	90.35	85.45
GFR	99.70	99.30	99.20	99.30	98.35	96.35
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	95.95	95.95	94.45	94.45	94.45	93.95
CYCLO	99.95	99.90	99.95	99.90	99.90	90.95
FK506	93.95	93.95	93.45	93.45	93.45	81.45
OTHER	99.45	98.95	98.90	98.95	98.90	88.95
GFR	99.60	99.95	99.55	99.90	99.95	96.80
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	98.15	98.70	97.90	97.10	97.15	97.95
CYCLO	99.45	99.40	99.45	99.45	99.40	90.90
FK506	95.45	95.45	95.45	95.45	95.45	83.95
OTHER	99.40	99.45	98.95	98.90	98.90	89.50
GFR	99.05	99.25	99.50	99.40	99.65	97.20

the fitted 4 knot model when $n = 500$. This power was about 100% in the fitted 0 knot and about 99% in the fitted 4 knot model when $n = 1500$. GFR2 and GFR3 have approximately the same results when the fitted 0 knot model is compared with the fitted 4 knot or the other spline models.

Table 7.16: The empirical power at α=0.05 in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

	$n = 500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	95.25	86.70	79.30	78.90	81.45	70.70
GFR2	96.85	89.70	82.50	82.60	84.80	73.80
GFR3	98.45	92.55	87.30	87.35	89.25	77.50
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	100.00	99.50	98.10	98.20	98.70	94.05
GFR2	100.00	99.50	98.65	98.65	98.90	94.35
GFR3	100.00	99.75	99.20	99.20	99.35	94.90
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	100.00	99.95	99.90	99.85	99.75	97.20
GFR2	100.00	99.90	99.90	99.90	99.75	97.40
GFR3	100.00	100.00	100.00	100.00	99.85	97.60

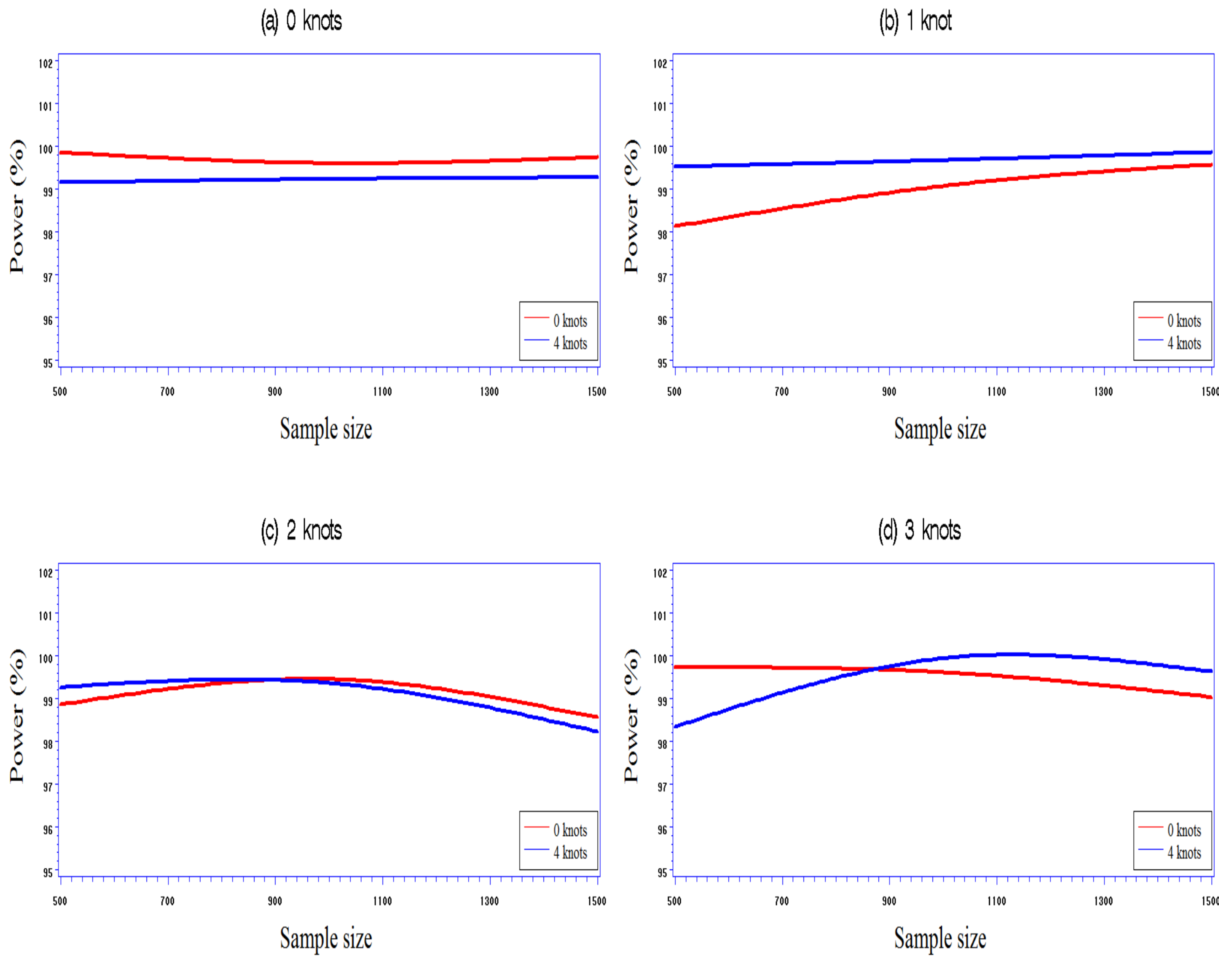

Figure 7.8: Power of GFR test in the fitted Weibull (0 knot) and the 4-knot models based on simulations from the Weibull (0 knot), 1, 2 and 3 knot models with 70% censoring.

In Tables 7.17, 7.18 and 7.19, the powers of covariate tests are presented when simulations were performed from the 1, 2 and 3 knot models with 70% censoring. The power of all the covariate tests across the results of the three tables are slightly lower than those obtained from the simulation of the Weibull model, particularly when $n = 500$. This means that the data of some samples were not generated correctly from the correct spline model for difficulties that may arise from the inappropriate selection for the knot positions that assumed before simulating these data sets. The results in Table 7.17 do not show clear difference in the estimated power of the covariates in the fitted 1 knot model where simulation was done from the same model. However, the results in Tables 7.18 and 7.19 show some differences in estimated power in the fitted 2 and 3 knot models when simulations were done from the same models. This implies that most of the samples in those two simulations were generated correctly from the desired models.

Figure 7.9 shows the power for GFR1 in the 0 and 4 knots models through the four simulations with 70% censoring. Figure 7.9(a) shows that the power of GFR1 in the fitted 0 knot model was higher than that obtained in the fitted 4 knot model when $n < 1000$, while the two models had the same power value for $n > 1000$. Figure 7.9(b) shows that the power in the fitted 0 knot model was about 83%, comparing to 81% in the 4 knot model. When $n = 500$, the power in the fitted 0 knot model was higher by about 2% at all sample sizes.

Table 7.17: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
	$n = 500$					
GFR1	83.25	81.10	80.70	80.50	80.50	74.90
GFR2	90.45	88.65	88.05	87.65	87.85	82.85
GFR3	90.05	88.45	88.25	88.80	89.05	86.45
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	96.65	94.65	94.45	94.45	94.50	93.05
GFR2	98.20	97.80	97.80	97.80	97.85	96.25
GFR3	98.25	97.65	97.45	97.45	97.25	96.65
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	98.05	97.85	98.25	97.85	97.85	97.45
GFR2	99.05	99.60	99.25	99.10	99.10	98.40
GFR3	98.40	98.65	98.55	98.05	98.45	98.20

Table 7.18: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
	$n = 500$					
GFR1	85.65	84.70	86.95	85.80	85.65	85.80
GFR2	82.85	80.90	85.10	84.50	84.30	84.70
GFR3	88.25	86.75	89.85	89.35	89.05	89.25
	$n = 1000$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	96.60	96.45	97.85	97.20	97.05	97.25
GFR2	95.65	94.85	96.85	96.45	96.45	96.65
GFR3	97.25	97.00	98.50	98.05	98.35	98.10
	$n = 1500$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	98.40	98.45	99.78	99.05	99.35	99.05
GFR2	98.05	98.25	99.70	99.00	99.45	99.10
GFR3	98.40	98.45	99.60	99.05	99.45	99.20

In Figure 7.9(c), the power in both models was approximately the same with difference by about 1% for the fitted 4 knot model. This difference increased to about 4% for the fitted 4 knot model as shown in Figure 7.9(d).

Figures 7.10 and 7.11 compare the powers for GFR2 and GFR3 in the fitted 0 and 4 knot models through the four simulated models with 70% censoring. As shown in Figures 7.9(a, b, c and d), the powers for the two covariates were higher in the fitted 0 knot model when simulation was done from the Weibull model and approximately the same for the simulation from the 1 knot model. On the other hand, the powers for those covariates were higher in the fitted 0 knot model when the simulation was done from the 2 and 3 knot models.

The bias percentages, MSE and the average confidence interval length were calculated

Table 7.19: The empirical power at α=0.05 in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

Parameter	$n = 500$					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	88.80	88.35	90.45	90.90	90.10	86.90
GFR2	85.70	84.90	89.90	89.45	89.15	85.50
GFR3	90.20	90.20	92.20	92.55	92.40	88.80
Parameter	$n = 1000$					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	95.90	95.70	98.25	98.65	98.60	96.35
GFR2	95.15	94.95	96.35	96.85	96.68	94.60
GFR3	96.25	96.20	97.80	97.95	97.50	95.70
Parameter	$n = 1500$					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	98.35	98.85	99.20	99.75	99.65	97.65
GFR2	98.45	98.40	99.15	99.85	99.80	97.25
GFR3	98.85	98.90	99.25	99.65	99.10	97.45

from simulation of the four models in order to compare the fitted 0 knot and 4 knot models. Tables E.13, E.14, E.15, and E.16 present the bias percentages of parameter estimates in simulations from the 0, 1, 2 and 3 knot models with 70% censoring respectively. The bias percentages in the fitted 4 knot model were lower than those obtained in the fitted 0 knot model when simulation was done from the 0 knot model, while these bias percentages were slightly close in the two compared models when simulations were done from the 1, 2 and 3 knot models. Tables E.17, E.18, E.19 and E.20 present the MSE of parameter estimates when simulations were done from the 0, 1, 2 and 3 knot models with 70% censoring respectively. The MSE of parameter estimates of the two fitted models were similar across the results of the four tables. Also, through the results in the Tables E.21, E.22, E.23, and E.24 for average confidence interval length of GFR1, GFR2 and GFR3, it was not found obvious difference between the fitted 0 and 4 knot models. Generally, the powers in the fitted 0 knot model were slightly higher than the power in the fitted 4 knot model, particularly when simulation was done from the Weibull model, while the fitted 4 knot model had higher powers for the three covariates when simulations from 2 and 3 knot models are considered. The bias percentages were lower in the fitted 4 knot model compared to the fitted 0 knot model particularly when the simulations were done from 0 and 1 knot models. The MSE in the 4 knot model was slightly smaller than those obtained in the fitted 0 knot model for most of parameter estimates. Finally, the AIC were calculated for all the six fitted models over all the replications with very close results to those found in the continuous time-dependent GFR case.

7.3.3 Simulation results for the cornea model

Table 7.20 presents the power of covariate tests for the cornea model when simulation was done from the Weibull model with 90% censoring. For RAGE, the power in the fitted 0 knot model was about 52% and then increased to about 60% in the fitted 5 knot model when $n = 400$. This power was about 89% in the fitted 0 knot and about 87% in the fitted 5 knot model when $n = 1200$. The other three covariates had powers of about 49%, 58% and 74%

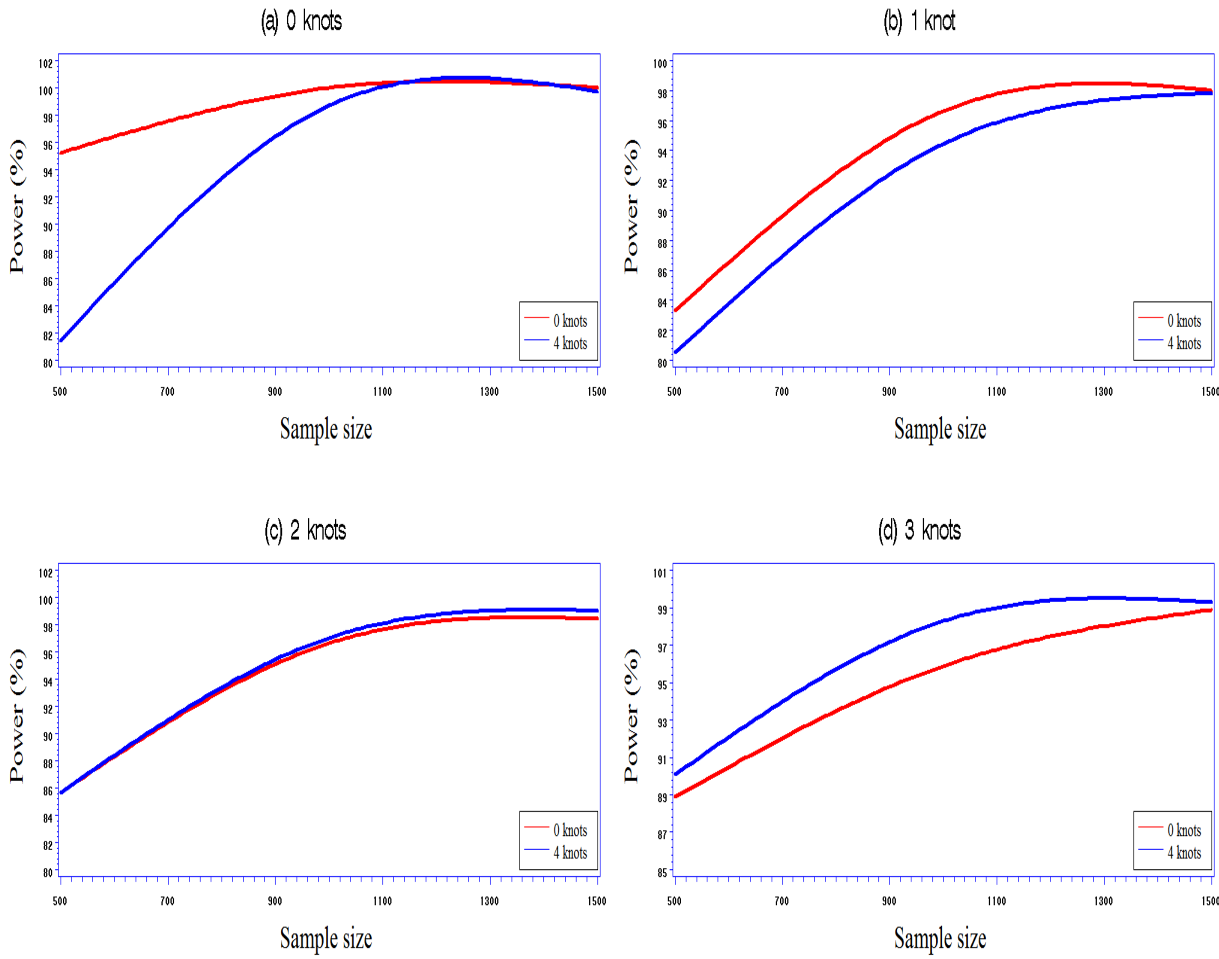

Figure 7.9: Power of GFR1 test in the fitted Weibull (0 knot) and 4-knot models based on simulations from the Weibull (0 knot), 1, 2 and 3 knot models with 70% censoring.

respectively in the fitted 0 knot model when $n = 400$, while the powers of the same covariates were higher by about 5% in the 5 knot model. For $n = 1200$, the power values of the four covariate tests were higher in the fitted 0 knot model compared to all the other fitted spline models. There were some differences in power for RAGE, CAUSE1 and CAUSE2 between the fitted 0 knot model and those obtained in the same fitted model when simulation was done from the Weibull model in Table 7.11, particularly for the $n = 400$ and 800. These differences may be due to the number of replications that was 10000 in the results of Table 7.11 while the simulation here was done based on 2000 replications only, in addition to the increasing sampling error when simulations were done with smaller samples ($n = 400$).

In Tables 7.21, 7.22 and 7.23, the powers for covariate tests are presented when simulations were performed from the 1, 2 and the 3 knot models with 90% censoring. The power for all covariates in fitted 1, 2 and 3 knot models was considerably higher than those obtained from the fitted 0, 4 and 5 knot models particularly, when $n = 400$ and 800. These results were expected because the simulations were done from 1, 2 and 3 knot models. To compare the powers for covariate tests in the fitted 0 and 5 knot models, it was found that power values in the fitted 5 knot model were slightly higher than those obtained in the fitted 0 knot model for RAGE and SECOND in the results of the three tables, while the two models had close powers for the covariate of CAUSE1 and CAUSE2 when $n = 1200$. The powers for all

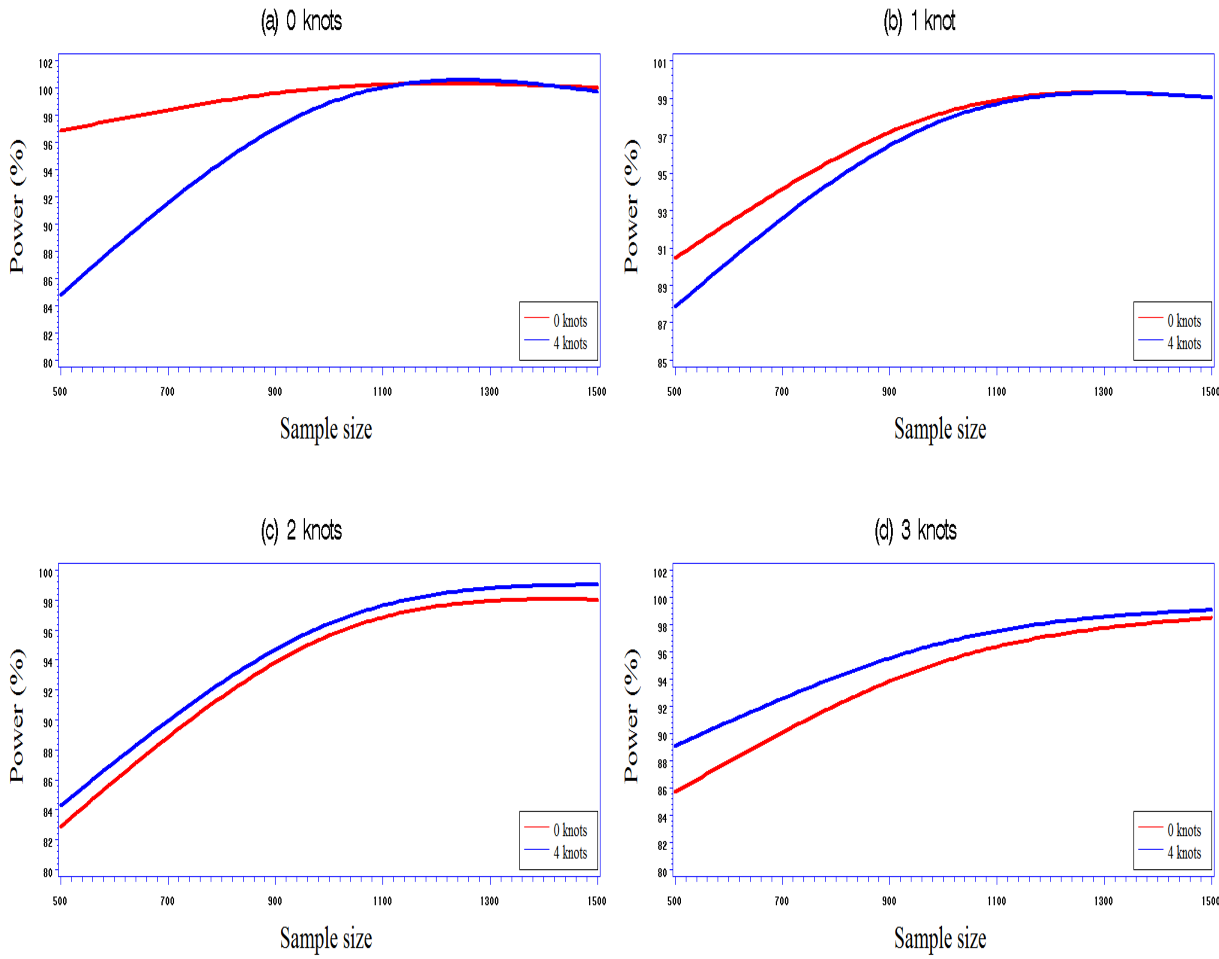

Figure 7.10: Power of GFR2 test in the fitted Weibull (0 knot) and 4-knot models based on simulations from the Weibull (0 knot), 1, 2 and 3 knot models with 70% censoring.

covariate tests increased as the censoring proportion decreased to 70% and 80%.

Figure 7.12 compares the power for SECOND in the fitted 0 and 5 knot models when the 0, 1, 2 and 3 knot models were simulated with 90% censoring. In Figure 7.12(a), the power in the 0 knot model was considerably higher than that obtained in the 5 knot model for $n > 500$. In Figures 7.12(b), 7.12(c) and 7.12(d), the power for SECOND in the fitted 5 knot model was higher than that calculated in the fitted 0 knot model for the simulation from 1, 2 and 3 knot models across all the sample sizes.

