# Modelling Graft Survival After Kidney Transplantation Using Semi-Parametric and Parametric Survival Models


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# Abstract

This study presents survival modelling and evaluation of risk factors of graft survival in the context of kidney transplant data generated in South Africa. Beyond the Kaplan-Meier estimator, the Cox proportional hazard (PH) model is the standard method used in identifying risk factors of graft survival after kidney transplant. The Cox PH model depends on the proportional hazard assumption, which is rarely met. Assessing and accounting for this assumption is necessary before using this model. When the PH assumption is not valid, modification of the Cox PH model could offer more insight into parameter estimates and the effect of time-varying predictors at different time points. This study aims to identify the survival model that will effectively describe the study data by employing the Cox PH and parametric accelerated failure time (AFT) models.

To identify the risk factors that mediate graft survival after kidney transplant, secondary data involving 751 adults that received a single kidney transplant in Charlotte Maxeke Johannesburg Academic Hospital between 1984 and 2004 was analysed. The graft survival of these patients was analysed in three phases (overall, short-term and long-term) based on the follow-up times. The Cox PH and AFT models were employed to determine the significant risk factors. The purposeful method of variable selection based on the Cox PH model was used for model building. The performance of each model was assessed using the Cox-Snell residuals and the Akaike Information Criterion. The fit of the appropriate model was evaluated using deviance residuals and the delta-beta statistics. In order to further assess how appropriately the best model fit the study data for each time period, we simulated a right-censored survival data based on the model parameter-estimates.

Overall, the PH assumption was violated in this study. By extending the standard Cox PH model, the resulting models out-performed the standard Cox PH model. The evaluation methods suggest that the Weibull model is the most appropriate in describing the overall graft survival, while the log-normal model is more reasonable in describing short-and long-term graft survival. Generally, the AFT models out-performed the standard Cox regression model in all the analyses. The simulation study resulted in parameter estimates comparable with the estimates from the real data. Factors that significantly influenced graft survival are recipient age, donor type, diabetes, delayed graft function, ethnicity, no surgical complications, and interaction between recipient age and diabetes. Statistical inferences made from the appropriate survival model could impact on clinical practices with regards to kidney transplant in South Africa. Finally, limitations of the study are discussed in the context of further studies.

*To*

*My late mother*

*Ihuoma Elizabeth Ezeh*

*and*

*My late sister*

*Ijeoma Dorothy Ezeh*

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To God be the glory and honour.

# Declaration

I declare that this dissertation is my own work. It is being submitted for the Degree of Master of Science in Statistics to the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

$11^{th}$ November, 2017

# List of Abbreviations

| | |
|---|---|
| AFT | Accelerated Failure Time |
| AIC | Akaike Information Criterion |
| AR | Acute Rejection |
| CI | Confidence Interval |
| CKD | Chronic Kidney Disease |
| CMJAH | Charlotte Maxeke Johannesburg Academic Hospital |
| CYA | Cyclosporine |
| DGF | Delayed Graft Function |
| EDA | Exploratory Data Analysis |
| ESKD | End Stage Kidney Disease |
| GFR | Glomerulus Filtration Rate |
| HR | Hazard Ratio |
| HV | Heaviside |
| KM | Kaplan-Meier |
| LL | Log-likelihood |
| LR | Likelihood Ratio |
| LT | Long-term |
| MLE | Maximum Likelihood Estimate |
| PH | Proportional Hazard |
| PMP | Per million population |

| | |
|---|---|
| RRT | Renal Replacement Therapy |
| SE | Standard Error |
| ST | Short-term |
| TR | Time Ratio |
| USA | United States of America |
| VIF | Variance Inflation Factor |

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# Chapter 1

# Introduction

## 1.1 Brief background on kidney transplant

Chronic kidney disease (CKD) is among the leading public health challenges worldwide (Schieppati and Remuzzi, 2005). South Africa is one of the countries with the highest incidence of CKD. CKD is clinically established with respect to the glomerulus filtration rate (GFR). The progression of CKD is characterised by stages depending on the GFR and the severest stage is known as end stage kidney disease (ESKD). It is at this stage that a patient with CKD is diagnosed with kidney failure and requires renal replacement therapy (RRT), which includes maintenance dialysis and kidney transplantation (Levey et al., 2003). A kidney transplant is considered to be the best treatment choice for patient with ESKD when compared to maintenance dialysis. A successful kidney transplant increases the life expectancy and the quality of life of a patient, and has been shown to be more cost effective than maintenance dialysis (Laupacis et al., 1996). Maintenance dialysis can only serve a limited number of patients due to limited health care facilities. Nonetheless, dialysis is the first line of treatment for a patient with ESKD until a suitable donor kidney is available.