The bias percentages, MSE and the average confidence interval length were calculated from the simulations from the four models in order to compare the. Tables E.25, E.26, E.27, and E.28 present the bias percentages of parameter estimates in simulations of the 0, 1, 2 and 3 knot models with 90% censoring respectively. For all the fitted models, the bias percentages were high, particularly for SECOND parameter estimate. Tables E.29, E.30, E.31 and E.32 present the MSE of parameter estimates when simulations were done from the 0, 1, 2 and the 3 knot models with 90% censoring respectively. The MSE in the 5 knots model were smaller than those obtained in the 0 knot model for SECOND. However, the MSE of CAUSE1 and CAUSE2 in the 0 knot model were slightly smaller compared to the MSE in the 5 knots model. Tables E.33, E.34, E.35 and E.36 present the average confidence interval length for estimates in the fitted models for simulations of the 0, 1, 2 and 3 knot models

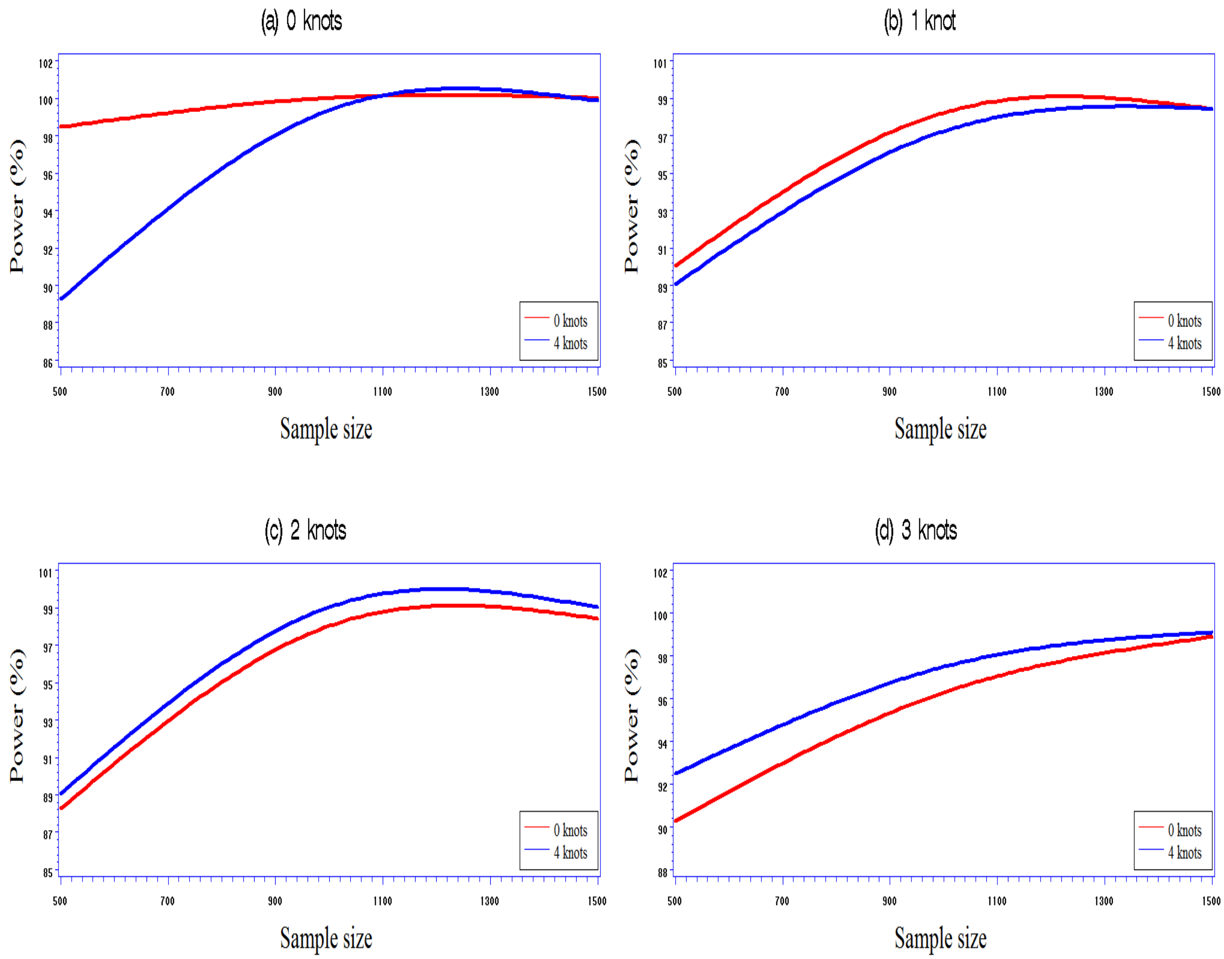

Figure 7.11: Power of GFR3 test in the fitted Weibull (0 knot) and 4-knot models based on simulations from the Weibull (0 knot), 1, 2 and 3 knot models with 70% censoring.

with 90% censoring respectively. Through the results of the four tables, there was no obvious difference in the average confidence interval length of parameter estimates across the fitted models. However, the results in all these tables show that parameter estimate of SECOND had unexpected high values for the the three measures. The first reason for these results is the high censoring proportion (about 90%) that may cause some difficulties in fitting of the model in some replications. Secondly, when the Weibull spline models are fitted to the data, the knots may be located before or after the change of SECOND as a time-dependent covariate from zero to one. In this case SECOND may have biased parameter estimates in the fitted spline models, particularly with the higher number of knots. The AIC values were calculated for all the fitted models over the different scenarios. Over the 2000 replications, the lowest AIC value was for the 5 knot model in 46% 51% 59% for n = 400, 800 and 1200 when simulation was done from the 0 knot model. In the simulation of the 1 knot model, the 5 knot model had the lowest AIC values in 35% 42% 52% for n = 400, 800 and 1200 respectively. These AIC results did not considerably change when simulations were done from the 2 and 3 knot models.

Table 7.20: The empirical power at α=0.05 in the cornea models based on generated survival times from ***the Weibull model*** with 90% censoring

	$n = 400$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	52.25	41.10	69.75	68.50	58.95	60.10
CAUSE1	49.40	38.70	70.40	64.90	57.80	60.80
CAUSE2	58.60	43.25	75.75	69.25	61.25	64.05
SECOND	74.90	74.50	52.95	50.95	71.30	77.90
	$n = 800$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	76.45	60.55	88.70	84.40	77.00	77.95
CAUSE1	76.45	59.85	90.45	84.05	74.35	77.65
CAUSE2	82.85	63.45	92.25	86.35	76.50	79.70
SECOND	98.70	75.10	55.55	55.15	76.95	81.75
	$n = 1200$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	89.10	75.40	94.80	90.55	86.90	87.25
CAUSE1	89.70	73.60	96.85	92.85	86.65	87.25
CAUSE2	94.60	79.35	97.90	94.65	88.35	89.65
SECOND	99.35	75.70	58.60	62.95	80.30	82.70

Table 7.21: The empirical power at α=0.05 in the cornea models based on generated survival times from ***the 1-knot Weibull spline model*** with 90% censoring

	$n = 400$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	58.20	85.55	88.10	78.30	46.85	50.75
CAUSE1	54.00	85.20	87.10	77.65	45.95	49.85
CAUSE2	60.20	87.55	90.20	80.25	47.85	51.75
SECOND	54.55	90.15	93.35	91.95	95.85	96.80
	$n = 800$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	78.95	99.20	98.20	96.75	78.30	82.25
CAUSE1	75.10	99.30	98.40	96.90	78.55	82.45
CAUSE2	82.50	99.40	98.65	97.00	78.70	82.80
SECOND	70.05	98.25	98.95	98.55	99.10	98.95
	$n = 1200$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	91.65	99.95	99.55	99.05	86.75	90.75
CAUSE1	87.60	99.95	99.45	99.10	87.05	91.10
CAUSE2	92.30	100.00	99.50	98.95	86.95	90.90
SECOND	89.10	99.20	99.55	99.10	99.10	99.35

7.4 Concluding remarks

In this chapter, simulations were performed based on the real survival data of heart and cornea transplantation. Specifications of these data sets have been employed to simulate the Weibull and the spline models in the two cases of fixed and time-dependent covariates. In section 7.1, the Weibull, 1, 2 and 3 knot spline models were simulated when all covariates were held fixed in time. When the heart model was simulated with continuous GFR, the simulation output for parameter estimates in the fitted 0 to 5 knot models were considered. The bias percentages and the MSE values were lower in the fitted 5 knot model compared to the fitted 0 knot model. Moreover, the AIC values were calculated for the fitted models

Table 7.22: The empirical power at α=0.05 in the cornea models based on generated survival times from ***the 2-knot Weibull spline model*** with 90% censoring

	$n = 400$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	58.05	91.90	92.25	83.10	66.85	67.50
CAUSE1	73.95	96.50	96.60	87.05	71.10	71.00
CAUSE2	80.65	97.45	97.45	87.90	71.15	71.70
SECOND	58.20	97.55	98.45	96.80	96.10	97.25
	$n = 800$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	79.80	99.70	99.20	98.10	91.75	91.70
CAUSE1	93.60	99.95	99.80	98.50	92.55	92.65
CAUSE2	97.10	99.95	99.90	98.50	93.15	93.15
SECOND	68.50	99.65	99.85	99.40	98.60	98.80
	$n = 1200$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	91.05	100.00	99.90	99.40	96.35	97.15
CAUSE1	98.50	100.00	100.00	99.65	96.75	97.40
CAUSE2	99.05	100.00	99.95	99.50	97.25	97.80
SECOND	90.30	99.80	99.80	99.75	99.55	99.55

Table 7.23: The empirical power at α=0.05 in the cornea models based on generated survival times from ***the 3-knot Weibull spline model*** with 90% censoring

	$n = 400$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	50.70	90.80	89.60	80.40	65.10	65.35
CAUSE1	68.05	93.85	93.40	83.65	68.65	68.10
CAUSE2	72.70	94.00	93.70	84.45	70.40	69.80
SECOND	54.50	96.05	97.55	98.35	97.75	98.15
	$n = 800$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	73.50	98.40	97.85	93.40	83.30	82.90
CAUSE1	89.40	99.05	98.60	95.00	86.05	85.65
CAUSE2	92.45	99.15	98.90	95.35	86.90	86.95
SECOND	87.40	98.80	99.50	99.35	99.60	99.80
	$n = 1200$					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	85.85	99.65	99.60	97.65	88.90	89.60
CAUSE1	96.90	99.75	99.75	98.90	92.30	93.00
CAUSE2	98.45	99.95	99.85	98.85	92.60	93.50
SECOND	97.30	99.60	99.80	99.80	99.90	99.45

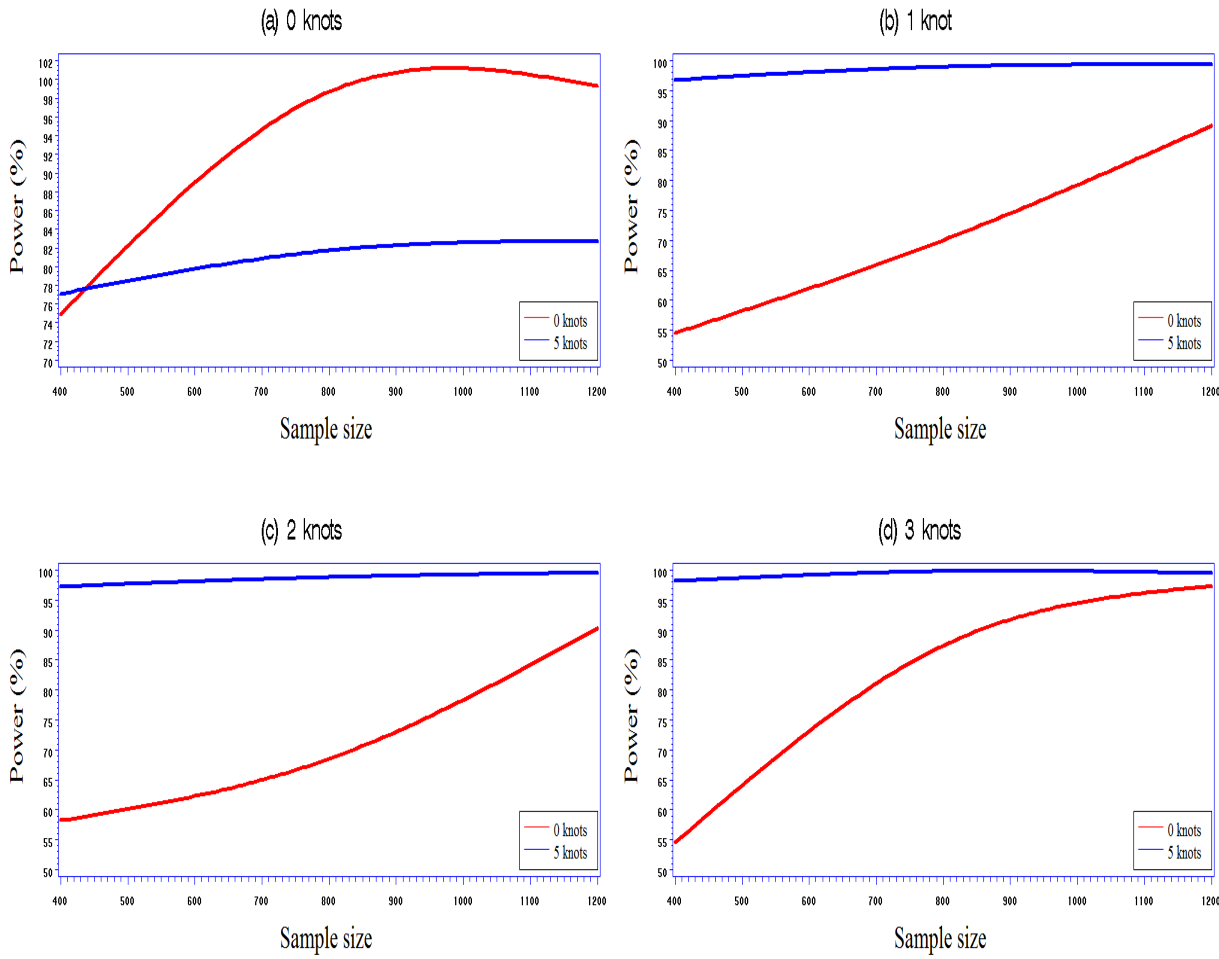

Figure 7.12: Power of SECOND test in the fitted Weibull (0 knot) and 5-knot models based on simulations from the Weibull (0 knot), 1, 2 and 3 knot models with 90% censoring.

from all the replications across the four simulations. The fitted 5 knot model had the lowest AIC in about 90% of the replications when simulation was done from the 0 knot model with $n = 1500$, while the fitted 3 knot model had the lowest AIC in about 76% of the replications when simulations were done from the 1, 2 and 3 knot with the same sample size. Similar results have been found when simulations were done from the heart model including GFR as a categorical covariate. There are some doubts about the possibility to compare different Weibull spline models using this criterion as described in section 7.1.2.

In section 7.2, the Weibull model was simulated when GFR was treated as a time-dependent covariate in heart model and SECOND as a time-dependent in cornea model. The algorithm that was used to generate data with time-dependent covariates was described in section 7.2.1. The estimated outputs were calculated to compare the Weibull model with the Cox and the log-logistic models. Heart model with continuous time-dependent GFR simulation produced slightly higher power compared to the log-logistic model and close to that obtained in the fitted Cox model. Also, the bias percentages and the MSE were slightly lower in the Weibull model compared to the other two models. When the time-dependent GFR was treated as a categorical covariate, similar results to the continuous case have been obtained. In the cornea model results, the power of RAGE and SECOND was higher in the fitted Weibull model compared to the other two models, while the power of CAUSE1 and

CAUSE2 was not different from that obtained in the Cox model.

Section 7.3 includes simulations of the Weibull and spline models with 1, 2 and 3 knots based on the heart data when GFR is treated as a time-dependent covariate in addition to the cornea data with SECOND as a time-dependent covariate. In these simulations, data sets were generated by an algorithm that combines between the numerical algorithm in section 7.1.1 and the algorithm that was described in section 7.2.1. In heart model simulation, the results of the continuous case were employed to compare the fitted 0 with 4 knot models. The powers of covariate tests were higher and the bias percentages of parameter estimates were slightly lower in the fitted 0 knot model compared to the 4 knot model (based on the simulation from the 0 knot model), while the fitted 4 knot model had the lowest AIC value. In the simulation of the categorical case, based on power of test for GFR1, GFR2 and GFR3 besides bias percentages and MSE of parameter estimates, the fitted 4 knot model had slightly higher power compared to the fitted 0 knot model when simulations were done from the 2 and 3 knot models. Finally, the results of the cornea model simulation showed that the power in the fitted 5 knot model was higher than that obtained in the fitted 0 knot model when simulation was done from the 2 and 3 knot models in addition to the AIC value of the fitted 5 knot model was lower than that obtained for the other fitted model across the different scenarios. However, the estimated bias percentages of parameter estimates were considerably higher than those obtained in the fitted 0 knot model, particularly when simulations were done from the 1, 2 and 3 knot models.

In simulation of survival data from different spline models, the estimated outputs should be checked carefully to ensure that all the samples were correctly generated from the desired spline model. Imprecise generation may be occurred as a result to the miss-specification of the knot positions when they are assumed at unsuitable positions in which the data have not been generated at this stage. Secondly, the high proportion censoring as, i.e. 70% in the heart transplant data and 90% in the cornea transplant data, may cause some estimation errors. These errors may lead to increase in the bias of some parameter estimates as for SECOND in the fitted spline models in cornea data, particularly when simulation was done from the 1, 2 and 3 knot models.

Chapter 8

Discussion and future work

8.1 Discussion

The most common choice in modelling time-dependent covariates is the Cox regression model that is easily extended to include such covariates. In this model, the baseline hazard function is unspecified. However, when a suitable probability distribution is assumed for the survival data, inferences based on the parametric model may be more precise in addition to obtaining estimates with possibly smaller standard errors (Collett, 2003). Hence, an alternative choice is to use AFT models with an underlying distribution such as: Weibull, log-logistic and log-normal that allow for one or more covariates to change over time. In general parametric models, the baseline hazard $h_0(t)$ is determined by small number of distributional parameters. This approach may adequately fit the data that include such covariates if an appropriate baseline hazard function has been specified.

The aim in this thesis was to consider parametric models that allow for time-varying covariates as alternatives to the traditional extended Cox regression model. Further, a more flexible parametric model, that was developed by Royston and Parmar (2002), is adopted by extending the standard model using natural cubic splines. In chapter 3, the mathematical functions for the Weibull and the log-logistic models were described. The cumulative hazard functions for such models were constructed to accumulate the hazard within the different intervals that represent the multiple records of each subject (see section 3.2). The standard Weibull model was modified using the spline technique to increase smoothness of the hazard function and possibly achieve better performance comparing to the standard model. This model depends on adapting the baseline cumulative hazard in the presence of time-dependent covariates to incorporate the spline function. The Cox model and the proposed parametric models were fitted to two data sets supplied by NHS Blood and Transplant for heart and cornea transplantation.

In the heart transplant data, the Cox, log-logistic and standard Weibull model were applied using values of GFR, a modification of the creatinine level, as a fixed and a time-dependent covariate. This covariate was modelled as a continuous and a categorical variable with four levels. This would help to determine the best form to model GFR when it is involved with its time varying values. The flexible Weibull model was applied with 0 (equivalent to the standard model), 1, 2, 3, 4 and 5 knots using GFR as a fixed and as a time-dependent covariate. Event though the fit of the 4 knot model was not better than the Cox model, it achieved more adequacy compared to the Weibull model (0 knot). Based on the AIC criterion to compare the spline models, the 5 knot model was the best when GFR was held fixed, while the 4 knot model was the most satisfactory model when GFR was treated as a time-dependent covariate. The two fixed covariates, DCMV and PCD, appeared to be non-significant at the 5% significance level when the models with a time-dependent covariate were fitted. This may occur as a result of masking their effects within the time-depending process. Consequently, their importance must be considered in the model excluding the time-dependent covariate. In order to evaluate the competitor models, analysis of residuals was applied. Cox-Snell and the martingale residuals of the Cox and the Weibull spline models (4 and 5 knots) reflected better performance for these models compared to the standard Weibull (0 knot) and the log-logistic models.

A further example is the cornea transplant data, where a second eye graft is done and its effect on the first eye graft is measured as a binary time-dependent covariate. RAGE was not significant at 5% significance level in the log-logistic and the standard Weibull models in the presence of the time-dependent covariate SECOND. In the time-dependent modelling of this data set, the best spline model (5 knot) based on AIC, produced biased parameters, particularly for SECOND. This result illustrates the unreliable model that may be obtained when spline extension is applied to the standard Weibull model with binary time-dependent covariate. Investigations using bias percentages and MSE of the estimated parameters from that model were considered in chapter 7. Model checking using these data reflected a slightly better performance for the Cox model with less adequacy for the Weibull spline model so that simulation results can be employed to compare the likelihood-based inferences within each model.

In order to evaluate the competitor models, the first step was to study the parameter standard errors and standardized variability (sv-values), particularly for the parameter of interest (e.g., GFR in the heart model and SECOND in the cornea model). It was found that the spline models had the lowest sv-values for most of parameter estimates compared to the Weibull standard (0 knot), log-logistic and Cox models. Cox-Snell and martingale residuals were calculated for each fitted model. The residual analysis concluded that the Cox and the Weibull spline models are more adequate than the standard Weibull and the log-logistic models that include both fixed and time-dependent covariates. A clear comparison among the alternative models via a simulation study was essential procedure.

The Weibull spline model was simulated when no covariates included in the model to determine the number of knots that may be included in the spline model in different scenarios. To achieve this aim, the Weibull spline models with 0 and 1 knot were simulated. To simulate these models, Weibull scale, shape parameters were assumed in addition to spline parameters that have to be specified carefully in order to yield a valid cumulative hazard function (i.e., monotone increasing function). The rejection sampling algorithm had low efficiency to generate survival times from such models as a result to the high rejection proportion that was found in applying this algorithm. The reason of this problem may be the inaccurate specifying of the envelope distribution. Also, there was not much better performance for the algorithm when the Weibull distribution was employed as an envelope distribution. A numerical algorithm was suggested as an alternative based on producing table of survival times and their relevant survival probabilities. Then results of the numerical inversion of the spline survivor function were obtained and validated to ensure accurate generated survival time at each iteration. The results of this simulation were affected by the difference between the assumed knot positions and the actual positions of those knots for the simulated model with shape 4. However, reasonable results were found for the other scenarios.

Simulation based on survival data after heart and cornea transplantation was performed to study the produced estimates of each model across different scenarios. When simulation was done from the Weibull spline models with fixed covariates, comparison between the fitted Weibull (0 knot) and Weibull spline models showed slightly higher power in the 0 knot model in simulation of the heart data and similar power in the cornea model simulation. However, the parameter estimates of the fitted spline models had less bias and slightly smaller MSE compared to those obtained in the fitted 0 knot model. Simulation of the Weibull model with time-dependent covariates introduced a comparison among the Weibull, log-logistic and the Cox model. The Weibull model results were close to those obtained in the fitted Cox model and slightly better compared to the log-logistic model based on the power of covariate tests. Simulations from spline models including time-dependent covariates were helpful to evaluate the performance of the Weibull spline models when the standard model is extended to more flexible form, particularly in the presence of time-dependent covariates. The criterion of AIC should not be used independently from the other criteria, since the models with a certain number of knots are not always nested within those with higher number of knots.

8.2 Future work

The aim of the study was to introduce a flexible Weibull model as a parametric alternative to the Cox model when some covariates change over time. In this case, it may be more informative to examine more parametric models besides comparing their performance with the Weibull and the log-logistic models. Further, one of these parametric models can be extended with natural cubic splines, particularly when time-dependent covariates are included in the model. The determination of the knot is an issue in the Weibull spline modelling, and more investigations about this issue are needed. The Weibull model can be extended by different types of splines (e.g., B-splines) and thus compared to the current Weibull spline model.

The Weibull spline model simulation can be performed through rejection sampling algorithm when a suitable envelope distribution is employed. In this case, a comparison between this algorithm and the numerical algorithm that has been applied in this thesis may be useful. Also, feasible spline parameter specification in the spline models with more than one knot needs more investigation to achieve more accurate specifications about these information prior to run the simulation. Finally, performance of the Weibull spline model with binary time-dependent covariate needs to be checked through more simulation scenarios to allow for more evaluations for such model against the Weibull standard model when one or more covariates are involved as time-dependent with one change.

Appendix A

Data codes (DCOD, PCD for heart data and CAUSE for cornea data)

Donor cause of death (DCOD)
0 Living donor
10 Intracranial haemorrhage
11 Intracranial thrombosis
12 Brain tumour
13 Hypoxic brain damage - all causes
19 Intracranial - type unclassified (CVA)
20 Trauma - RTA - car
21 Trauma - RTA - motorbike
22 Trauma - RTA - pushbike
23 Trauma - RTA - pedestrian
29 Trauma - RTA - unknown type
30 Other trauma - suicide
31 Other trauma - accident
39 Other trauma - unknown cause
40 Cardiac arrest
41 Myocardial infarction
42 Aneurysm
43 Ischaemic heart disease
44 Congestive cardiac failure
45 Pulmonary embolism
49 Cardiovascular - type unclassified
50 Chronic pulmonary disease
51 Pneumonia
52 Asthma
53 Respiratory failure
54 Carbon monoxide poisoning
59 Respiratory - type unclassified (inc smoke inhalation)
60 Cancer, other than brain tumour
70 Meningitis
71 Septicaemia
72 Infections - type unclassified
73 Acute blood loss/hypovolaemia
74 Liver failure (not self poisoning)

75 Renal failure
76 Multi-organ failure
77 Sudden infant death syndrome
80 Alcohol poisoning
81 Paracetamol overdose
82 Other drug overdose (please specify)
85 Self poisoning - type unclassified
88 Not reported
90 Other
99 Unknown

Primary cardiothoracic disease (PCD)
310 Coronary heart disease
311 Dilated cardiomyopathy - type unspecified
313 Valvular heart disease
314 Congenital heart disease
319 Other heart disease
320 Primary pulmonary hypertension
321 Eisenmengers syndrome - type unspecified
322 Cystic fibrosis
323 Fibrosing lung disease
324 Inhalation
325 Alpha-1-antitrypsin deficiency
326 Sarcoid
327 Emphysema
328 Bronchiectasis
330 Immediate graft failure
331 Acute rejection
332 Coronary occlusive disease
333 Hyper acute rejection
334 Chronic rejection
335 Non-specific graft failure
337 Bronchiolitis obliterans
338 Allograft vascular disease
341 Dilated cardiomyopathy - idiopathic
342 Dilated cardiomyopathy - familial
343 Dilated cardiomyopathy - myocarditis
344 Dilated cardiomyopathy - alcohol
345 Dilated cardiomyopathy - post partum
346 Dilated cardiomyopathy - adriamycin
349 Dilated cardiomyopathy - other, specify
350 Hypertrophic cardiomyopathy
351 Restrictive cardiomyopathy
361 Eisenmengers syndrome - ASD
362 Eisenmengers syndrome - VSD
363 Eisenmengers syndrome - PDA
364 Eisenmengers syndrome - other, specify
370 Other congenital heart/lung disease
398 Other

399 Unknown
888 Not reported

Cause of corneal graft failure (CAUSE)

1 Ectasias
2 Dystrophies
3 Prev ocular surgery-pseudophakic corneal odema
4 Prev ocular surgery-aphakic corneal odema
5 Prev ocular surgery-other
6 Infection
7 Chronic inflammation
8 Injury
9 Opacification
10 Ulcerative keratitis/corneal melt
11 Other

Appendix B

SAS codes for heart transplant models

B.1 SAS codes for heart data input in Counting process style

```
data creat1;
infile cards missover;
input obs time dead dage dcmv1 dcmv2 rpcd1 rpcd2
rpcd3 cyclo fk506 other  c1-c14;
array tt{14} t1-t14 (1 90  360 720 1080  1440
1800 2160 2520 2880 3240 3600 3960 4320);
     datalines;
1 3290 0 33 1 0 1 0 0 2 1 1 52.24 47.33 37.43
50.27 57.65 39.52 50.07 49.88 41.89 45.66 51.463 56.64
2 92 1 52 0 1 0 0 0 2 1 1 36.54 37.79 11.78
3 2756 1 24 1 0 1 0 0 2 1 1 50.04 50.05 42.31
33.01 38.35 39.02 38.89 46.8 37.34 40.48 37.61
run;
data creat2(keep=obs time dead dage dcmv1 dcmv2 rpcd1
rpcd2 rpcd3 cyclo fk506 other T1
 T2 Time2 creat status);
   array pp{*} c1-c13;
   array qq{*} c2-c14;
   array tt{1:14} _temporary_
      (1 90  360 720 1080  1440 1800 2160 2520 2880 3240 3600
      3960 4320  );
   set creat1(drop=t1-t14);
   T1 = 0;
   T2 = 0;
   Status = 0;
   if ( Time = tt[1] ) then do;
      T2 = tt[1];
      Time2 = T2-T1;
      creat = c1;
      Status = Dead;

   end;
```

```
   else do _i_=1 to dim(pp);
      if ( tt[_i_] = Time ) then do;
         T2= Time;
         Time2 = T2-T1;
        creat = pp[_i_] ;
         Status = Dead;

      end;
      else if (tt[_i_]  < Time ) then do;
         if (pp[_i_]  ^= qq[_i_] ) then do;
            if qq[_i_]  = . then T2= Time;
            else                 T2= tt[_i_] ;
           Time2 = T2-T1;
         creat= pp[_i_] ;
            Status= 0;
            output;
            T1 = T2;
         end;
      end;
   end;
   if ( Time >= tt[1] ) then do;
      T2 = Time;
      Time2 = T2-T1;
  if t1=0 then creat=c1 ;


  else if t1=1 and t1<90 then   creat = c2 ;
  else if t1=90 and t1<360 then creat=c3;
else if t1=360 and t1<720 then creat=c4;
else if t1=720 and t1<1080 then creat=c5;
else if t1=1080 and t1<1440 then creat=c6;
else if t1=1440 and t1<1800 then creat=c7;
else if t1=1800 and t1<2160 then creat=c8;
else if t1=2160 and t1<2520 then creat=c9;
else if t1=2520 and t1<2880 then creat=c10;
else if t1=2880 and t1<3240 then creat=c11;
else if t1=3240 and t1<3600 then creat=c12;
else if t1=3600 and t1<3960 then creat=c13;
else if t1=3960  then creat=c14;

      Status = Dead;
      output;
   end;

run;
proc print data=creat2
run;

data creat3;
```

```
set creat2;
if time>T2 then delete;
if T1<time then status=0;
else if time=T2 then dead=dead;


dage=dage;
dcmv1=dcmv1;
dcmv2=dcmv2;
rpcd1=rpcd1;
rpcd2=rpcd2;
rpcd3=rpcd3;
rpcd=rpcd;
cyclo=cyclo;
fk506=fk506;
other=other;
T1=time;
T2=time;
status=dead;
gfr=creat;

if time>T1 then status=0;
if t1=0 then t1=.0000001;
if creat>89 then gfr1=1;
else gfr1=0;
if 60<creat<=89 then gfr2=1;
else gfr2=0;
if 30<creat<=59 then gfr3=1;
else gfr3=0;
inter1=cyclo*fk506;
inter2=cyclo*other;
run;
proc sort data=creat4;
by obs;
run;
data creat5;
set creat4;
if status=0 then delete;
run;
```

B.2 SAS codes for fitting parametric models with time-dependent covariate

```
 data par2b(type=est);
keep _type_ b0 b1 b2 b3 b4 b5 b6 b7 b8 b9 b10 b11 alpha;
_type_='parms';
b0 = 1; b1 = 1; b2 = 1; b3 = 1; b4 = 1 ; b5 = 1; b6 =1 ; b7 = 1; b8 = 1;
b9 = 1 ;b10 = 1;b11 = 1; alpha = 1;
```

```
   output;
run;
proc nlp data=creat5 tech=newrap inest=par2b cov=2 vardef=n;
   max loglik;
   parms b0 b1 b2 b3 b4 b5 b6 b7 b8 b9 b10 b11 alpha;
   sig=exp(b0+b1*dage+b2*dcmv1+b3*dcmv2+b4*rpcd1+b5*rpcd2+b6*cyclo
   +b7*fk506+b8*other
   +b9*inter1+b10*inter2+b11*creat);
   s    =  (time1 / sig)**(1/alpha) - (time2 / sig)**(1/alpha);
   if status=1 then s + log(1/alpha) - (1/alpha)*log(sig)
    + (1/alpha-1)*log(time1);
   loglik = s;
   title 'Weibull model (continuous GFR) ';
run;

data par2b(type=est);
   keep _type_ b0 b1 b2 b3 b4 b5 b6 b7 b8 b9 b10 b11 alpha;
   _type_='parms';
   b0 = 1; b1 = 1; b2 = 1; b3 = 1; b4 = 1 ; b5 = 1; b6 =1 ; b7 = 1;
    b8 = 1;b9 = 1 ;b10 = 1;b11 = 1; alpha = 1;
   output;
run;
proc nlp data=creat tech=newrap inest=par3b cov=2 vardef=n;
   max loglik;
   parms b0 b1 b2 b3 b4 b5 b6 b7 b8 b9 b10 b11 scale;
   sig=b0+b1*dage+b2*dcmv1+b3*dcmv2+b4*rpcd1+b5*rpcd2+b6*cyclo+b7*fk506
   +b8*other+b9*inter1+b10*inter2+b11*creat;
   gamma=1/scale;
   alpha=exp(-sig/scale);
   f2=alpha*gamma*time1**(gamma-1)/((1+alpha*time1**gamma)**2);
   if time1=0 then s1=1;
           else s1=1/(1+alpha*time1**gamma);
   s2=1/(1+alpha*time2**gamma);
   if status=1 then loglik = log(f2)-log(s1);
               else loglik = log(s2)-log(s1);
   title 'Log-logistic model (continuous GFR)';
run;
```

B.3 SAS codes for generating survival times from Weibull standard model with time-dependent covariates based on heart data

```
data g;
nsam=10000;
n=1500;
do sample=1 to nsam;
do i=1 to n;
```

```
obs=i;
Z3=0.73877+0.58843*RANNOR(1234);
Z4=0.30754+0.35241*RANNOR(1234);
Z5=0.64560+0.17526*rannor(1234);
Z6= 0.03156+0.14455*rannor(1234);
Z7=0.17052+0.29862*rannor(1234);
y3=exp(z3);
y4=exp(z4);
y5=exp(z5);
y6=exp(z6);
y7=exp(z7);
if y3<= 1.69 then rpcd1=1;
 else rpcd1=0;
 if 1.69<y3<=1.97  then rpcd2=1;
 else rpcd2=0;
 if 1.97<y3<=2.95 then rpcd3=1;
 else rpcd3=0;
if y4<= 1.43 then dcmv1=1;
 else dcmv1=0;
 if 1.43<y4<=2.99  then dcmv2=1;
 else dcmv2=0;
 if y5 <= 1.47 then cyclo=1;
 else cyclo=0;
 if y6 <=1.31   then fk506=1;
 else fk506=0;
 if y7 <=1.45 then other=1;
 else other=0;

dd=3.49744+0.38541*rannor(1234);
dage=exp(dd);
in=270+85*rannor(12344);
v=33*rannor(12356);
         rho = -.52;

            /* first error term */
         eps = rho * rannor( 47392 ) + 20*rannor( 82745 );
c1 = in+v+1 + 1.5 * 0 + eps;
c2 = in+v+1 + 1.5 * .03 + eps;
c3 = in+v+1 + 1.5 * .25 + eps;
c4 = in+v+1 + 1.5 * 1 + eps;
c5 = in+v+1 + 1.5 * 2 + eps;
c6 = in+v+1 + 1.5 * 3 + eps;
c7 = in+v+1 + 1.5 * 4 + eps;
c8 = in+v+1 + 1.5 * 5 + eps;
c9 = in+v+1 + 1.5 * 6 + eps;
c10 = in+v+1 + 1.5 * 7 + eps;
c11= in+v+1 + 1.5 * 8 + eps;
c12= in+v+1 + 1.5 * 9 + eps;
c13= in+v+1 + 1.5 * 10 + eps;
```

```
c14= in+v+1 + 1.5 * 11 + eps;
            eps=eps;
            eps = rho * eps  + rannor( 32815 );
b=.01;
la=.00000002;

factor=la+.015*dage+.7673*dcmv1+1.298*dcmv2+.2395*rpcd1
+.1365*rpcd2-.4571*rpcd3-2.545*cyclo-2.504*fk506-.5769*other;


f0=(exp((factor-b*c1)))**.5;
f1=(exp((factor-b*c2)))**.5;
f2=(exp((factor-b*c3)))**.5;
f3=(exp((factor-b*c4)))**.5;
f4=(exp((factor-b*c5)))**.5;
f5=(exp((factor-b*c6)))**.5;
f6=(exp((factor-b*c7)))**.5;
f7=(exp((factor-b*c8)))**.5;
f8=(exp((factor-b*c9)))**.5;
f9=(exp((factor-b*c10)))**.5;
f10=(exp((factor-b*c11)))**.5;
f11=(exp((factor-b*c12)))**.5;
f12=(exp((factor-b*c13)))**.5;
f13=(exp((factor-b*c14)))**.5;
f14=(exp((factor-b*c15)))**.5;
f15=(exp((factor-b*c16)))**.5;

H0=f0*1**.5;
H1=H0+f1*(10-1)**.5;
H2=H1+f2*(90-10)**.5;
H3=H2+f3*(360-90)**.5;



H4=H3+f4*(720-360)**.5;
H5=H4+f5*(1080-720)**.5;
H6=H5+f6*(1440-1080)**.5;

H7=H6+f7*(1800-1440)**.5;
H8=H7+f8*(2160-1800)**.5;
H9=H8+f9*(2520-2160)**.5;


H10=H9+f10*(2880-2520)**.5;
H11=H10+f11*(3240-2880)**.5;
H12=H11+f12*(3600-3240)**.5;
H13=H12+f13*(3960-3600)**.5;
H14=H13+f14*(4320-3960)**.5;
```

```
u0=1-exp(-H0);
u1=1-exp(-H1);
u2=1-exp(-H2);
u3=1-exp(-H3);
u4=1-exp(-H4);
u5=1-exp(-H5);
u6=1-exp(-H6);
u7=1-exp(-H7);
u8=1-exp(-H8);
u9=1-exp(-H9);
u10=1-exp(-H10);
u11=1-exp(-H11);
u12=1-exp(-H12);
u13=1-exp(-H13);
u14=1-exp(-H14);


if 0<=u<u0 then time=((((-log(1-u)))/f0))**2;
else if u0<=u<u1 then time=(((((-log(1-u))-f0*1**.5)/f1)+0)**2)+1;
else if u1<=u<u2 then time=(((((-log(1-u))-f1*10**.5)/f2)+0)**2)+10;
else if u2<=u<u3 then time=(((((-log(1-u))-f2*90**.5)/f3)+0)**2)+90;
else if u3<=u<u4 then time=(((((-log(1-u))-f3*360**.5)/f4)+0)**2)+360;
else if u4<=u<u5 then time=(((((-log(1-u))-f4*720**.5)/f5)+0)**2)+720;
else if u5<=u<u6 then time=(((((-log(1-u))-f5*1080**.5)/f6)+0)**2)+1080;
else if u6<=u<u7 then time=(((((-log(1-u))-f6*1440**.5)/f7)+0)**2)+1440;
else if u7<=u<u8 then time=(((((-log(1-u))-f7*1800**.5)/f8)+0)**2)+1800;
else if u8<=u<u9 then time=(((((-log(1-u))-f8*2160**.5)/f9)+0)**2)+2160;
else if u9<=u<u10 then time=(((((-log(1-u))-f9*2520**.5)/f10)+0)**2)+2520;
else if u10<=u<u11 then time=(((((-log(1-u))-f10*2880**.5)/f11)+0)**2)+2880;
else if u11<=u<u12 then time=(((((-log(1-u))-f11*3240**.5)/f12)+0)**2)+3240;
else if u12<=u<u13 then time=(((((-log(1-u))-f12*3600**.5)/f13)+0)**2)+3600;
else if u13<=u<=u14 then time=(((((-log(1-u))-f13*3960**.5)/f14)+0)**2)+3960;


if mod(i,3) then censor=0;
else censor=1;


array tt{14} t1-t14 (1 90  360 720 1080  1440 1800 2160 2520 2880 3240 3600 3960 );
output;
end;
end;
run;
```