In kidney transplantation, numerous prognostic factors are known to influence both short and long-term survival of either the patient and/or the graft. These factors are either associated with the recipient, the donor or the transplantation. Some of these factors can influence the impact of other factors in predicting graft survival outcomes. For instance, acute graft rejection post-transplant could be as result of human leukocyte antigen (HLA) mismatch that could lead

to delayed graft function (DGF) and consequently lead to early graft failure (Żukowski et al., 2014).

Many kidney transplant studies focus on factors that influence short-term (graft survival up to one year) and long-term graft survival (graft survival beyond one year). Considerable progress made towards improving immunosuppression therapy, preservation techniques and other well-developed supportive therapies, studies have shown significant improvement in short-term (ST) graft survival (Hariharan et al., 2000; Irish et al., 2010); however, long-term (LT) graft survival has not been significantly improved (Paul, 1999). This is because some factors still compromise the efficacy of renal transplant outcomes. Measurement and identification of the impact of each factor on graft survival is crucial. In addition, modifying and managing these factors such as delayed graft function and diabetes may help to optimise success in LT kidney transplant outcome. This is important, especially in developing countries where there is limited resources for kidney re-transplant.

## 1.2 Overview on survival analysis

One of the primary goals in kidney transplant studies is to model time to graft failure. The time could be in weeks, months or years, from the date of transplantation to the time of graft failure, which is known as survival time. In kidney transplant studies, patients are followed-up to a certain period after transplant, either the period is pre-specified before the start of the follow-up or the investigator decides to terminate the study due to the number of targeted events having occurred, financial reasons or ethical reasons. Observation of any patient is terminated once the graft fails or the patient dies, except a study that involves re-transplants. However, some of the patients may not have experienced graft failure or are still alive by the end of the study. Sometimes, the patient may withdraw from the study before the graft fails. The observation of such a patient is incomplete and the status of the case is considered censored. In this situation, the data point is said to be right censored. Right censoring is a common type of censoring in kidney transplant studies. Censoring is one of the key features of survival data. Generally, survival data are not normally distributed (mostly positive skewed), Thus, standard statistical methods such as linear regression cannot be used to analyse survival data due to the difficulty in accommodating censored observations and time-varying predictors in such a model (Hosmer Jr and Lemeshow, 1999; Vittinghoff et al., 2011).

Statistical techniques known as survival analysis have been developed to model the time to graft failure and factors that impact on the time to graft failure. Survival analysis is a collection of several statistical techniques employed to analyse censored data. Most of these techniques are valid when censoring in the data is non-informative, that is, the probability of censoring a subject in a given follow-up time is independent of the subsequent failure times. This is known as independent censoring assumption. Unfortunately, there is no statistical method for testing this type of assumption (Bradburn et al., 2003; Prentice and Kalbfleisch, 2015). Unlike standard regression methods, survival analysis techniques properly incorporate information from both censored and uncensored observations in estimating the model parameters. Generally, survival analysis is classified as non-parametric, semi-parametric or parametric methods.

Beyond non-parametric techniques such as the Kaplan-Meier (KM) estimator, Cox proportional hazard (PH) model (a semi-parametric model also known as the Cox regression model) is the most popular regression model in survival analysis. Researchers frequently employ this model in kidney transplant studies due to its flexibility and ease of interpretation of its hazard ratio. However, the flexibility of the Cox regression model does not make it assumption-free. The fundamental assumption of the Cox regression model assumes that factors under study have a constant effect on the hazard over time. In most cases, the Cox PH assumption is not met. Previous studies including one by Lagakos and Schoenfeld (1984) have shown that violating the assumption of the Cox PH model could lead to poor model fit and over-estimation of the covariate hazard ratio. This assumption may not be tenable in some applications because some of the study factors may have a non-constant effect over time. Assessing the PH assumption should be vital in the use of the Cox PH model because violation of this assumption could lead to misleading parameter interpretation. However, if the assumption of PH is violated for any covariate, modifying the Cox regression model should be considered. One modification of the Cox model is to stratify the covariate that does not satisfy the proportional hazard assumption. In this scenario, all other covariates except the stratified covariate are incorporated in the model and their parameters are estimated. The second method is to add the interaction with time for the covariate that violates the assumption. This method enables the verification of PH assumption and provides a solution to non-proportional hazard.