B.4 SAS codes for simulation from the 1-knot spline model without covariates using the numerical algorithm

```
    data a1;
do sample=1 to 100;
do i=1 to 150;
u=ranuni(0);
if .999400>=u>0.391332 then do
b=log(-log(u))-log(.037);

x0 = 5;
     diff = 10e-8 ;
     abdiff = 10 ;
     iter = 0 ;
     iterlim = 50 ;
     do iter = 1 to 50 while (abdiff gt diff) ;
     x1 = x0 - ((-.0019*(x0)**3+1*(x0)**1-b)
     / (-.0057*(x0)**2+1 )) ;
      abdiff = abs(x1 - x0) ;
        eval = -.0019*(x0)**3+1*(x0)**1-b ;
        iter = iter + 0;
x0 = x1 ;
time2=exp(x1);
output;
end;
end;
if  0.288804<=u<=0.391332 then do
b=(log(-log(u)))-log(9e-6)+19.5329;
x0 = 1 ;
diff = 10e-8 ;
abdiff = 10 ;
iter = 0 ;
iterlim = 50 ;
do iter = 1 to 50 while (abdiff gt diff) ;
x1 = x0 - (.0231*(x0)**3-.6908*(x0)**2+7.3623*(x0)**1-b)
/ (0.0693*(x0)**2-1.3816*(x0)**1+7.3623) ;
abdiff = abs(x1 - x0) ;
eval =.0231*(x0)**3-.6908*(x0)**2+7.3623*(x0)**1-b ;
iter = iter + 0 ;
x0 = x1 ;
time2=exp(x1);
output;
end;end;end;end;
run;
data a2;
set a1;
if abdiff gt diff then delete;
```

```
if mod(i,1) then censor=0;
else censor=1;
run;
data final;
set a2;
by sample;
run;
proc means data=final n min max median q1 q3 noprint;
by sample;
var time1;
run;
proc means data=final  noprint;
by sample;
var u time1;
run;
proc means data=final n min max median q1 q3 noprint;
by sample;
var time1;
run;
proc means data=final min max median mean q3 q1 noprint;
by sample;
var  time1  censor t;
run;
proc univariate data=final noprint;
by sample;
var time1;
output out=final1 pctlpre=P_ pctlpts= 0, 17, 20,
 25, 40, 33, 60, 67, 50, 75, 80, 83, 100;
run;
data final2;
set final1;
by sample;
do i=1 to 100;
s11=P_0;s12=P_100;s13=P_17;s14=P_20;s114=P_25;s15=P_33;
s115=P_40;s16=P_50;s116=P_60;s17=P_67;s18=P_75;s19=P_80;s20=P_83;
output;end;
run;
data par3b(type=est);
   keep _type_ b0   alpha;
   _type_='parms';
   b0 =  .000001; alpha = 1;
   output;
run;
proc nlp data=final tech=newrap inest=par3b out=q
cov=2 vardef=n noprint;
by sample;
   max loglik;
   parms  b0  alpha;
   eta2=b0+(1/alpha)*(log(time1));
```

```
expterm2=exp(eta2);
hazard=abs(expterm2*((1/time1)*((1/alpha))));
survivor=-expterm2;
   if censor=1 then survivor + log(hazard);
   loglik = survivor;
title 'Weibull with 0 knots';
 run;
data final3;
set final;
set final2;
by sample;
kmin=log(s11);
kmax=log(s12);
k2=log(s16);
lambda2=(kmax-k2)/(kmax-kmin);
if (log(time1)-k2)<0 then cond1=0;
else cond1=(log(time1)-k2);
if (log(time1)-kmin)<0 then cond2=0;
else cond2=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond3=0;
else cond3=(log(time1)-kmax);
basisfunc2=(cond1**3)-(lambda2*(cond2**3))-((1-lambda2)*(cond3**3));
run;
data par3b(type=est);
   keep _type_ b0  b12 alpha;
   _type_='parms';
   b0 =.001;b12=-.01;alpha =.6;
   output;
run;
proc nlp data=final3 tech=newrap inest=par3b out=q1 cov=2 vardef=n noprint ;
by sample;
   max loglik;
   parms  b0  b12  alpha;
   eta2=b0+b12*basisfunc2+(1/alpha)*(log(time1));
expterm2=exp(eta2);
hazard=(expterm2*((1/time1)*((1/alpha)+((3*b12)*((cond1**2)
-(lambda2*(cond2**2))-(1-lambda2)*(cond3**2))))));
survivor=-expterm2;
   if censor=1 then survivor +log( hazard);
   loglik = survivor;
title 'Weibull with 1 knot';
run;
data final3;
set final;
set final2;
by sample;
kmin=log(s11);
kmax=log(s12);
k3=log(s15);
```

```
k2=log(s17);
lambda2=(kmax-k2)/(kmax-kmin);
if (log(time1)-k2)<0 then cond1=0;
else cond1=(log(time1)-k2);
if (log(time1)-kmin)<0 then cond2=0;
else cond2=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond3=0;
else cond3=(log(time1)-kmax);
basisfunc2=(cond1**3)-(lambda2*(cond2**3))-((1-lambda2)*(cond3**3));
lambda3=(kmax-k3)/(kmax-kmin);
if (log(time1)-k3)<0 then cond4=0;
else cond4=(log(time1)-k3);
if (log(time1)-kmin)<0 then cond5=0;
else cond5=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond6=0;
else cond6=(log(time1)-kmax);
basisfunc3=(cond4**3)-(lambda3*(cond5**3))-((1-lambda3)*(cond6**3));
run;
data par3b(type=est);
   keep _type_ b0  b12 b13 alpha;
   _type_='parms';
   b0 =.001; b12=-.01;b13 =-.01;alpha =.6;
   output;
run;
proc nlp data=final3 tech=newrap inest=par3b out=q2 cov=2 vardef=n noprint;
by sample;
   max loglik;
   parms  b0  b12 b13  alpha;
   eta2=b0+b12*basisfunc2+b13*basisfunc3+(1/alpha)*(log(time1));
expterm2=exp(eta2);
der1= ((cond1**2)-(lambda2*(cond2**2))-((1-lambda2)*(cond3**2)))     ;
if der1<0 then der1=der1;
der2=((cond4**2)-(lambda3*(cond5**2))-((1-lambda3)*(cond6**2)))  ;
if der2<0 then der2=der2;
hazard=(expterm2*((1/time1)*((1/alpha)+((3*b12)*der1)+((3*b13)*der2))));
survivor=-expterm2;
   if censor=1 then survivor +log( hazard);
   loglik = survivor;
title 'Weibull with 2 knots';
run;
data final3;
set final;
set final2;
by sample;
kmin=log(s11);
kmax=log(s12);
k5=log(s19);
k4=log(s18 );
k3=log(s16);
```

```
k2=log(s114);
lambda2=(kmax-k2)/(kmax-kmin);
if (log(time1)-k2)<0 then cond1=0;
else cond1=(log(time1)-k2);
if (log(time1)-kmin)<0 then cond2=0;
else cond2=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond3=0;
else cond3=(log(time1)-kmax);
basisfunc2=((cond1**3)-(lambda2*(cond2**3))-((1-lambda2)*(cond3**3)));
lambda3=(kmax-k3)/(kmax-kmin);
if (log(time1)-k3)<0 then cond4=0;
else cond4=(log(time1)-k3);
if (log(time1)-kmin)<0 then cond5=0;
else cond5=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond6=0;
else cond6=(log(time1)-kmax);
basisfunc3=((cond4**3)-(lambda3*(cond5**3))-((1-lambda3)*(cond6**3)));
lambda4=(kmax-k4)/(kmax-kmin);
if (log(time1)-k4)<0 then cond7=0;
else cond7=(log(time1)-k4);
if (log(time1)-kmin)<0 then cond8=0;
else cond8=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond9=0;
else cond9=(log(time1)-kmax);
basisfunc4=((cond7**3)-(lambda4*(cond8**3))-((1-lambda4)*(cond9**3)));
run;
data par3b(type=est);
   keep _type_ b0  b12 b13 b14   alpha;
   _type_='parms';
   b0 =  .001;b12=  -.01;b13 = -.01;b14 = -.01;alpha =.6;
   output;
run;
proc nlp data=final3 tech=newrap inest=par3b out=q3 cov=2 vardef=n noprint;
by sample;
   max loglik;
   parms  b0  b12 b13 b14    alpha;
   eta2=b0+b12*basisfunc2+b13*basisfunc3+b14*basisfunc4+(1/alpha)*(log(time1));
expterm2=exp(eta2);
hazard=(expterm2*((1/time1)*((1/alpha)+(
(3*b12)*((cond1**2)-(lambda2*(cond2**2))-((1-lambda2)*(cond3**2)))
+((3*b13)*((cond4**2)-(lambda3*(cond5**2))-((1-lambda3)*(cond6**2))))
+((3*b14)*((cond7**2)-(lambda4*(cond8**2))-((1-lambda4)*(cond9**2)))))));
survivor=-expterm2;
   if censor=1 then survivor +log( hazard);
   loglik = survivor;
title 'Weibull with 3 knots';
run;
data final3;
set final;
```

```
set final2;
by sample;
kmin=log(s11);
kmax=log(s12);
k5=log(s19);
k4=log(s18 );
k3=log(s16);
k2=log(s114);
lambda2=(kmax-k2)/(kmax-kmin);
if (log(time1)-k2)<0 then cond1=0;
else cond1=(log(time1)-k2);
if (log(time1)-kmin)<0 then cond2=0;
else cond2=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond3=0;
else cond3=(log(time1)-kmax);
basisfunc2=((cond1**3)-(lambda2*(cond2**3))-((1-lambda2)*(cond3**3)));
lambda3=(kmax-k3)/(kmax-kmin);
if (log(time1)-k3)<0 then cond4=0;
else cond4=(log(time1)-k3);
if (log(time1)-kmin)<0 then cond5=0;
else cond5=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond6=0;
else cond6=(log(time1)-kmax);
basisfunc3=((cond4**3)-(lambda3*(cond5**3))-((1-lambda3)*(cond6**3)));
lambda4=(kmax-k4)/(kmax-kmin);
if (log(time1)-k4)<0 then cond7=0;
else cond7=(log(time1)-k4);
if (log(time1)-kmin)<0 then cond8=0;
else cond8=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond9=0;
else cond9=(log(time1)-kmax);
basisfunc4=((cond7**3)-(lambda4*(cond8**3))-((1-lambda4)*(cond9**3)));
lambda5=(kmax-k5)/(kmax-kmin);
if (log(time1)-k5)<0 then cond10=0;
else cond10=(log(time1)-k5);
if (log(time1)-kmin)<0 then cond11=0;
else cond11=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond12=0;
else cond12=(log(time1)-kmax);
basisfunc5=((cond10**3)-(lambda5*(cond11**3))-((1-lambda5)*(cond12**3)));
run;
data par3b(type=est);
   keep _type_ b0  b12 b13 b14 b15  alpha;
   _type_='parms';
   b0 =  .001;b12= -.01;b13 =-.01;b14 =-.01;b15=-.01;alpha =.6;
   output;
run;
proc nlp data=final3 tech=newrap inest=par3b out=q4 cov=2 vardef=n  noprint;
by sample;
```

```
   max loglik;
   parms  b0  b12 b13 b14  b15  alpha;
   eta2=b0+b12*basisfunc2+b13*basisfunc3+b14*basisfunc4+b15*basisfunc5
   +(1/alpha)*(log(time1));
expterm2=exp(eta2);
hazard=(expterm2*((1/time1)*((1/alpha)+
((3*b12)*((cond1**2)-(lambda2*(cond2**2))-((1-lambda2)*(cond3**2))))
+((3*b13)*((cond4**2)-(lambda3*(cond5**2))-((1-lambda3)*(cond6**2))))
+((3*b14)*((cond7**2)-(lambda4*(cond8**2))-((1-lambda4)*(cond9**2))))
+((3*b15)*((cond10**2)-(lambda5*(cond11**2))-((1-lambda5)*(cond12**2)))))));
survivor=-expterm2;
   if censor=1 then survivor +log( hazard);
   loglik = survivor;
 title 'Weibull with 4 knots';
   run;
data final3;
set final;
set final2;
by sample;
kmin=log(s11);
kmax=log(s12);
k6=log(s20);
k5=log(s17);
k4=log(s18 );
k3=log(s16);
k2=log(s114);
lambda2=(kmax-k2)/(kmax-kmin);
if (log(time1)-k2)<0 then cond1=0;
else cond1=(log(time1)-k2);
if (log(time1)-kmin)<0 then cond2=0;
else cond2=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond3=0;
else cond3=(log(time1)-kmax);
basisfunc2=((cond1**3)-(lambda2*(cond2**3))-((1-lambda2)*(cond3**3)));
lambda3=(kmax-k3)/(kmax-kmin);
if (log(time1)-k3)<0 then cond4=0;
else cond4=(log(time1)-k3);
if (log(time1)-kmin)<0 then cond5=0;
else cond5=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond6=0;
else cond6=(log(time1)-kmax);
basisfunc3=((cond4**3)-(lambda3*(cond5**3))-((1-lambda3)*(cond6**3)));
lambda4=(kmax-k4)/(kmax-kmin);
if (log(time1)-k4)<0 then cond7=0;
else cond7=(log(time1)-k4);
if (log(time1)-kmin)<0 then cond8=0;
else cond8=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond9=0;
else cond9=(log(time1)-kmax);
```

```
basisfunc4=((cond7**3)-(lambda4*(cond8**3))-((1-lambda4)*(cond9**3)));
lambda5=(kmax-k5)/(kmax-kmin);
if (log(time1)-k5)<0 then cond10=0;
else cond10=(log(time1)-k5);
if (log(time1)-kmin)<0 then cond11=0;
else cond11=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond12=0;
else cond12=(log(time1)-kmax);
basisfunc5=((cond10**3)-(lambda5*(cond11**3))-((1-lambda5)*(cond12**3)));
lambda6=(kmax-k6)/(kmax-kmin);
if (log(time1)-k6)<0 then cond13=0;
else cond13=(log(time1)-k6);
if (log(time1)-kmin)<0 then cond14=0;
else cond14=(log(time1)-kmin);
if (log(time1)-kmax)<0 then cond15=0;
else cond15=(log(time1)-kmax);
basisfunc6=((cond13**3)-(lambda6*(cond14**3))-((1-lambda6)*(cond15**3)));
run;
data par3b(type=est);
   keep _type_ b0  b12 b13 b14 b15  b16 alpha;
   _type_='parms';
   b0 = .01;b12= -.01;b13 =-.01;b14 =-.01;b15=-.01;b16= -.01;alpha = .6;
   output;
run;
proc nlp data=final3 tech=newrap inest=par3b out=q5 cov=2 vardef=n noprint;
by sample;
   max loglik;
   parms  b0  b12 b13 b14  b15  b16 alpha;
   eta2=b0+b12*basisfunc2+b13*basisfunc3+b14*basisfunc4
   +b15*basisfunc5+b16*basisfunc6+(1/alpha)*(log(time1));
expterm2=exp(eta2);
hazard=(expterm2*((1/time1)*((1/alpha)
+((3*b12)*((cond1**2)-(lambda2*(cond2**2))-((1-lambda2)*(cond3**2))))
+((3*b13)*((cond4**2)-(lambda3*(cond5**2))-((1-lambda3)*(cond6**2))))
+((3*b14)*((cond7**2)-(lambda4*(cond8**2))-((1-lambda4)*(cond9**2))))
+((3*b15)*((cond10**2)-(lambda5*(cond11**2))-((1-lambda5)*(cond12**2))))
+((3*b16)*((cond13**2)-(lambda6*(cond14**2))-((1-lambda6)*(cond15**2)))))));
survivor=-expterm2;
   if censor=1 then survivor +log( hazard);
   loglik = survivor;
title 'Weibull with 5 knots';
   run;
```

B.5 SAS codes for fitting Weibull spline model with time-dependent covariates (heart data)

```
proc univariate data=creat5 noprint;
var t1;
output out=final1 pctlpre=P_ pctlpts= 0, 17, 20, 25, 40, 33, 60, 67, 50, 75,
80, 83, 100;
run;
data final2;
set final1;
do i=1 to n;
s11=P_0; s12=P_100; s13=P_17; s14=P_20; s15=P_25; s16=P_33; s17=P_40;
s18=P_50;s19=P_60; s20=P_67; s21=P_75; s22=P_80; s23=P_83;
output;
end;
run;
data n;
set creat4;
set final2;
kmin=log(s11);
kmax=log(s12);
k6=log(s13);
k5=log(s16);
k4=log(s18);
k3=log(s20);
k2=log(s23);
lambda2=(kmax-k2)/(kmax-kmin);
if (log(t1)-k2)<0 then cond1=0;
else cond1=(log(t1)-k2);
if (log(t1)-kmin)<0 then cond2=0;
else cond2=(log(t1)-kmin);
if (log(t1)-kmax)<0 then cond3=0;
else cond3=(log(t1)-kmax);
basisfunc2=((cond1**3)-(lambda2*(cond2**3))-((1-lambda2)*(cond3**3)));
lambda3=(kmax-k3)/(kmax-kmin);
if (log(t1)-k3)<0 then cond4=0;
else cond4=(log(t1)-k3);
if (log(t1)-kmin)<0 then cond5=0;
else cond5=(log(t1)-kmin);
if (log(t1)-kmax)<0 then cond6=0;
else cond6=(log(t1)-kmax);
basisfunc3=((cond4**3)-(lambda3*(cond5**3))-((1-lambda3)*(cond6**3)));
lambda4=(kmax-k4)/(kmax-kmin);
if (log(t1)-k4)<0 then cond7=0;
else cond7=(log(t1)-k4);
if (log(t1)-kmin)<0 then cond8=0;
else cond8=(log(t1)-kmin);
if (log(t1)-kmax)<0 then cond9=0;
```

```
else cond9=(log(t1)-kmax);
basisfunc4=((cond7**3)-(lambda4*(cond8**3))-((1-lambda4)*(cond9**3)));
lambda5=(kmax-k5)/(kmax-kmin);
if (log(t1)-k5)<0 then cond10=0;
else cond10=(log(t1)-k5);
if (log(t1)-kmin)<0 then cond11=0;
else cond11=(log(t1)-kmin);
if (log(t1)-kmax)<0 then cond12=0;
else cond12=(log(t1)-kmax);
basisfunc5=((cond10**3)-(lambda5*(cond11**3))-((1-lambda5)*(cond12**3)));
lambda6=(kmax-k6)/(kmax-kmin);
if (log(t1)-k5)<0 then cond13=0;
else cond13=(log(t1)-k6);
if (log(t1)-kmin)<0 then cond14=0;
else cond14=(log(t1)-kmin);
if (log(t1)-kmax)<0 then cond15=0;
else cond15=(log(t1)-kmax);
basisfunc6=((cond13**3)-(lambda6*(cond14**3))-((1-lambda6)*(cond15**3)));
run;
data par3b(type=est);
   keep _type_ b0 b1 b2 b3 b4  b5 b6 b7 b8 b9 b10 b11 b12 b13  alpha;
   _type_='parms';
   b0 = .0001; b1 = .09; b2 = .01; b3 = .01; b4 = .001; b5 = .01;
   b6 = .01;b7 = .1; b8 = .01; b9 = .01; b10 = .001; b11= .001;
   b12= .001; b13= .01;alpha = 1.1;
   output;
run;
proc nlp data=n tech=newrap inest=par3b cov=2 maxiter=300 vardef=n ;
max loglik;
   parms  b0 b1 b2 b3 b4  b5 b6 b7 b8 b9 b10 b11 b12 b13 alpha;
   eta2=b0+b1*dage+b2*dcmv1+b3*dcmv2+b4*rpcd1+b5*rpcd2+b6*rpcd3
   +b7*cyclo+b8*fk506+b9*other+b10*gfr1+b11*gfr2+b12*gfr3
   +b13*inter1+(1/alpha)*(log(t2));
eta1=b0+b1*dage+b2*dcmv1+b3*dcmv2+b4*rpcd1+b5*rpcd2+b6*rpcd3
+b7*cyclo+b8*fk506+b9*other+b10*gfr1++b11*gfr2+b12*gfr3
+b13*inter1+(1/alpha)*(log(t1));
expterm2=exp(eta2);
expterm1=exp(eta1);
hazard=log(expterm1*((1/t1)*((1/alpha))));
survivor=expterm1-expterm2;
   if status=1 then survivor + hazard;
   loglik = survivor;
title 'Weibull with 0 knots';
   run;
data par3b(type=est);
   keep _type_ b0 b1 b2 b3 b4  b5 b6 b7 b8 b9 b10 b11  b12 b13
   b14 b15 b16 b17 b18 alpha;
   _type_='parms';
   b0 = .0001; b1 = .09; b2 = .01; b3 = .01; b4 = .001; b5 = .01;
```

```
   b6 = .01; b7 = .1; b8 = .01; b9 = .01; b10 = .001; b11= .001;
   b12= .001; b13= .01; b14 =  -.01; b15 = .01; b16 = .01;
   b17 = .01; b18 = .01; alpha = 1.1;
   output;
run;
proc nlp data=n tech=newrap inest=par3b cov=2 maxiter=300 vardef=n ;
max loglik;
   parms  b0 b1 b2 b3 b4  b5 b6 b7 b8 b9 b10 b11  b12 b13  b14 b15
   b16 b17 b18 alpha;
   eta2=b0+b1*dage+b2*dcmv1+b3*dcmv2+b4*rpcd1+b5*rpcd2+b6*rpcd3
   +b7*cyclo+b8*fk506+b9*other+b10*gfr1+b11*gfr2+b12*gfr3
   +b13*inter1+b14*basisfunc2+b15*basisfunc3
   +b16*basisfunc4+b17*basisfunc5+b18*basisfunc6
   +(1/alpha)*(log(t2));
eta1=b0+b1*dage+b2*dcmv1+b3*dcmv2+b4*rpcd1+b5*rpcd2+b6*rpcd3
+b7*cyclo+b8*fk506+b9*other+b10*gfr1+b11*gfr2+b12*gfr3
+b13*inter1+b14*basisfunc2+b15*basisfunc3+b16*basisfunc4
+b17*basisfunc5+b18*basisfunc6+(1/alpha)*(log(t1));
expterm2=exp(eta2);
expterm1=exp(eta1);
hazard=log(expterm1*((1/t1)*((1/alpha)
+((-3*b13)*((cond1**2)-(lambda2*(cond2**2))-((1-lambda2)*(cond3**2))))
+((-3*b14)*((cond4**2)-(lambda3*(cond5**2))-((1-lambda3)*(cond6**2))))
+((-3*b15)*((cond7**2)-(lambda4*(cond8**2))-((1-lambda4)*(cond9**2))))
+((-3*b16)*((cond10**2)-(lambda5*(cond11**2))-((1-lambda5)*(cond12**2)))
+((-3*b17)*((cond13**2)-(lambda6*(cond14**2))-((1-lambda6)*(cond15**2))))))));
survivor=expterm1-expterm2;
   if status=1 then survivor + hazard;
   loglik = survivor;
title 'Weibull with 5 knots';
   run;
```

B.6 SAS codes for generating survival times from Weibull spline model (1 knot) with time-dependent covariates based on heart data

```
    data g;
do sample=1 to 2000;
do i=1 to 1800;
if mod(i, 3) then dead=0;
else dead=1;
obs=i;
Z3=0.73877+0.58843*RANNOR(1234);
Z4=0.30754+0.35241*RANNOR(1234);
Z5=0.64560+0.17526*rannor(1234);
```

```
Z6= 0.03156+0.14455*rannor(1234);
Z7=0.17052+0.29862*rannor(1234);
y3=exp(z3);
y4=exp(z4);
y5=exp(z5);
y6=exp(z6);
y7=exp(z7);
if y3<= 1.69 then rpcd1=1;
 else rpcd1=0;
 if 1.69<y3<=1.97  then rpcd2=1;
 else rpcd2=0;
 if 1.97<y3<=2.95 then rpcd3=1;
 else rpcd3=0;
if y4<= 1.43 then dcmv1=1;
 else dcmv1=0;
 if 1.43<y4<=2.99  then dcmv2=1;
 else dcmv2=0;
 if y5 <= 1.47 then cyclo=1;
 else cyclo=0;
 if y6 <=1.31   then fk506=1;
 else fk506=0;
 if y7 <=1.45 then other=1;
 else other=0;

dd=3.49744+0.38541*rannor(1234);
dage=exp(dd);
in=270+85*rannor(12344);
v=33*rannor(12356);
         rho = -.52;

            /* first error term */
         eps = rho * rannor( 47392 ) + 20*rannor( 82745 );
c1 = in+v+1 + 1.5 * 0 + eps;
c2 = in+v+1 + 1.5 * .03 + eps;
c3 = in+v+1 + 1.5 * .25 + eps;
c4 = in+v+1 + 1.5 * 1 + eps;
c5 = in+v+1 + 1.5 * 2 + eps;
c6 = in+v+1 + 1.5 * 3 + eps;
c7 = in+v+1 + 1.5 * 4 + eps;
c8 = in+v+1 + 1.5 * 5 + eps;
c9 = in+v+1 + 1.5 * 6 + eps;
c10 = in+v+1 + 1.5 * 7 + eps;
c11= in+v+1 + 1.5 * 8 + eps;
c12= in+v+1 + 1.5 * 9 + eps;
c13= in+v+1 + 1.5 * 10 + eps;
c14= in+v+1 + 1.5 * 11 + eps;
            eps=eps;
            eps = rho * eps  + rannor( 32815 );
```

```
output;
 end;
 end;
run;
data a1;
do sample=1 to 1;
do i=1 to 1;
set g;
la1=(8.63)/1;
be=.007;
u=ranuni(0);
beta1 = 2;
  beta2 = -1;
  lambdat = 0.002; *baseline hazard;
  lambdac = 0.008; *censoring hazard;
  y=2+22-1+4-2+4;
  do i = 1 to 1;
    x1 = normal(0);
    x2 = normal(0);
    linpred = exp(-beta1*x1 - beta2*x2);
    t = rand("WEIBULL", 1, lambdaT * linpred);
    * time of event;
    c = rand("WEIBULL", 1, lambdaC);
           * time of censoring;
    time = min(t, c);    * which came first?;
    dead = (c lt t);

f0=(exp((factor-b1*c1)))**.5;
f1=(exp((factor-b1*c2)))**.5;
f2=(exp((factor-b1*c3)))**.5;
f3=(exp((factor-b1*c4)))**.5;
f4=(exp((factor-b1*c5)))**.5;
f5=(exp((factor-b1*c6)))**.5;
f6=(exp((factor-b1*c7)))**.5;
f7=(exp((factor-b1*c8)))**.5;
f8=(exp((factor-b1*c9)))**.5;
f9=(exp((factor-b1*c10)))**.5;
f10=(exp((factor-b1*c11)))**.5;
f11=(exp((factor-b1*c12)))**.5;
f12=(exp((factor-b1*c13)))**.5;
f13=(exp((factor-b1*c14)))**.5;
f14=(exp((factor-b1*c15)))**.5;
f15=(exp((factor-b1*c16)))**.5;

*************************************************************;

H0=(.5*log(f0))+(.5*log(1))+((.01)*(-.19)*(log(1)**3));
H1=H0+(.5*log(f1))+(.5*log(10))+((.01)*(-.19)*(log(10)**3));
H2=H1+(.5*log(f2))+(.5*log(90))+((.01)*(-.19)*(log(90)**3));
```

```
H3=H2+(.5*log(f3))+(.5*log(360))+((.01)*(-.19)*(log(360)**3));
H4=H3+(.5*log(f4))+(.5*log(720))+((.01)*(-.19)*(log(720)**3));
H5=H4+(.5*log(f5))+(.5*log(1080))+((.01)*(-.19)*(log(1080)**3));
H6=H5+(.5*log(f6))+(.5*log(1440))+((.01)*((log(1440)-6.908)**3
-.19*(log(1440))**3));
H7=H6+(.5*log(f7))+(.5*log(1800))+((.01)*((log(1800)-6.908)**3
-.19*(log(1800))**3));
H8=H7+(.5*log(f8))+(.5*log(2160))+((.01)*((log(2160)-6.908)**3
-.19*(log(2160))**3));
H9=H8+(.5*log(f9))+(.5*log(2520))+((.01)*((log(2520)-6.908)**3
-.19*(log(2520))**3));
H10=H9+(.5*log(f10))+(.5*log(2880))+((.01)*((log(2880)-6.908)**3
-.19*(log(2880))**3));
H11=H10+(.5*log(f11))+(.5*log(3240))+((.01)*((log(3240)-6.908)**3
-.19*(log(3240))**3));
H12=H11+(.5*log(f12))+(.5*log(3600))+((.01)*((log(3600)-6.908)**3
-.19*(log(3600))**3));
H13=H12+(.5*log(f13))+(.5*log(3960))+((.01)*((log(3860)-6.908)**3
-.19*(log(3960))**3));
H14=H13+(.5*log(f14))+(.5*log(4320))+((.01)*((log(4320)-6.908)**3
-.19*(log(4320))**3));


u0=1-exp(-exp(H0));
u1=1-exp(-exp(H1));
u2=1-exp(-exp(H2));
u3=1-exp(-exp(H3));
u4=1-exp(-exp(H4));
u5=1-exp(-exp(H5));
u6=1-exp(-exp(H6));
u7=1-exp(-exp(H7));
u8=1-exp(-exp(H8));
u9=1-exp(-exp(H9));
u10=1-exp(-exp(H10));
u11=1-exp(-exp(H11));
u12=1-exp(-exp(H12));
u13=1-exp(-exp(H13));
u14=1-exp(-exp(H14));

b1=.01;
if 0<=u<u0 then

b=log(-log(u))-f0;
    x0 = 1;
     diff = 10e-8 ;
     abdiff = 10 ;
     iter = 0 ;
     iterlim = 50 ;
```

```
     do iter = 1 to 50 while (abdiff gt diff) ;

        x1 = x0 - ((-.0019*(x0)**3+.5*(x0)**1-b) / (-.0057*(x0)**2
        +.5 )) ;
        abdiff = abs(x1 - x0) ;
        eval = -.0019*(x0)**3+.5*(x0)**1-b ;
        iter = iter + 0;
       x0 = x1 ;
 ttt=exp(x1);
 t0=1;


if u0<=u<u1 then
t=exp(((log(-log(1-u))-(.5*(log(f0)+log(f1)))-(.5*(log(1)))
+(-.17*b1*(log(1))**3))/.5 )+1;
if u1<=u<u2 then
t=exp(((log(-log(1-u))-(.5*(log(f1)+log(f2)))-(.5*(log(10)))
+(-.17*b1*(log(10))**3))/.5 )+10;
if u2<=u<u3 then
t=exp(((log(-log(1-u))-(.5*(log(f2)+log(f3)))-(.5*(log(90)))
+(-.17*b1*(log(90))**3))/.5 )+90;
if u3<=u<u4 then
t=exp(((log(-log(1-u))-(.5*(log(f3)+log(f4)))-(.5*(log(360)))
+(-.17*b1*(log(360))**3))/.5 )+360;
if u4<=u<u5 then
t=exp(((log(-log(1-u))-(.5*(log(f4)+log(f5)))-(.5*(log(720)))
+(-.17*b1*(log(720))**3))/.5 )+720;


if u5<=u<u6 then
t=exp(((log(-log(1-u))-(.5*(log(f5)+log(f6)))
-(-.0025*.83*b1*(log(1080))**3)+(3*.0025*6.98*(log(1080))**2)
-(.5+3*.0025*(6.98)**2)*(log(1080))+(.0025*(6.98)**3))/.5 )+1080;
if u6<=u<u7 then
t=exp(((log(-log(1-u))-(.5*(log(f6)+log(f7)))
-(-.0025*.83*b1*(log(1440))**3)+(3*.0025*6.98*(log(1440))**2)
-(.5+3*.0025*(6.98)**2)*(log(1440))+(.0025*(6.98)**3))/.5 )+1440;
if u7<=u<u8 then
t=exp(((log(-log(1-u))-(.5*(log(f7)+log(f8)))
-(-.0025*.83*b1*(log(1800))**3)+(3*.0025*6.98*(log(1800))**2)
-(.5+3*.0025*(6.98)**2)*(log(1800))+(.0025*(6.98)**3))/.5 )+1800;
if u8<=u<u9 then
t=exp(((log(-log(1-u))-(.5*(log(f8)+log(f9)))
-(-.0025*.83*b1*(log(2160))**3)+(3*.0025*6.98*(log(2160))**2)
-(.5+3*.0025*(6.98)**2)*(log(2160))+(.0025*(6.98)**3))/.5 )+2160;
if u9<=u<u10 then
t=exp(((log(-log(1-u))-(.5*(log(f9)+log(f10)))
-(-.0025*.83*b1*(log(2520))**3)+(3*.0025*6.98*(log(2520))**2)
-(.5+3*.0025*(6.98)**2)*(log(2520))+(.0025*(6.98)**3))/.5 )+2520;
```

```
if u10<=u<u11 then
t=exp(((log(-log(1-u)))-(.5*(log(f10)+log(f11)))
-(-.0025*.83*b1*(log(2880))**3)+(3*.0025*6.98*(log(2880))**2)
-(.5+3*.0025*(6.98)**2)*(log(2880))+(.0025*(6.98)**3))/.5 )+2880;
if u11<=u<u12 then
t=exp(((log(-log(1-u)))-(.5*(log(f11)+log(f12)))
-(-.0025*.83*b1*(log(3240))**3)+(3*.0025*6.98*(log(3240))**2)
-(.5+3*.0025*(6.98)**2)*(log(3240))+(.0025*(6.98)**3))/.5 )+3240;
if u12<=u<u13 then
t=exp(((log(-log(1-u)))-(.5*(log(f12)+log(f13)))
-(-.0025*.83*b1*(log(3600))**3)+(3*.0025*6.98*(log(3600))**2)
-(.5+3*.0025*(6.98)**2)*(log(3600))+(.0025*(6.98)**3))/.5 )+3600;
if u13<=u<u14 then
t=exp(((log(-log(1-u)))-(.5*(log(f13)+log(f14)))
-(-.0025*.83*b1*(log(3960))**3)+(3*.0025*6.98*(log(3960))**2)
-(.5+3*.0025*(6.98)**2)*(log(3960))+(.0025*(6.98)**3))/.5 )+3960;
time=t;

if mod(i,3) then censor=0;
else censor=1;


array tt{14} t1-t14 (1 90  360 720 1080  1440 1800 2160
 2520 2880 3240 3600 3960 );
output;
end;
end;
end;
end;

run;

data a2;
set a1;
by sample;
if abdiff gt diff then delete;
run;

********************************
*((Email: hishastat@yahoo.com))*
********************************
```

Appendix C

Simulation results of the Weibull spline models with fixed covariates

Table C.1: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	30.94	16.04	19.52	22.99	22.81	21.14
CYCLO	-33.28	-26.54	-21.29	-21.47	-19.99	-19.95
FK506	29.63	-4.92	53.29	62.27	26.77	30.42
OTHER	33.34	19.78	21.06	31.54	25.11	23.15
GFR	30.53	19.63	17.34	20.40	21.63	18.35
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	30.09	15.21	17.63	20.96	21.51	19.50
CYCLO	-33.25	-26.52	-21.23	-21.88	-20.49	-20.19
FK506	25.72	-9.45	46.09	56.36	18.54	21.96
OTHER	32.34	18.83	18.66	29.23	23.55	21.34
GFR	28.35	17.41	14.33	16.97	19.25	16.99
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	29.64	14.63	16.65	20.06	20.81	18.70
CYCLO	-33.19	-26.44	-21.12	-20.92	-20.58	-20.13
FK506	25.43	-10.03	44.18	55.89	16.53	19.89
OTHER	30.63	17.08	16.48	27.05	21.69	19.53
GFR	29.59	18.71	15.23	17.78	20.39	18.29

Table C.2: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	31.41	10.81	10.54	10.24	11.32	11.77
CYCLO	-45.49	-34.42	-29.86	-28.82	-24.89	-24.94
FK506	-59.19	-76.01	-70.35	-81.48	-71.42	-71.82
OTHER	28.85	12.55	10.45	16.36	11.93	12.40
GFR	20.96	11.08	6.93	8.16	8.73	8.73
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	34.69	11.56	14.67	11.77	14.07	14.21
CYCLO	-43.15	-35.98	-32.13	-26.90	-27.34	-27.42
FK506	-54.91	-73.99	-64.68	-77.05	-66.56	-67.50
OTHER	32.02	13.28	13.65	18.45	13.92	14.18
GFR	22.39	10.04	7.84	7.31	8.58	8.41
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	28.00	7.78	7.08	6.16	7.74	8.14
CYCLO	-46.33	-36.98	-32.44	-31.81	-28.49	-28.58
FK506	-58.30	-76.03	-70.30	-81.46	-71.44	-71.88
OTHER	25.03	9.42	6.77	13.05	8.16	8.66
GFR	16.80	8.02	3.70	4.12	5.35	5.51

Table C.3: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	37.61	14.20	17.98	15.51	17.33	17.35
CYCLO	-42.86	-34.74	-30.78	-28.06	-25.51	-25.58
FK506	-55.54	-73.76	-64.61	-76.63	-66.42	-67.30
OTHER	33.50	14.34	15.44	19.91	15.53	15.67
GFR	24.70	11.80	10.01	9.61	10.61	10.37
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	34.69	11.56	14.67	11.77	14.07	14.21
CYCLO	-43.15	-35.98	-32.13	-26.90	-27.34	-27.42
FK506	-54.91	-73.99	-64.68	-77.05	-66.56	-67.50
OTHER	32.02	13.28	13.65	18.45	13.92	14.18
GFR	22.39	10.04	7.84	7.31	8.58	8.41
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	33.29	10.12	12.97	9.99	12.42	12.50
CYCLO	-43.24	-36.42	-32.58	-29.36	-27.98	-28.08
FK506	-54.14	-73.54	-64.25	-76.61	-66.13	-67.10
OTHER	29.57	11.24	11.28	15.79	11.59	11.86
GFR	21.83	9.82	7.43	6.74	8.19	8.25

Table C.4: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	25.52	2.39	6.87	6.08	6.16	5.90
CYCLO	-46.67	-39.57	-36.15	-36.53	-36.09	-35.71
FK506	-53.65	-73.13	-61.39	-65.28	-67.18	-65.77
OTHER	22.85	3.04	4.91	9.26	5.41	4.88
GFR	16.16	1.92	0.56	0.13	1.96	1.45
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	22.67	-0.47	3.45	2.35	2.93	2.53
CYCLO	-46.42	-39.90	-36.34	-36.85	-36.52	-36.12
FK506	-53.17	-73.57	-61.61	-65.86	-67.73	-66.22
OTHER	20.93	1.53	2.64	6.69	3.57	2.88
GFR	13.50	-0.46	-2.26	-3.06	-0.65	-1.25
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	22.67	-0.44	3.84	2.00	2.86	2.42
CYCLO	-46.18	-39.86	-35.27	-36.99	-36.44	-36.04
FK506	-52.10	-72.94	-59.68	-64.98	-67.10	-65.57
OTHER	19.23	0.03	1.04	4.71	1.91	1.13
GFR	14.02	0.35	-1.93	-2.80	0.05	-0.62

Table C.5: The Mean square error of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.10521	0.76236	0.55189	2.91185	0.50697	0.50603
FK506	9.25855	9.47249	13.83500	27.36630	12.31355	7.85428
OTHER	0.03984	0.03750	0.03790	0.04225	0.03849	0.03791
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.03091	0.68408	0.46788	1.81275	0.44143	0.43117
FK506	0.67227	0.23769	2.09588	3.00995	0.59485	0.74159
OTHER	0.02095	0.01876	0.01881	0.02168	0.01947	0.01908
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.00477	0.65634	0.43839	3.76460	0.41901	0.40323
FK506	0.61249	0.18887	1.82837	2.82245	0.42288	0.54419
OTHER	0.01462	0.01259	0.01256	0.01485	0.01319	0.01288
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table C.6: The Mean square error of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.94543	1.18740	0.93769	0.74130	0.70914	0.71162
FK506	4.56567	5.80217	5.63505	8.01784	5.17063	5.56587
OTHER	0.03924	0.03688	0.03688	0.03966	0.03702	0.03703
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.92544	1.22172	0.95583	0.96700	0.73866	0.74346
FK506	2.91943	4.82078	4.15165	5.55040	4.27359	4.32120
OTHER	0.02012	0.01809	0.01798	0.01957	0.01808	0.01810
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.91567	1.23879	0.96490	1.85800	0.75630	0.76115
FK506	2.82596	4.76265	4.08489	5.46609	4.21592	4.26587
OTHER	0.01366	0.01194	0.01183	0.01297	0.01190	0.01192
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table C.7: The Mean square error of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.74356	1.20386	0.98127	0.96550	0.72992	0.73290
FK506	4.73015	6.32093	6.17373	9.30215	4.80450	5.79296
OTHER	0.04003	0.03699	0.03731	0.04010	0.03734	0.03732
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.69079	1.19946	0.97189	0.98900	0.72568	0.72987
FK506	2.55302	4.55354	3.51665	4.95006	3.71743	3.81856
OTHER	0.02093	0.01822	0.01832	0.01994	0.01835	0.01836
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.67465	1.20254	0.97166	0.73750	0.73028	0.73527
FK506	2.44790	4.46181	3.42957	4.84995	3.62851	3.73301
OTHER	0.01443	0.01206	0.01209	0.01324	0.01212	0.01213
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table C.8: The Mean square error of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	2.24974	1.58993	1.39972	1.89500	1.29737	1.27383
FK506	4.20555	6.11927	3.70819	6.27622	5.09500	5.37680
OTHER	0.03813	0.03631	0.03659	0.03902	0.03656	0.03658
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.95068	1.46227	1.22642	1.04150	1.23803	1.21285
FK506	2.39637	4.49772	3.20012	3.65517	3.83781	3.67722
OTHER	0.01907	0.01764	0.01773	0.01894	0.01773	0.01773
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	1.90653	1.43414	1.13459	1.87400	1.20720	1.18189
FK506	2.27029	4.38809	2.97015	3.51683	3.73026	3.56787
OTHER	0.01283	0.01164	0.01168	0.01247	0.01168	0.01167
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table C.9: The confidence interval length average of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.46	1.50	1.55	1.55	1.56	1.56
FK506	11.35	12.00	13.22	19.21	13.42	10.37
OTHER	0.75	0.75	0.75	0.78	0.75	0.75
GFR	0.02	0.02	0.02	0.02	0.02	0.02
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.01	1.04	1.07	1.63	1.07	1.08
FK506	1.44	1.59	2.38	2.57	2.20	2.32
OTHER	0.52	0.52	0.52	0.54	0.52	0.52
GFR	0.01	0.01	0.01	0.01	0.01	0.01
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.01	0.01	0.01	0.01	0.01	0.01
CYCLO	0.82	0.84	0.87	.93	0.87	0.87
FK506	1.16	1.28	1.93	2.09	1.76	1.85
OTHER	0.42	0.42	0.42	0.44	0.42	0.42
GFR	0.01	0.01	0.01	0.01	0.01	0.01

Table C.10: The confidence interval length average of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.46	1.53	1.56	1.43	1.61	1.61
FK506	5.10	4.09	4.84	6.33	3.87	4.56
OTHER	0.75	0.75	0.75	0.77	0.75	0.75
GFR	0.02	0.02	0.02	0.02	0.02	0.02
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.00	1.04	1.05	1.47	1.08	1.08
FK506	1.24	1.25	1.29	1.33	1.29	1.28
OTHER	0.52	0.52	0.52	0.54	0.52	0.52
GFR	0.01	0.01	0.01	0.01	0.01	0.01
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.01	0.01	0.01	0.01	0.01	0.01
CYCLO	0.80	0.83	0.84	0.87	0.86	0.86
FK506	0.99	1.00	1.03	1.07	1.03	1.03
OTHER	0.42	0.42	0.42	0.44	0.42	0.42
GFR	0.01	0.01	0.01	0.01	0.01	0.01