Parametric models including the exponential and Weibull models (Hosmer Jr and Lemeshow, 1999; Collett, 2003) are alternatives to the Cox PH model in the analysis of time-to-event data. Parametric models assume that the underlying survival times have a defined probability distribution, and thus are not as flexible and widely applied as the Cox PH model. If the assumption of the parametric form for a survival time data is valid, the model could lead to a

more meaningful and precise inference. This results in smaller standard errors in the estimate of the median survival times and the relative hazard. Thus, caution should be applied when using parametric models because the baseline hazard function needs to be correctly specified. However, these models are susceptible to misspecification because identifying the distributional requirement may be difficult (Hosmer Jr and Lemeshow, 1999). Nonetheless, parametric models provide insight into the shape of the baseline hazard if correctly specified .

Simulation-based methods for model-fit assessment play a vital role in contemporary research methods in statistics. In a situation in which mathematical and analytical derivations could not be realistic, data simulation may enable examination of statistical model-fit performance (Burton et al., 2006). Of paramount importance in any statistical data simulation is the presence of a suitable process for data-generation, and the simulated data is usually based on an underlying statistical model. Thus, parameters estimated by the reliant statistical model are used as the template to simulate a population of a dataset. The model estimates from the simulated dataset is used to evaluate how compatible the real dataset is to the simulated dataset. There are several algorithms designed and developed for simulation of survival data, and each algorithm presents different complexities and challenges. 'Survsim', an R package for simulation of censored survival data was used in this study (Moriña and Navarro, 2014).

## 1.3 Rationale and motivation for the study

The application of survival analysis models to transplantation data, especially kidney transplant data, is not novel in South Africa. Some of these studies used non-parametric survival techniques such as KM and log rank test to model graft or patient survival outcome (Myburgh et al., 1983; O'Donnell et al., 1986; Rafique Moosa, 2004; Pitcher et al., 2006). However, these techniques are suited for only categorical variables, and they cannot be used to model the impact of one predictor adjusting for other predictors. Moosa (2003) showed the impact of demographic factors on patient and graft survival post kidney transplantation using Cox PH model. More recently, Fabian et al. (2016) used the Cox PH model to provide insight into between-group graft and patient survival. Moosa (2003) and Fabian et al. (2016) did not report in their studies whether the Cox PH assumptions were met. Many existing kidney transplant studies that employed the Cox PH model focuses primarily on the impact of risk factors on graft and patient survival. The statistical tests of the assumptions, checks on the model adequacy and the use of this model to incorporate interaction (when there is evidence of interaction

between variables) are rarely reported. Failure to check all these aforementioned requirements for the Cox PH model before proceeding to interpretation, especially when the assumptions of the model are not met, may lead to invalid estimates and conclusions. Although the Cox PH has gained popularity in the kidney transplant studies, it is essential to consider other survival models such as parametric models. The choice should not be driven by the model that results in significant predictors, rather the model that summarises the fit of the data (George et al., 2014).

## 1.4 Aims and objectives

Even though the Cox PH has gained popularity in kidney transplant studies, it is essential to consider other survival models such as parametric models. In addition to what has been done in kidney graft survival studies and more specifically in South Africa, this study will provide a more comprehensive analysis of graft survival after kidney transplantation. The aim of this study is to compare the Cox PH model and accelerated failure time (AFT) models in order to identify the best model for analysing graft survival after kidney transplant. In order to achieve the study aim, the following objectives were accomplished:

- The purposeful variable selection method based on the Cox PH model was used to select candidate predictors for inclusion in the study.
- The need to consider extension of the Cox PH model for predictors with time-varying effects and by stratification, when the PH assumption is not tenable was demonstrated.
- Performance of parametric AFT and Cox PH models were compared using Akaike information criterion and Cox-Snell residuals.
- Survival data was simulated as a means of assessing the goodness-of-fit of the appropriate survival model choice.