Table C.11: The confidence interval length average of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.47	1.52	1.54	127.20	1.58	1.58
FK506	5.33	5.14	6.53	8.31	4.19	5.61
OTHER	0.75	0.75	0.75	0.77	0.75	0.75
GFR	0.02	0.02	0.02	0.02	0.02	0.02
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.01	1.03	1.04	43.27	1.06	1.06
FK506	1.26	1.27	1.34	1.39	1.34	1.34
OTHER	0.52	0.52	0.52	0.54	0.52	0.52
GFR	0.01	0.01	0.01	0.01	0.01	0.01
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.01	0.01	0.01	0.01	0.01	0.01
CYCLO	0.81	0.83	0.83	19.25	0.85	0.85
FK506	1.01	1.02	1.08	1.12	1.08	1.07
OTHER	0.42	0.42	0.42	0.44	0.42	0.42
GFR	0.01	0.01	0.01	0.01	0.01	0.01

Table C.12: The confidence interval length average of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	2.20	1.83	1.96	220.28	1.57	1.57
FK506	5.24	5.21	3.15	6.58	4.68	5.26
OTHER	0.75	0.75	0.75	0.77	0.75	0.75
GFR	0.02	0.02	0.02	0.02	0.02	0.02
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.03	1.06	1.06	93.25	1.07	1.07
FK506	1.24	1.24	1.34	1.42	1.30	1.33
OTHER	0.52	0.52	0.52	0.54	0.52	0.52
GFR	0.01	0.01	0.01	0.01	0.01	0.01
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.01	0.01	0.01	0.01	0.01	0.01
CYCLO	0.83	0.85	0.86	45.38	0.86	0.86
FK506	1.00	1.00	1.08	1.15	1.05	1.07
OTHER	0.42	0.42	0.42	0.44	0.42	0.42
GFR	0.01	0.01	0.01	0.01	0.01	0.01

Table C.13: The percentage bias of parameters in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	25.53	17.38	31.82	39.74	49.75	43.94
GFR2	19.74	16.60	34.07	30.94	39.06	34.48
GFR3	26.45	18.47	32.67	40.63	50.56	44.78
Parameter	**n=1000**					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	27.50	13.85	33.51	27.95	29.12	29.94
GFR2	27.13	14.35	31.21	26.87	27.66	28.62
GFR3	28.50	14.93	34.55	28.96	30.15	30.96
Parameter	**n=1500**					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	23.52	9.38	29.19	23.22	23.88	25.12
GFR2	23.38	10.21	27.05	22.43	22.78	24.10
GFR3	23.84	9.79	29.48	23.55	24.21	25.44

Table C.14: The percentage bias of parameters in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	33.37	11.77	18.53	17.90	18.67	19.17
GFR2	39.79	9.34	15.01	12.66	12.89	18.68
GFR3	33.58	12.49	19.17	18.56	16.31	19.81
Parameter	**n=1000**					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	27.89	2.35	11.09	8.28	9.10	8.90
GFR2	28.71	4.75	12.12	9.93	10.56	10.41
GFR3	28.53	3.10	11.83	9.01	9.84	9.63
Parameter	**n=1500**					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	23.06	-3.25	5.49	2.58	3.32	3.13
GFR2	24.17	-0.44	6.85	4.61	5.15	5.02
GFR3	23.24	-2.97	5.71	2.83	3.56	3.37

Table C.15: The percentage bias of parameters in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	58.09	19.62	46.11	42.51	45.95	44.46
GFR2	46.10	18.92	43.84	40.83	43.67	42.44
GFR3	59.91	19.74	48.24	44.66	48.09	46.60
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	41.67	13.60	27.41	22.55	24.52	23.88
GFR2	41.03	14.84	26.71	22.69	24.29	23.80
GFR3	42.48	14.53	28.27	23.44	25.39	24.76
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	33.58	5.06	18.82	13.94	15.74	15.18
GFR2	34.25	7.66	19.47	15.43	16.89	16.47
GFR3	34.50	6.03	19.78	14.89	16.69	16.13

Table C.16: The percentage bias of parameters in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	46.94	33.54	27.68	24.45	29.43	26.64
GFR2	42.53	20.46	22.86	20.02	24.14	21.85
GFR3	47.33	34.25	28.38	25.13	30.10	27.34
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	29.22	1.30	18.26	10.60	13.11	12.11
GFR2	27.12	1.23	15.83	9.34	11.42	10.61
GFR3	28.97	1.30	18.17	10.52	13.03	12.05
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	21.93	-7.01	10.35	2.01	4.81	3.73
GFR2	21.26	-5.57	9.32	2.31	4.59	3.71
GFR3	22.33	-6.52	10.77	2.46	5.24	4.17

Table C.17: The mean square error of parameters in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	15.6080	4.5990	7.5860	4.4740	2.0046	2.2160
GFR2	13.2770	4.8350	5.0100	3.1180	2.1994	2.2890
GFR3	13.1680	2.7580	4.8630	3.0160	2.1119	2.1950
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.8535	1.1843	2.3565	1.3553	0.7699	1.0103
GFR2	1.7850	1.1232	2.2789	1.2983	0.7306	0.9647
GFR3	1.7717	1.1180	2.2654	1.2866	0.7199	0.9523
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.2727	0.2589	0.2553	0.2142	0.1745	0.1772
GFR2	0.2593	0.2373	0.2427	0.2022	0.1645	0.1685
GFR3	0.2487	0.2342	0.2333	0.1937	0.1564	0.1592

Table C.18: The mean square error of parameters in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	10.3490	4.6910	5.1395	5.4545	5.5180	5.4625
GFR2	8.2225	4.8305	5.0985	5.3490	5.5530	5.4705
GFR3	8.1000	4.7620	5.0115	5.2645	5.4710	5.3890
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.5746	1.7554	1.4340	1.7690	1.7217	1.8016
GFR2	1.5191	1.6772	1.3674	1.6929	1.6461	1.7251
GFR3	1.4999	1.6740	1.3618	1.6877	1.6408	1.7198
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.1715	0.1481	0.1498	0.1485	0.1490	0.1489
GFR2	0.1674	0.1292	0.1332	0.1312	0.1318	0.1317
GFR3	0.1531	0.1291	0.1310	0.1297	0.1301	0.1300

Table C.19: The mean square error of parameters in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	14.2505	6.3090	9.0035	11.6325	10.4580	9.1385
GFR2	13.1055	5.4940	8.9135	11.4575	9.5095	8.1380
GFR3	13.9550	5.4050	8.7825	11.3345	9.3910	8.0195
Parameter	n=1000					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	2.7042	1.7612	2.0013	3.3257	3.1628	2.9321
GFR2	2.6409	1.6875	1.9324	3.2289	3.0705	2.8426
GFR3	2.6093	1.6801	1.9184	3.2158	3.0568	2.8292
Parameter	n=1500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.2327	0.1482	0.1995	0.1968	0.1891	0.1969
GFR2	0.2383	0.1325	0.1882	0.1830	0.1766	0.1838
GFR3	0.2148	0.1297	0.1802	0.1767	0.1697	0.1770

Table C.20: The mean square error of parameters in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	13.6720	11.0850	9.6055	10.6480	6.9995	5.8685
GFR2	11.6220	10.1720	9.4530	10.6200	6.4090	5.1580
GFR3	11.5355	10.1255	9.3685	10.5515	6.3525	5.0975
Parameter	n=1000					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.8689	1.6027	1.3386	2.2730	1.5560	1.4719
GFR2	1.7964	1.5258	1.2714	2.1830	1.4822	1.4001
GFR3	1.7841	1.5237	1.2672	2.1792	1.4787	1.3967
Parameter	n=1500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.1677	0.1484	0.1527	0.1474	0.1490	0.1485
GFR2	0.1572	0.1297	0.1353	0.1292	0.1310	0.1304
GFR3	0.1497	0.1291	0.1341	0.1285	0.1302	0.1296

Table C.21: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	14.81	8.79	11.69	6.43	5.51	5.88
GFR2	14.64	8.61	11.52	6.25	5.43	5.70
GFR3	14.63	8.61	11.52	6.24	5.32	5.69
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	5.29	4.25	5.95	4.50	3.35	3.86
GFR2	5.17	4.13	5.83	4.38	3.23	3.74
GFR3	5.16	4.13	5.83	4.38	3.23	3.74
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.95	1.97	1.83	1.70	1.51	1.51
GFR2	1.85	1.88	1.73	1.60	1.42	1.42
GFR3	1.85	1.87	1.73	1.60	1.41	1.41

Table C.22: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	12.80	10.90	11.87	11.85	10.94	11.15
GFR2	12.62	10.72	11.69	11.67	10.76	11.98
GFR3	12.62	10.72	11.69	11.67	10.76	11.97
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	4.81	5.12	4.60	5.14	5.12	5.17
GFR2	4.69	5.00	4.48	5.02	5.00	5.05
GFR3	4.69	4.99	4.47	5.02	4.99	5.05
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.51	1.51	1.51	1.51	1.51	1.51
GFR2	1.41	1.41	1.41	1.41	1.41	1.41
GFR3	1.41	1.41	1.41	1.41	1.41	1.41

Table C.23: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	16.14	12.81	16.13	16.46	15.39	15.74
GFR2	16.96	12.64	15.96	16.28	15.21	15.56
GFR3	16.96	12.63	15.95	16.28	15.21	15.56
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	6.18	5.17	5.38	7.03	6.80	6.61
GFR2	6.06	5.05	5.26	6.91	6.68	6.49
GFR3	6.06	5.05	5.25	6.90	6.68	6.48
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.67	1.50	1.67	1.69	1.65	1.68
GFR2	1.57	1.41	1.58	1.59	1.55	1.59
GFR3	1.56	1.40	1.57	1.59	1.55	1.58

Table C.24: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	15.35	13.71	13.41	14.91	12.37	11.75
GFR2	15.18	13.54	13.23	14.73	12.19	11.58
GFR3	15.17	13.53	13.23	14.72	12.19	11.57
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	5.30	4.96	4.51	5.90	4.88	4.75
GFR2	5.18	4.84	4.39	5.78	4.76	4.63
GFR3	5.18	4.84	4.39	5.78	4.75	4.62
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.50	1.50	1.51	1.50	1.51	1.51
GFR2	1.40	1.40	1.41	1.41	1.41	1.41
GFR3	1.40	1.40	1.41	1.40	1.41	1.41

Appendix D

Simulation results of the standard Weibull model with time-dependent covariates

Table D.1: The percentage bias of parameters in the heart model based on generated survival times from ***the Weibull model*** with 70% censoring

	n=500			n=1000			n=1500		
Parameter	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
DAGE	-10.79	1.55	-3.66	-12.15	0.05	-13.78	-13.75	-1.59	-10.60
CYCLO	-20.84	-18.85	-22.21	-20.51	-18.71	-20.85	-19.75	-18.07	-19.79
FK506	17.31	29.34	16.66	-19.37	-7.02	-16.20	-23.01	-10.49	-19.59
OTHER	-11.47	2.01	-3.16	-12.78	0.28	-4.34	-13.42	-0.43	-4.68
GFR	-13.35	-2.66	-7.90	-14.13	-3.86	-8.59	-14.37	-4.23	-7.75

Table D.2: The mean square error of parameters in the heart model based on generated survival times from ***the Weibull model*** with 70% censoring

	n=500			n=1000			n=1500		
Parameter	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
DAGE	<0.0001	<0.0001	0.0002	<0.0001	<0.0001	0.0001	<0.0001	<0.0001	0.0001
CYCLO	0.1731	0.1621	0.5536	0.1101	0.1005	0.2953	0.0871	0.0785	0.2091
FK506	1.9300	1.0997	2.7066	7.9265	0.2977	2.0100	0.5873	0.2380	1.2171
OTHER	0.0455	0.0413	0.1978	0.0253	0.0199	0.0996	0.0191	0.0131	0.0668
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table D.3: The average confidence interval length at (α=0.05) of parameter estimates in the heart model based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500			n=1000			n=1500		
	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
DAGE	0.02	0.02	0.05	0.02	0.02	0.04	0.01	0.01	0.03
CYCLO	1.33	1.33	2.74	0.91	0.91	1.91	0.73	0.73	1.55
FK506	7.09	2.93	6.24	10.87	2.02	5.33	1.98	1.61	3.87
OTHER	0.80	0.80	1.74	0.55	0.55	1.23	0.45	0.45	1.01
GFR	0.00	0.00	0.01	0.00	0.00	0.01	0.00	0.00	0.00

Table D.4: The percentage bias of parameters in the heart model based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500			n=1000			n=1500		
	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
GFR1	30.03	18.51	32.46	28.28	19.53	30.95	25.37	20.21	28.24
GFR2	30.72	19.30	33.22	28.70	20.24	31.38	26.38	21.73	29.29
GFR3	30.56	18.98	33.07	28.91	20.58	31.65	25.95	21.20	28.87

Table D.5: The mean square error of parameters in the heart model based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500			n=1000			n=1500		
	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
GFR1	0.1337	0.1362	0.7260	0.0819	0.0862	0.3624	0.0675	0.0720	0.2434
GFR2	0.1258	0.1287	0.6643	0.0782	0.0826	0.3322	0.0660	0.0708	0.2238
GFR3	0.1182	0.1210	0.6184	0.0753	0.0799	0.3103	0.0635	0.0683	0.2085

Table D.6: The average confidence interval length at (α=0.05) of parameter estimates in the heart model based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500			n=1000			n=1500		
	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
GFR1	1.30	1.29	3.31	0.90	0.89	2.31	0.73	0.72	1.88
GFR2	1.24	1.23	3.15	0.86	0.85	2.21	0.70	0.69	1.80
GFR3	1.20	1.18	3.04	0.83	0.82	2.13	0.68	0.67	1.73

Table D.7: The percentage bias of parameters in the cornea model based on generated survival times from ***the Weibull model*** with 90% censoring

Parameter	n=400			n=800			n=1200		
	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
RAGE	2.24	3.49	1.02	2.90	2.68	-0.02	3.17	3.28	0.85
CAUSE1	2.14	3.92	1.50	3.21	3.49	0.83	3.15	3.89	1.56
CAUSE2	3.07	3.75	1.21	3.18	3.40	0.75	2.89	3.51	1.13
SECOND	63.46	46.77	34.09	-12.19	-12.58	-23.26	-22.98	-20.51	-30.77

Table D.8: The mean square error of parameters in the cornea model based on generated survival times from ***the Weibull model*** with 90% censoring

	n=400			n=800			n=1200		
Parameter	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
RAGE	0.0001	0.0001	0.0002	<0.0001	<0.0001	0.0001	<0.0001	<0.0001	0.0001
CAUSE1	0.1676	0.1659	0.3315	0.0811	0.0803	0.1535	0.0535	0.0534	0.1011
CAUSE2	0.1753	0.1721	0.3382	0.0844	0.0834	0.1569	0.0556	0.0553	0.1030
SECOND	55.8050	54.7700	83.5900	8.7002	7.3520	12.7370	1.4921	0.6271	1.7202

Table D.9: The average confidence interval length at (α=0.05) of parameter estimates in the cornea model based on generated survival times from ***the Weibull model*** with 90% censoring

	n=400			n=800			n=1200		
Parameter	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic	Cox	Weibull	log-logistic
RAGE	0.04	0.04	0.05	0.03	0.03	0.03	0.02	0.02	0.03
CAUSE1	1.60	1.59	2.26	1.11	1.10	1.54	0.90	0.90	1.24
CAUSE2	1.64	1.62	2.28	1.13	1.12	1.55	0.92	0.91	1.26
SECOND	76.06	69.39	85.56	15.62	6.99	17.65	4.44	2.63	3.84

Appendix E

Simulation results of the Weibull spline models with time-dependent covariates

Table E.1: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	47.20	36.23	41.61	49.35	-63.31	60.34
CYCLO	-11.75	-17.42	2.91	18.45	1.41	6.77
FK506	9.18	0.92	-4.30	-0.85	-13.82	-15.54
OTHER	19.63	10.52	13.72	19.27	4.82	3.66
GFR	1.87	-5.39	2.13	8.32	-5.56	-1.92
Parameter	**n=1000**					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	44.43	33.19	38.61	46.20	-13.99	50.44
CYCLO	-11.68	-17.33	2.52	17.72	6.30	11.77
FK506	8.27	-0.24	-5.02	-1.55	-9.42	-8.18
OTHER	18.38	9.03	12.28	17.78	9.11	10.33
GFR	0.91	-6.51	0.95	7.03	-2.19	1.91
Parameter	**n=1500**					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	43.69	32.52	37.52	45.10	18.88	46.90
CYCLO	-11.99	-17.53	1.96	17.22	9.29	13.72
FK506	7.84	-0.65	-5.56	-2.01	-6.64	-5.08
OTHER	17.86	8.60	11.58	17.16	12.24	13.21
GFR	0.51	-6.83	0.36	6.54	1.15	3.54

Table E.2: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	11.68	4.58	0.66	-0.11	0.73	-5.59
CYCLO	-15.03	-21.29	-22.38	-23.44	-22.31	-25.79
FK506	59.95	55.98	52.94	54.87	53.43	43.38
OTHER	-12.20	-17.60	-20.68	-21.36	-20.63	-24.03
GFR	11.37	5.15	4.47	3.37	4.49	-0.90
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	2.99	-3.26	-6.60	-7.37	-6.54	-16.70
CYCLO	-18.43	-24.09	-25.25	-26.15	-25.21	-27.70
FK506	-9.12	-12.81	-15.99	-15.90	-15.89	-18.81
OTHER	-16.60	-21.60	-24.48	-25.08	-24.44	-27.10
GFR	6.05	0.50	0.02	-0.97	0.03	-3.98
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	1.89	-4.26	-7.60	-8.34	-7.53	-12.92
CYCLO	-19.84	-25.14	-26.19	-27.01	-26.14	-27.72
FK506	-22.79	-26.74	-29.82	-30.12	-29.75	-30.97
OTHER	-18.03	-22.94	-25.82	-26.39	-25.77	-27.11
GFR	4.91	-0.49	-0.92	-1.86	-0.91	-2.96

Table E.3: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	7.63	0.62	-2.66	-4.86	-2.74	-20.59
CYCLO	-11.79	-18.01	-19.46	-21.39	-19.44	-25.05
FK506	29.71	25.91	22.77	23.81	22.66	12.67
OTHER	-12.76	-18.31	-21.21	-22.92	-21.29	-27.09
GFR	1.08	-4.41	-5.09	-7.04	-5.16	-12.97
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	5.75	-1.07	-4.54	-6.50	-4.62	-22.54
CYCLO	-15.79	-21.49	-22.67	-24.42	-22.66	-27.32
FK506	-19.05	-23.24	-26.25	-27.16	-26.33	-31.34
OTHER	-16.24	-21.65	-24.56	-26.10	-24.64	-29.27
GFR	-2.32	-7.43	-7.94	-9.71	-8.02	-14.92
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	1.89	-4.55	-7.72	-9.62	-7.81	-22.97
CYCLO	-15.82	-21.44	-22.70	-24.41	-22.70	-26.36
FK506	-27.46	-31.70	-34.93	-35.97	-34.98	-37.89
OTHER	-17.84	-23.04	-25.98	-27.46	-26.03	-29.52
GFR	-3.23	-8.22	-8.75	-10.47	-8.83	-14.08

Table E.4: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	11.03	4.36	0.47	-1.85	0.19	-16.72
CYCLO	-5.54	-11.35	-13.50	-15.56	-13.79	-20.11
FK506	37.73	33.62	30.51	31.32	30.22	16.39
OTHER	-10.00	-15.39	-18.55	-20.47	-18.77	-25.50
GFR	5.49	0.08	-1.89	-4.00	-2.18	-10.75
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	9.80	3.21	-0.68	-2.90	-0.91	-23.43
CYCLO	-7.97	-13.38	-15.49	-17.34	-15.75	-21.30
FK506	-15.98	-20.22	-23.44	-24.62	-23.61	-29.80
OTHER	-12.08	-17.37	-20.56	-22.36	-20.75	-26.75
GFR	2.06	-3.02	-4.97	-6.88	-5.22	-13.76
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	7.72	1.34	-2.34	-4.50	-2.59	-28.43
CYCLO	-10.01	-15.10	-17.14	-18.87	-17.40	-22.32
FK506	-25.10	-29.28	-32.57	-33.93	-32.72	-37.07
OTHER	-13.25	-18.45	-21.51	-23.26	-21.69	-26.96
GFR	0.81	-4.09	-5.85	-7.71	-6.10	-13.59

Table E.5: The mean square error of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.0001	<0.0001	<0.0001	0.0001	0.0001	0.0001
CYCLO	0.1241	0.1522	0.1063	0.1659	0.0933	0.1180
FK506	0.1827	0.1504	0.1559	0.1507	0.2115	0.2355
OTHER	0.0447	0.0360	0.0384	0.0445	0.0287	0.0319
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.0708	0.0986	0.0506	0.1040	0.0540	0.0747
FK506	0.0998	0.0721	0.0818	0.0731	0.1053	0.0968
OTHER	0.0267	0.0185	0.0206	0.0261	0.0175	0.0191
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.0557	0.0834	0.0332	0.0835	0.0470	0.0653
FK506	0.0724	0.0473	0.0597	0.0488	0.0645	0.0569
OTHER	0.0208	0.0129	0.0148	0.0200	0.0150	0.0161
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table E.6: The mean square error of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.1550	0.1779	0.1827	0.1877	0.1825	0.1978
FK506	2.8230	2.5348	2.3362	2.4822	2.3747	1.9777
OTHER	0.0566	0.0616	0.0653	0.0662	0.0653	0.0692
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.0963	0.1211	0.1270	0.1317	0.1268	0.1393
FK506	0.4237	0.4742	0.5321	0.5317	0.5307	0.5853
OTHER	0.0337	0.0399	0.0441	0.0451	0.0441	0.0480
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.0804	0.1050	0.1106	0.1151	0.1104	0.1189
FK506	0.5759	0.6979	0.8067	0.8184	0.8044	0.8478
OTHER	0.0268	0.0333	0.0379	0.0388	0.0378	0.0400
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table E.7: The mean square error of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.1278	0.1467	0.1523	0.1602	0.1523	0.1745
FK506	1.0932	0.9610	0.8678	1.2051	0.8662	0.6444
OTHER	0.0500	0.0555	0.0591	0.0615	0.0593	0.0666
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.0791	0.1011	0.1065	0.1149	0.1065	0.1290
FK506	0.5444	0.6548	0.7478	0.7784	0.7507	0.9184
OTHER	0.0302	0.0368	0.0411	0.0436	0.0413	0.0486
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.0607	0.0824	0.0882	0.0965	0.0882	0.1060
FK506	0.6759	0.8324	0.9668	1.0131	0.9690	1.0948
OTHER	0.0245	0.0314	0.0361	0.0387	0.0362	0.0421
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table E.8: The mean square error of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DDAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.1127	0.1225	0.1280	0.1339	0.1288	0.1480
FK506	1.4080	1.2248	1.1010	1.2695	1.0908	0.7078
OTHER	0.0465	0.0508	0.0542	0.0566	0.0545	0.0625
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.0578	0.0697	0.0760	0.0822	0.0768	0.0961
FK506	0.4728	0.5689	0.6565	0.6920	0.6616	0.8514
OTHER	0.0256	0.0307	0.0346	0.0371	0.0348	0.0431
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CYCLO	0.0437	0.0570	0.0638	0.0703	0.0648	0.0837
FK506	0.5973	0.7392	0.8665	0.9227	0.8721	1.0518
OTHER	0.0195	0.0248	0.0288	0.0313	0.0290	0.0367
GFR	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table E.9: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.24	1.25	1.27	1.29	1.20	1.30
FK506	1.50	1.52	1.51	1.52	1.41	1.42
OTHER	0.70	0.71	0.70	0.71	0.66	0.69
GFR	0.00	0.00	0.00	0.00	0.00	0.00
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.01	0.01	0.01	0.01	0.01	0.01
CYCLO	0.86	0.86	0.87	0.88	0.85	0.89
FK506	1.04	1.05	1.04	1.05	1.01	1.02
OTHER	0.49	0.49	0.49	0.49	0.48	0.49
GFR	0.00	0.00	0.00	0.00	0.00	0.00
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.01	0.01	0.01	0.01	0.01	0.01
CYCLO	0.70	0.70	0.71	0.72	0.71	0.72
FK506	0.84	0.85	0.84	0.85	0.84	0.84
OTHER	0.40	0.40	0.40	0.40	0.40	0.40
GFR	0.00	0.00	0.00	0.00	0.00	0.00

Table E.10: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.03	0.03	0.03	0.03	0.03	0.03
CYCLO	1.42	1.42	1.42	1.42	1.42	1.41
FK506	2.98	2.98	3.00	3.04	3.01	3.51
OTHER	0.89	0.89	0.89	0.89	0.89	0.88
GFR	0.01	0.01	0.01	0.01	0.01	0.01
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	0.97	0.97	0.97	0.96	0.97	0.96
FK506	2.39	2.39	2.39	2.40	2.39	2.37
OTHER	0.62	0.62	0.62	0.62	0.62	0.61
GFR	0.00	0.00	0.00	0.00	0.00	0.00
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.01	0.01	0.01	0.01	0.01
CYCLO	0.78	0.78	0.78	0.78	0.78	0.77
FK506	1.96	1.96	1.96	1.97	1.96	1.95
OTHER	0.50	0.50	0.50	0.50	0.50	0.50
GFR	0.00	0.00	0.00	0.00	0.00	0.00

Table E.11: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.32	1.32	1.32	1.32	1.32	1.30
FK506	2.89	2.88	2.89	3.62	2.89	2.89
OTHER	0.83	0.83	0.83	0.83	0.83	0.81
GFR	0.00	0.00	0.00	0.00	0.00	0.00
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	0.90	0.90	0.90	0.90	0.90	0.89
FK506	2.21	2.21	2.21	2.21	2.21	2.16
OTHER	0.58	0.58	0.58	0.57	0.58	0.56
GFR	0.00	0.00	0.00	0.00	0.00	0.00
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.01	0.01	0.01	0.01	0.01	0.01
CYCLO	0.73	0.73	0.73	0.73	0.73	0.72
FK506	1.77	1.77	1.77	1.77	1.77	1.74
OTHER	0.47	0.47	0.47	0.47	0.47	0.46
GFR	0.00	0.00	0.00	0.00	0.00	0.00

Table E.12: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	1.30	1.29	1.29	1.29	1.29	1.28
FK506	2.82	2.82	2.82	3.18	2.83	2.88
OTHER	0.82	0.81	0.81	0.81	0.81	0.80
GFR	0.00	0.00	0.00	0.00	0.00	0.00
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.02	0.02	0.02	0.02	0.02	0.02
CYCLO	0.89	0.89	0.89	0.88	0.89	0.87
FK506	2.19	2.19	2.19	2.19	2.19	2.13
OTHER	0.57	0.57	0.57	0.57	0.57	0.55
GFR	0.00	0.00	0.00	0.00	0.00	0.00
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
DAGE	0.01	0.01	0.01	0.01	0.01	0.01
CYCLO	0.72	0.72	0.71	0.71	0.71	0.70
FK506	1.77	1.77	1.77	1.77	1.77	1.72
OTHER	0.46	0.46	0.46	0.46	0.46	0.45
GFR	0.00	0.00	0.00	0.00	0.00	0.00

Table E.13: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	24.49	5.39	-4.63	-4.49	-1.01	-13.94
GFR2	23.68	4.69	-5.31	-5.21	-1.76	-14.47
GFR3	24.14	5.17	-4.80	-4.66	-1.23	-14.08
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	21.64	2.65	-7.18	-7.11	-3.71	-9.93
GFR2	21.40	2.42	-7.47	-7.44	-4.00	-10.18
GFR3	21.80	2.82	-7.05	-7.02	-3.61	-9.81
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	20.53	1.57	-8.06	-8.06	-4.77	-8.73
GFR2	20.20	1.26	-8.37	-8.37	-5.06	-9.02
GFR3	20.33	1.39	-8.23	-8.23	-4.94	-8.95

Table E.14: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	59.70	48.63	48.77	48.20	48.13	47.46
GFR2	51.95	41.44	37.22	36.70	36.48	35.75
GFR3	47.18	35.61	33.07	32.65	32.37	31.69
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	42.98	33.06	33.62	33.11	32.86	32.62
GFR2	42.55	33.21	29.31	28.65	28.49	28.15
GFR3	40.04	29.91	28.39	27.83	27.62	27.41
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	37.00	27.59	27.65	27.07	26.86	26.69
GFR2	38.31	29.30	25.34	24.70	24.53	24.34
GFR3	37.17	27.47	26.08	25.48	25.26	25.13

Table E.15: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	50.25	44.63	56.63	56.10	55.77	50.45
GFR2	54.81	49.06	52.04	51.75	51.63	47.53
GFR3	47.28	41.32	49.69	49.32	49.08	44.99
Parameter	n=1000					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	38.37	33.18	44.98	44.57	44.42	42.93
GFR2	44.26	38.94	43.57	43.28	43.29	42.36
GFR3	40.37	34.91	44.38	44.06	43.97	42.75
Parameter	n=1500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	36.29	31.18	42.69	42.32	42.30	41.68
GFR2	40.43	35.21	39.86	39.68	39.77	39.60
GFR3	37.86	32.54	42.03	41.75	41.75	41.30

Table E.16: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	36.57	35.08	54.35	47.58	46.50	25.97
GFR2	40.85	38.97	52.12	45.32	44.48	27.27
GFR3	32.45	30.70	48.69	41.62	40.61	23.42
Parameter	n=1000					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	28.53	26.78	45.06	38.95	38.09	22.99
GFR2	32.52	30.40	43.94	37.59	36.92	22.95
GFR3	27.81	25.87	43.32	36.96	36.12	22.02
Parameter	n=1500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	21.54	20.02	40.34	34.37	33.51	20.46
GFR2	28.04	26.00	40.81	34.59	33.95	21.27
GFR3	22.74	20.99	40.16	33.99	33.17	20.50

Table E.17: The mean square error of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.1873	0.1310	0.1289	0.1288	0.1279	0.1333
GFR2	0.1722	0.1191	0.1184	0.1183	0.1169	0.1245
GFR3	0.1665	0.1117	0.1100	0.1099	0.1088	0.1161
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.1078	0.0621	0.0659	0.0657	0.0625	0.0687
GFR2	0.1015	0.0567	0.0610	0.0609	0.0574	0.0640
GFR3	0.0995	0.0532	0.0566	0.0565	0.0534	0.0596
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.0820	0.0404	0.0462	0.0462	0.0422	0.0470
GFR2	0.0773	0.0369	0.0433	0.0433	0.0391	0.0441
GFR3	0.0753	0.0345	0.0406	0.0405	0.0365	0.0415

Table E.18: The mean square error of parameter estimates in the heart models based on generated survival times from ***1-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.5719	0.4317	0.4306	1.4647	1.1283	0.9226
GFR2	1.1698	0.4029	0.3834	0.3815	0.3806	1.0207
GFR3	0.2379	0.2078	0.2014	0.2007	0.2002	0.1979
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.2140	0.1937	0.1940	0.1932	0.1928	0.1919
GFR2	0.2401	0.2009	0.1868	0.1848	0.1843	0.1828
GFR3	0.1256	0.1037	0.1005	0.0996	0.0993	0.0987
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.1422	0.1260	0.1257	0.1249	0.1246	0.1242
GFR2	0.1709	0.1373	0.1251	0.1233	0.1229	0.1222
GFR3	0.0917	0.0726	0.0700	0.0691	0.0688	0.0685

Table E.19: The mean square error of parameter estimates in the heart models based on generated survival times from ***2-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.3164	0.3019	0.3328	0.3312	0.3302	0.3082
GFR2	0.3746	0.3417	0.3573	0.3556	0.3549	0.3269
GFR3	0.1848	0.1686	0.1911	0.1900	0.1893	0.1748
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.1530	0.1430	0.1666	0.1656	0.1653	0.1604
GFR2	0.2042	0.1799	0.2006	0.1991	0.1992	0.1936
GFR3	0.1036	0.0910	0.1135	0.1126	0.1124	0.1086
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.1086	0.0995	0.1214	0.1205	0.1205	0.1186
GFR2	0.1524	0.1307	0.1497	0.1489	0.1493	0.1481
GFR3	0.0786	0.0672	0.0885	0.0878	0.0877	0.0864

Table E.20: The mean square error of parameter estimates in the heart models based on generated survival times from ***3-knot Weibull spline model*** with 70% censoring

	n=500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.2300	0.2272	0.2715	0.2530	0.2503	0.1970
GFR2	0.2550	0.2470	0.3124	0.2756	0.2714	0.1922
GFR3	0.1236	0.1203	0.1636	0.1438	0.1413	0.1027
	n=1000					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.1123	0.1098	0.1437	0.1302	0.1285	0.0966
GFR2	0.1348	0.1275	0.1826	0.1541	0.1514	0.0988
GFR3	0.0666	0.0634	0.1000	0.0844	0.0825	0.0544
	n=1500					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.0713	0.0696	0.1014	0.0897	0.0882	0.0648
GFR2	0.0932	0.0871	0.1413	0.1156	0.1132	0.0704
GFR3	0.0437	0.0414	0.0769	0.0630	0.0613	0.0385

Table E.21: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.40	1.40	1.40	1.40	1.40	1.32
GFR2	1.34	1.34	1.33	1.33	1.34	1.26
GFR3	1.29	1.29	1.29	1.29	1.29	1.22
Parameter	n=1000					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.97	0.97	0.97	0.97	0.97	0.95
GFR2	0.93	0.93	0.92	0.92	0.93	0.91
GFR3	0.89	0.90	0.89	0.89	0.89	0.88
Parameter	n=1500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.78	0.79	0.78	0.78	0.78	0.78
GFR2	0.75	0.75	0.75	0.75	0.75	0.74
GFR3	0.72	0.73	0.72	0.72	0.72	0.72

Table E.22: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	3.41	2.39	2.38	4.65	4.05	3.64
GFR2	3.96	2.18	2.17	2.17	2.17	3.82
GFR3	1.62	1.61	1.61	1.61	1.61	1.60
Parameter	n=1000					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.60	1.59	1.59	1.59	1.59	1.59
GFR2	1.47	1.47	1.47	1.47	1.47	1.46
GFR3	1.09	1.09	1.08	1.08	1.08	1.08
Parameter	n=1500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.28	1.28	1.28	1.28	1.28	1.27
GFR2	1.18	1.18	1.18	1.18	1.18	1.17
GFR3	0.88	0.87	0.87	0.87	0.87	0.87

Table E.23: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.96	1.96	1.96	1.96	1.96	1.93
GFR2	1.80	1.80	1.79	1.79	1.79	1.77
GFR3	1.34	1.34	1.34	1.34	1.34	1.32
Parameter	n=1000					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.33	1.33	1.32	1.32	1.32	1.31
GFR2	1.22	1.22	1.22	1.22	1.22	1.21
GFR3	0.91	0.91	0.91	0.91	0.91	0.90
Parameter	n=1500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.07	1.07	1.07	1.07	1.07	1.06
GFR2	0.98	0.98	0.98	0.98	0.98	0.98
GFR3	0.74	0.73	0.73	0.73	0.73	0.73

Table E.24: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 70% censoring

Parameter	n=500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.73	1.73	1.73	1.73	1.73	1.66
GFR2	1.59	1.59	1.59	1.58	1.58	1.53
GFR3	1.19	1.19	1.19	1.19	1.19	1.15
Parameter	n=1000					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	1.18	1.18	1.18	1.18	1.18	1.13
GFR2	1.09	1.09	1.09	1.09	1.09	1.04
GFR3	0.81	0.81	0.81	0.81	0.81	0.78
Parameter	n=1500					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
GFR1	0.95	0.95	0.95	0.95	0.95	0.91
GFR2	0.88	0.88	0.88	0.88	0.88	0.84
GFR3	0.66	0.66	0.66	0.66	0.66	0.63

Table E.25: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 90% censoring

Parameter	n=400					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	-1.86	-19.07	42.75	-191.99	-285.74	-59.79
CAUSE1	-18.25	-32.04	25.40	7.87	-15.19	11.46
CAUSE2	-16.39	-30.59	29.44	10.84	-11.41	14.67
SECOND	235.56	382.89	396.31	370.01	429.94	447.14
Parameter	n=800					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	-7.23	-18.01	27.15	-110.89	-379.09	-78.36
CAUSE1	-19.89	-30.31	25.64	12.85	-19.46	8.72
CAUSE2	-18.75	-29.25	28.73	15.81	-15.64	11.91
SECOND	170.88	256.33	205.65	184.96	224.86	218.51
Parameter	n=1200					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	-9.04	-17.80	23.47	-101.07	-373.40	-55.95
CAUSE1	-19.49	-23.94	28.70	17.66	-12.48	14.35
CAUSE2	-18.74	-23.13	32.00	20.55	-8.22	17.86
SECOND	85.11	154.96	123.56	58.92	93.95	89.63

Table E.26: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 90% censoring

	n=400					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	-11.42	61.53	80.43	37.99	-42.12	-31.79
CAUSE1	-13.59	58.99	78.81	56.05	-12.17	-6.74
CAUSE2	-12.10	60.97	80.56	57.47	-10.99	-5.82
SECOND	615.61	490.87	370.40	410.40	698.53	674.21
	n=800					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	-15.64	85.30	83.05	73.52	31.44	46.69
CAUSE1	-17.52	84.16	83.37	79.21	44.38	51.48
CAUSE2	-15.88	85.51	83.94	79.91	44.70	51.96
SECOND	285.97	-189.34	-262.73	-269.96	-111.01	-149.26
	n=1200					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	-14.18	94.51	86.95	82.54	58.83	65.67
CAUSE1	-17.22	90.33	84.68	83.25	59.95	66.75
CAUSE2	-16.59	90.39	84.13	82.56	58.99	65.84
SECOND	201.17	-354.37	-425.98	-437.90	-337.16	-382.45

Table E.27: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 90% censoring

	n=400					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	17.58	166.05	200.64	143.76	92.79	97.44
CAUSE1	16.43	164.37	199.00	164.63	112.50	114.91
CAUSE2	17.95	168.24	204.26	169.39	117.20	119.84
SECOND	444.63	-57.06	-232.05	-166.43	21.45	13.42
	n=800					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	11.49	180.11	176.68	168.71	139.86	148.15
CAUSE1	10.79	181.56	179.73	175.02	155.13	156.52
CAUSE2	12.06	180.50	177.78	173.17	153.16	154.65
SECOND	181.41	-579.15	-694.90	-694.63	-637.15	-645.47
	n=1200					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	11.14	180.73	169.44	167.35	156.33	155.89
CAUSE1	11.78	179.69	169.85	168.38	158.42	159.32
CAUSE2	12.39	182.29	171.58	170.01	159.81	160.80
SECOND	113.88	-688.29	-791.27	-793.55	-760.55	-787.25

Table E.28: The percentage bias of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 90% censoring

	n=400					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	6.61	210.50	243.04	188.40	127.13	139.75
CAUSE1	6.63	210.90	244.15	200.75	144.68	147.76
CAUSE2	7.77	215.66	251.67	206.37	149.87	153.17
SECOND	160.53	-350.71	-478.00	-383.90	-251.32	-245.40
	n=800					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.38	203.68	197.88	186.60	158.52	159.40
CAUSE1	1.43	203.53	199.71	189.87	164.14	163.73
CAUSE2	1.28	205.83	201.37	191.23	165.39	164.93
SECOND	46.90	-545.22	-629.72	-596.55	-508.79	-510.68
	n=1200					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	-0.88	201.77	190.63	186.39	165.63	166.81
CAUSE1	0.55	199.95	190.44	187.16	166.70	167.73
CAUSE2	0.46	201.22	191.03	187.67	167.11	168.16
SECOND	27.29	-571.79	-649.33	-637.16	-560.09	-574.27

Table E.29: The mean square error of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 90% censoring

	n=400					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	<0.0001	<0.0001	<0.0001	0.0004	0.0008	0.0001
CAUSE1	0.1760	0.2240	0.2111	0.1370	0.1600	0.1653
CAUSE2	0.1815	0.2398	0.2541	0.1500	0.1605	0.1830
SECOND	8.0800	7.3170	8.0650	9.0400	8.0100	9.9100
	n=800					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	<0.0001	<0.0001	<0.0001	0.0001	0.0015	0.0001
CAUSE1	0.1040	0.1406	0.1302	0.0797	0.0976	0.0778
CAUSE2	0.1094	0.1541	0.1632	0.0943	0.0937	0.0887
SECOND	8.4700	2.0550	1.8500	8.1300	8.9000	7.0100
	n=1200					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	<0.0001	<0.0001	<0.0001	0.0001	0.0014	<0.0001
CAUSE1	0.0793	0.0919	0.1185	0.0711	0.0582	0.0649
CAUSE2	0.0851	0.1006	0.1566	0.0900	0.0541	0.0820
SECOND	3.0400	7.0645	2.4860	5.8300	3.8700	5.7500

Table E.30: The mean square error of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 90% censoring

Parameter	n=400					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.0001	0.0002	0.0003	0.0001	0.0001	0.0001
CAUSE1	0.1593	0.4502	0.6799	0.4180	0.1557	0.1484
CAUSE2	0.1664	0.5526	0.8396	0.5053	0.1632	0.1556
SECOND	7.2200	2.6490	1.4486	5.9410	2.7840	3.0270
Parameter	n=800					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	<0.0001	0.0003	0.0003	0.0003	0.0001	0.0001
CAUSE1	0.0938	0.6541	0.6445	0.5883	0.2348	0.2912
CAUSE2	0.0980	0.8178	0.7919	0.7245	0.2798	0.3514
SECOND	7.5700	4.5547	7.9444	1.3207	3.1700	3.8761
Parameter	n=1200					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	<0.0001	0.0004	0.0003	0.0003	0.0002	0.0002
CAUSE1	0.0725	0.7168	0.6370	0.6172	0.3445	0.4152
CAUSE2	0.0783	0.8768	0.7678	0.7411	0.4047	0.4911
SECOND	7.4600	3.3015	8.9433	1.8806	2.3174	2.8779

Table E.31: The mean square error of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 90% censoring

Parameter	n=400					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.0001	0.0007	0.0010	0.0005	0.0003	0.0003
CAUSE1	0.1691	2.3871	3.4250	2.3927	1.2052	1.2506
CAUSE2	0.1882	3.0498	4.4155	3.0886	1.5703	1.6347
SECOND	9.9400	2.1382	9.7402	2.7920	2.6150	3.9270
Parameter	n=800					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	<0.0001	0.0008	0.0007	0.0007	0.0005	0.0005
CAUSE1	0.0804	2.7629	2.7113	2.5747	2.0391	2.0750
CAUSE2	0.0896	3.3574	3.2620	3.0988	2.4416	2.4884
SECOND	5.1400	3.5010	4.3581	4.9754	2.8640	2.7460
Parameter	n=1200					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	<0.0001	0.0008	0.0007	0.0007	0.0006	0.0006
CAUSE1	0.0605	2.6769	2.3984	2.3581	2.0934	2.1167
CAUSE2	0.0675	3.3903	3.0114	2.9577	2.6198	2.6516
SECOND	4.6320	4.0394	4.1912	5.5092	6.4362	6.1368

Table E.32: The mean square error of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 90% censoring

Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
	n=400					
RAGE	0.0001	0.0011	0.0014	0.0009	0.0004	0.0005
CAUSE1	0.1460	3.8174	5.0618	3.4743	1.8834	1.9587
CAUSE2	0.1567	4.8935	6.6008	4.4958	2.4542	2.5569
SECOND	6.7800	4.6421	4.2132	3.1723	3.8993	2.3239
	n=800					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	<0.0001	0.0010	0.0009	0.0008	0.0006	0.0006
CAUSE1	0.0688	3.4513	3.3289	3.0158	2.2734	2.2627
CAUSE2	0.0723	4.3420	4.1630	3.7614	2.8343	2.8195
SECOND	3.4840	6.7505	4.2175	5.8906	5.7623	5.7034
	n=800					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	<0.0001	0.0009	0.0008	0.0008	0.0006	0.0007
CAUSE1	0.0479	3.3027	3.0025	2.9014	2.3129	2.3406
CAUSE2	0.0502	4.1191	3.7197	3.5918	2.8598	2.8950
SECOND	8.4538	4.1381	5.5180	4.9854	4.1586	4.8018

Table E.33: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the Weibull model*** with 90% censoring

Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
	n=400					
RAGE	0.02	0.02	0.02	0.02	0.02	0.02
CAUSE1	1.51	1.47	1.56	1.42	1.47	1.54
CAUSE2	1.54	1.50	1.60	1.46	1.51	1.58
SECOND	21.79	10.64	79.47	19.07	19.43	19.78
	n=800					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.01	0.01	0.01	0.01	0.01	0.01
CAUSE1	1.05	1.01	1.09	1.01	1.01	1.05
CAUSE2	1.07	1.03	1.11	1.03	1.03	1.07
SECOND	40.55	4.85	8.39	21.10	24.95	25.43
	n=1200					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.01	0.01	0.01	0.01	0.01	0.01
CAUSE1	0.86	0.84	0.89	0.84	0.84	0.86
CAUSE2	0.88	0.85	0.91	0.86	0.85	0.88
SECOND	36.87	2.77	5.26	28.78	23.57	28.99

Table E.34: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 1-knot Weibull spline model*** with 90% censoring

Parameter	n=400					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.03	0.04	0.04	0.03	0.03	0.03
CAUSE1	1.49	1.61	1.65	1.59	1.49	1.49
CAUSE2	1.53	1.67	1.71	1.64	1.52	1.53
SECOND	16.56	4.89	5.15	18.79	13.75	15.66
Parameter	n=800					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.02	0.02	0.02	0.02	0.02	0.02
CAUSE1	1.03	1.11	1.12	1.11	1.08	1.08
CAUSE2	1.06	1.15	1.16	1.15	1.11	1.12
SECOND	43.00	3.86	4.00	19.22	22.84	23.07
Parameter	n=1200					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.01	0.01	0.01	0.01	0.01	0.01
CAUSE1	0.86	0.84	0.89	0.84	0.84	0.86
CAUSE2	0.88	0.85	0.91	0.86	0.85	0.88
SECOND	36.87	2.77	5.26	28.78	23.57	21.99

Table E.35: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 2-knot Weibull spline model*** with 90% censoring

Parameter	n=400					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.03	0.04	0.04	0.04	0.03	0.03
CAUSE1	1.50	1.75	1.83	1.74	1.66	1.67
CAUSE2	1.55	1.84	1.93	1.84	1.74	1.75
SECOND	11.44	5.28	8.18	27.90	21.50	18.63
Parameter	n=800					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.02	0.02	0.02	0.02	0.02	0.02
CAUSE1	1.04	1.19	1.21	1.20	1.18	1.18
CAUSE2	1.07	1.24	1.25	1.24	1.21	1.22
SECOND	23.50	3.84	4.05	17.85	35.34	36.16
Parameter	n=1200					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.02	0.02	0.02	0.02	0.02	0.02
CAUSE1	0.87	0.97	0.97	0.97	0.96	0.96
CAUSE2	0.89	1.02	1.02	1.02	1.01	1.01
SECOND	14.92	3.20	4.93	6.24	13.35	10.49

Table E.36: The average confidence interval length at (α=0.05) of parameter estimates in the heart models based on generated survival times from ***the 3-knot Weibull spline model*** with 90% censoring

Parameter	n=400					
	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.03	0.04	0.04	0.04	0.04	0.04
CAUSE1	1.48	1.82	1.89	1.80	1.70	1.71
CAUSE2	1.52	1.93	2.03	1.91	1.79	1.80
SECOND	35.19	17.07	6.57	9.61	17.83	14.55
	n=800					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.02	0.02	0.03	0.02	0.02	0.02
CAUSE1	1.03	1.21	1.23	1.21	1.18	1.18
CAUSE2	1.05	1.27	1.29	1.27	1.23	1.23
SECOND	7.34	3.65	3.91	5.29	4.83	3.97
	n=1200					
Parameter	0 knots	1 knot	2 knots	3 knots	4 knots	5 knots
RAGE	0.02	0.02	0.02	0.02	0.02	0.02
CAUSE1	0.86	0.99	1.00	0.99	0.98	0.97
CAUSE2	0.88	1.04	1.04	1.04	1.02	1.02
SECOND	11.28	2.97	3.17	3.14	2.98	3.04

References

Abrahamowicz M, Mackenzie T, Esdaile JM. 1996. Time-Dependent Hazard Ratio: Modeling and Hypothesis Testing with Application in Lupus Nephritis. *Journal of the American Statistical Association* 91: 1432-1439.

Ake CF, Carpenter AL. 2002. Survival Analysis with PREG: Using MI and MIANALYZE to accommodate missing data. In: Proceedings of the 10th Annual Western Users of SAS Software Regional Users Group Conference, Cary, NC, SAS Institute: 102-107.

Allison PD. 1995. *Survival Analysis using SAS: A practical guide.* Cary, NC: SAS publishing.

Allison PD. 2004. *Event History Analysis.* Handbook of data analysis: 369-386.

Altman DG, De Stavola BL. 1994. Practical problems in fitting a proportional hazards model to data with updated measurements of the covariates. *Statistics in Medicine* 13: 301-341.

Amorim LD, Cai J, Zeng D, Barreto ML. 2008. Regression splines in the time-dependent coefficient rates model for recurrent event data. *Statistics in Medicine* 27: 5890-5906.

Anshu A, Lim LS, Htoon HM, Tan DT. 2010. Postoperative risk factors influencing corneal graft survival in the Singapore Corneal Transplant Study. *American Journal of Ophthalmology* 151: 442-449

Aydemir S, Dirschedl P. 1999. Analysis of time-dependent covariates in failure time data. *Statistics in Medicine* 18: 2123-2134.

Bender R, Augustin T, Blettner M. 2005. Generating survival times to simulate Cox proportional, hazards models. *Statistics in Medicine* 24: 1713-1723.

Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Connor E, Hulley SB, Grady D, Shlipak MG. 2004. Predictors of heart failure among women with coronary, disease. *American Heart Association* 110: 1424-1430.

Breslow NE. 1974. Analysis of survival data under the proportional hazards model. *International Statistical Review* 43: 45-57.

Burton A, Altman DG, Royston P, Holder RL. 2006. The design of simulation studies in medical statistics., *Statistics in Medicine* 25: 4279-4292.

Cavender JB, Rogers WJ, Lloyd D, Bernard JG, Charlotte JC, Coggin,Charlotte JC, William

OM. 1992. Effect of smoking on survival and morbidity in patients randomized to medical or surgical therapy in the coronary artery surgery study (CASS): 10-Year follow-up. *Journal of the American College of Cardiology* 20: 287-294.

Cimato TR, and Jessup, M. 2002. Recipient selection in cardiac transplantation: Contraindications and risk factors of mortality. *Journal of Heart and Lung Transplantation* 21: 1161-1173.

Collett D. 2003. *Modelling Survival Data in Medical Research.* London: Chapman and Hall/CRC.

Collett D, Kimber AC, Allan E, and Gallagher J. 2006. Flexible Parametric Modelling, Advanced topics in survival analysis. Statistical Service Centre: University of Reading.

Collins LM, Schafer JL, Kam CM. 2001. A comparison of inclusive and restrictive strategies in modern missing data procedures. *Psychological Methods* 6: 330-351.

Cox DR. 1975. Partial likelihood. *Biometrika* 62: 269-276.

Cox DR. and Oakes D. 1984. Analysis of Survival Data. London: Chapman and Hall/CRC.

De Angelis D, Young GA. Bootstrap method. 1998. *In Encyclopedia of Biostatistics*, Armitage P, Colton T (eds). Wiley: New York : 426-433.

De Boor C. 1978. A practical guide to splines. *Number 27 in Applied Mathematical Sciences*: Springer, New York.

De Boor C. 2000. *A Practical Guide to Splines (revised edn).* Springer: Berlin.

Demirtas H. 2005. Pseudo-random number generation in R for some univariate distributions. *Journal of Modern Applied Statistical Methods* 3: 300-311.

Di Filippo S, Cochat P., and Bozio A. 2007. The challenge of renal function in heart transplant children. *Pediatric Nephrology* 22: 333-342.

Dietz WH. 2004. Overweight in childhood and adolescence. *New England Journal of Medicine* 350: 855-857.

Dupont WD. 2002. *Statistical Modeling for Biomedical Researchers: A Simple Introduction to the Analysis of Complex Data.* Cambridge, U.K: Cambridge University Press.

Durrleman S, Simon R. 1989. Flexible regression models with cubic splines. *Statistics in Medicine* 8: 551-561.

Efron B. 1977. The efficiency of Cox's likelihood function for censored data. *Journal of the American Statistical Association* 72: 557-565.

Eisen E, Agalliu I, Thurston DW, Coull BA, Checkoway H. 2004. Smoothing in occupational cohort studies: an illustration based on penalised splines. *Occupational and Environmental Medicine* 61: 854-860.

Esteve J, Benhamou E, Croasdale M, Raymond L. 1990. Relative survival and the estimation of net survival: elements for further discussion. *Statistics in Medicine* 9: 529-538.

Fisher LD, Lin D. 1999. Time-dependent covariates in the Cox proportional-hazards regression model. *Annual Review of Public Health* 20: 145-157.

Fishman GS. 2006. *A First Course in Monte Carlo*. Belmont, CA: Thomson Brooks/Cole.

Friedman JH. 1991. Multivariate adaptive regression splines. *Annals of Statistics* 19: 1-67.

Gamerman D, Lopes HF. 2006. *Markov Chain Monte Carlo: Stochastic Simulation for Bayesian Inference*. London: Chapman and Hall/CRC.

Ganesh SK, and Nabel EG. 2005. Genomics of in-stent restenosis: early insights into a complex disease. *Circulation* 112: 2378-2379.

Gao F, Manatunga AK, Chen S. 2007. Non-parametric estimation for baseline hazards function and covariate effects with time-dependent covariates. *Statistics in Medicine* 26: 857-868.

Gijbels I. 2010. Censored data. Wiley Interdisciplinary Reviews: *Computational Statistics* 2: 178-188.

Giorgi R, Gouvernet J. 2005. Analysis of time-dependent covariates in a regressive relative survival model. *Statistics in Medicine* 24: 3863-3870.

Ghosh S, and Henderson SG. 2000. Chessboard Distributions and Random Vectors with Specified Marginals and Covariance Matrix: Department of Industrial and Operations Engineering. University of Michigan.

Goldstein EB. 2007. Cognitive psychology: Connecting mind, research and everyday experience. Belmont, CA : Wadsworth Cengage Learning.

Grambsch PM, Therneau TM. 1994. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 81: 515-526.

Gray RJ. 1992. Flexible methods for analyzing survival data using splines, with applications to breast cancer prognosis. *Journal of the American Statistical Association* 87: 942-951.

Green PJ. 1995. Reversible jump Markov chain Monte Carlo computation and Bayesian model determination. *Biometrika* 82: 711-732.

Grohn YT, Eicker, SW, Ducrocq, V, and Hertl JA. 1998. Effect of diseases on the culling of holstein dairy cows in New York state. *Journal of Dairy Science* 81: 1755-1766.

Hastings WK. 1970. Monte Carlo Sampling Methods Using Markov Chains and Their Applications. *Biometrika* 57: 97-109.

Heinzl H, Kaider A, Zlabinger G. 1996. Assessing interactions of binary time-dependent covariates with time in Cox proportional hazards regrssion models using cubic spline functions. *Statistics in Medicine* 15: 2589-2601.

Hess K. 1994. Assessing time-by-covariate interactions in proportional hazards regression models using cubic spline functions. *Statistics in Medicine* 13: 1045-1062.

Huang X, Chen S, Soong S. 1998. Piecewise exponential survival trees with time-dependent covariates. *Biometrics*: 1420-1433.

Ingle, S. M. 2004. Analysis of Bivariate Corneal Graft Data. Unpublished MSc dissertation, University of Reading.

Inoue K, Amano, S., Oshika, T., and Tsuru, T. 2001. Risk factors for corneal graft failure and rejection in penetrating keratoplasty. *Acta Ophthalmologica Scandinavica* 79: 251-255.

James I. 2005. Accelerated Failure-time Models. *Encyclopedia of Biostatistics*. London: John Wiley & Sons, Ltd

Jessup M, Abraham WT, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009. Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults. *Journal of the American College of Cardiology* 119: 1977-2016

Jimenez FR 2006. Impact of Brain Stem Death on Transplant Outcome. Unpublished MSc dissertation, University of Reading.

Jurt U, Delgado D, et al. 2002. Heart Transplant: What to Expect. *Circulation* 106: 1750-1752.

Kaut M, and Wallace SW. 2003. Evaluation of scenario-generation methods for stochastic programming. http://citeseer.ist.psu.edu/cache/papers/cs/29430/http:zSzzSzwww.iot. 2 June 2011.

Kaw A. 2010. *Introduction to Numerical Methods*. http://numericalmethods.eng.usf.edu/.

Kruger CJC. 2003. Constrained cubic spline interpolation. *Chemical Engineering Applications* 1: 1-5.

Lapin L. 1983. Probability and statistics for modern engineering. USA: Waveland Press.

L'Ecuyer P. 2004. *Random Number Generation*. In Handbook of Computational Statistics GJ, Haerdle W,, Mori Y (eds). Springer-Verlag: New York.

Lachin JM. 1998. Sample size determination. *In Encyclopedia of Biostatistics*. Wiley:, New York.

LeBlanc M, Crowley J. 1999. Adaptive regression splines in the Cox model. *Biometrics* 55: 204-213.

Lee ET, GO OT. 1997. Survival analysis in public health research. *Annual Review of Public Health* 18: 105-134.

Leemis LM SL-H, Reynertson K. 1989. Variate generation for accelerated life and proportional hazards models with time dependent covariates. *Statistics and Probability Letters* 10: 335 -339.

Leffondre K, Abrahamowicz M, Siemiatycki J. 2003. Evaluation of Cox's model and logistic regression for matched case-control data with time-dependent covariates: a simulation study. *Statistics in Medicine* 22: 3781-3794.

Leemis LM. 1987. Variate generation for accelerated life and proportional hazards models. *Operations Research* 35: 892- 894.

Liu Y., Criag BA. 2006. Incorporating time-dependent covariates in survival analysis using the LVAR method. *Statistics in Medicine* 25: 1729-1740.

MacCallum RC, Zhang S, Preacher KJ, Rucker DD. 2007. On the practice of dichotomization of quantitative variables. *Psychological Methods* 7: 19-40.

Mackenzie T, Abrahamowicz M. 2002. Marginal and hazard ratio specific random data generation: applications to semi-parametric bootstrapping. *Statistics and Computing* 12: 245-252.

Marsaglia G. 2003. Random number generators. *Journal of Modern Applied Statistical Methods* 2: 2-13.

Masuda N, Prnglib ZF. 1996. A parallel random number generator library. *Swiss Center for Scientific Computing*, Switzerland.

Mckinley S, and Levine M. 2000. Cubic Spline Interpolation Pages 1-15. *Math45*: Linear Alegebra. http://online.redwoods.cc.ca.us/instruct/darnold/laproj/Fall98/SkyMeg/Proj. PDF. 25 February 2012.

Mehra MR, Uber P A, Ventura HO, Scott RL, Park MH. 2004. The impact of mode of donor brain death on cardiac allograft vasculopathy an intravascular ultrasound study. *Journal of the American College of Cardiology* 43: 806-810.

Murray L. 2007. Advances in Markov chain Monte Carlo methods. Unpublished PhD thesis, University College London, London.

Nardi A, Schemper M. 2003. Comparing Cox and parametric models in clinical studies. *Statistics in Medicine* 22: 3597-3610.

Nelson C.P., Lambert, P. C., Squire, I. B., and Jones, D. R. 2007. Flexible parametric models for relative survival, with application in coronary heart disease. *Statistics in Medicine* 26: 5486-5498.

NHS Blood and Transplant. 2010. *Transplant Activity Report*: http://www.uktransplant.org.uk/ukt/statistics/ statistics.jsp. 25 February 2012.

Odell PM, Anderson K M, and D'Agostino, R. B. 1992. Maximum likelihood estimation for interval censored, data using a Weibull-based accelerated failure time model. *Biometrics* 48: 951-959.

Petersen T. 1986. Fitting parametric survival models with time-dependent covariates. *Applied Statistics* 35: 281-288.

Royston P. 2001. Flexible parametric alternatives to the Cox model, and more. *Stata Journal* 1: 1-28.

Royston P, and Parmar M. 2002. Flexible parametric proportional-hazards and, proportional-odds models for censored survival data watpm, and estimation of treatment effects. *Statistics in Medicine* 21: 2175-2197.

Sarnak MJ, Levey AS, Coresh J, Culleton B, Hamm LL . 2003. Kidney disease as a risk factor for development of cardiovascular disease. *Circulation* 108: 2154-2169.

Schemper M. 1992. Cox analysis of survival data with non-proportional hazard functions. *The Statistician* 41: 455-465.

Schultz LR, Peterson EL, Breslau N. 2002. Graphing survival curve estimates for time-dependent covariates. *International Journal of Methods in Psychiatric Research* 11: 68-74.

Simon R, Makuch RW. 1984. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: Application to responder versus non-responder bias. *Statistics in Medicine* 3: 35-44.

Sleeper LA, and Harrington DP. 1990. Regression splines in the Cox model with application to covariate effects in liver disease. *Journal of the American Statistical Association* 85: 941-949.

Sparling YH, Younes N, Lachin JM, and Bautista OM. 2006. Parametric survival, models for interval-censored data with time-dependent covariates. *Biostatistics* 7: 599-614.

Stacey J, Nicholas HG, et al. 2006. Simulation of Correlated Continuous and Categorical Variables using a Single Multivariate Distribution. *Journal of Pharmacokinetics and Pharmacodynamics* 33: 773-794.

Stuart, PM, Griffith TS, et al. 1997. Induced apoptosis is necessary for corneal allograft survival. *Journal of Clinical Investigation* 99: 396-402.

Sylvestre MP, Abrahamowicz M. 2008. Comparison of algorithms to generate event times conditional on time-dependent covariates. *Statistics in Medicine* 27: 2618-2634.

Therneau TM, Grambsch PM. 2000. *Modeling Survival Data: Extending the Cox model*. New York: Springer.

Thiebaut A, Benichou J. 2004. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Statistics in Medicine* 23: 3803-3820.

Turnbull BW, Brown BW, and Hu M. 1974. Survivorship analysis of heart transplant data. *Journal of the American Statistical Association* 69: 74-80.

Villar E, Boissonnat P, Sebbag L, Hendawy A, Cahen R, Trolliet P, Labeeuw M, Ecochard R, Pouteil-Noble C. 2007. Poor prognosis of heart transplant patients with end-stage renal failure. *Oxford Journal* 22: 1383-1389.

Yang DC, Whitmarsh AJ, Barrett T, Davis RJ, Rincon M, and Flavell RA. 1998. Differentiation of CD4+ T cells to Th1 cells requires MAP kinase JNK2. *Immunity* 9: 575-585.

Zevitz ME. 2006. Myocardial Ischemia. *eMedicine*. http://www.emedicine.com/med/topi c1568.htm. 25 February 2012.