## 1.5 Data source

To accomplish the aim and objectives of this study, we reviewed secondary data of 751 adult kidney transplants performed in Charlotte Maxeke Johannesburg Academic Hospital

(CMJAH) between 1984 and 2000, known as the cyclosporine (CYA) era . The first kidney transplant in South Africa was performed in this centre and kidney transplants continue in this centre to date. Also, CMJAH is among the three organ transplantation referral hospitals in Johannesburg. Graft survival time, patient survival time and a pool of pre-transplant, transplant and post-transplant variables were measured. However, this study focused on graft survival because maximising the graft function is crucial for the patient and for the provider of RRT (Rafique Moosa, 2004).

## 1.6 Scope of the study

The geographical scope of this study is restricted to patients 18 years and above that received a single kidney transplant in CMJAH between 1984 and 2000. The scope of statistical analysis will be limited to survival analysis techniques, which includes the non-parametric Kaplan-Meier method, semi-parametric regression models (Cox regression model and extension of the Cox model) and parametric survival models.

## 1.7 Structure of the dissertation

The remainder of the dissertation is structured as follows: Chapter 2 reviews literature on CKD, ESKD, kidney transplant and applications of survival analysis methods in kidney transplant studies. Chapter 3 reviews the theoretical basis of survival analysis. Chapter 4 presents description of the dataset and the methodology used in the study. Results of the study are presented in Chapter 5. Chapter 6 focuses on the discussion of the research findings followed by summary, conclusion, recommendations and suggestion of areas for future research.

# Chapter 2

# Review on kidney disease and transplantation

In this Chapter, a summary of CKD, ESKD, kidney transplantation and factors shown to influence graft survival after kidney transplant is discussed.

## 2.1 Background of chronic kidney disease

The global challenge of CKD remains on the increase, with high incidence in developing countries compared to developed countries. Sub-Saharan Africa and Asia have the highest rates of CKD worldwide. The prevalence of CKD is associated with poor socio-economic factors, environmental factors and racial group. CKD is among the leading causes of death worldwide with over 10% of the worlds population affected by this disease (Jha et al., 2012). CKD was ranked the $27^{\text{th}}$ major leading cause of death in 1990 by the world health organisation, by 2010, it had risen to become the $18^{\text{th}}$ leading cause of death (De Nicola and Zoccali, 2016). Low income third world countries where access and affordability of quality health care is non-existent are the epicentre of this global crisis (Ojo, 2014).

As previously mentioned (in Section 1.1), CKD is clinically established with respect to glomerulus filtration rate (GFR) or level of urinary protein excretion. The progression of CKD is characterised by five stages depending on the GFR as shown in Table 2.1 (Levey et al., 2003), with Stage 1 being the mildest and Stage 5 being the most severe stage of CKD. At all

stages of CKD, patients are inclined to (1) increased use of health care facilities, (2) increased risk of cardiovascular disease and (3) premature death. Patients at Stage 5 CKD require RRT either by kidney transplantation or continuous maintenance dialysis.

**Table 2.1:** Stages of chronic kidney disease defined by glomerular filtration rate.

| Stage | Description | GFR (mL/min/$1.73m^2$) |
|---|---|---|
| 1 | Kidney damage with normal or increased GFR | $\geq 90$ |
| 2 | Kidney damage with mild or decreased GFR | $60 - 89$ |
| 3 | Moderately decreased GFR | $30 - 59$ |
| 4 | Severely decreased GFR | $15 - 29$ |
| 5 | Kidney failure | $< 15$ (or dialysis) |

On a global level, it is estimated that the number of people with ESKD is greater than 1 billion. However, there is limited access to maintenance dialysis or kidney transplantation. Thus, leading to more than 1 million people dying yearly because of ESKD (Ojo, 2014). In the next few decades, the prevalence of ESKD is projected to rise sharply due to ageing population and increase in the prevalence of hypertension and diabetes (White et al., 2008). Developing countries are expected to experience a greater rise in the prevalence of ESKD compared to developed nations (Alebiosu and Ayodele, 2005). This rise in the incidence of ESKD will challenge the economies of many developing countries because of the provision of treatments to an increasing number of patients with ESKD. There is no global equity in access to transplantation, especially in developing countries where there is poor infrastructure, low affordability of immunosuppressive drugs and inadequate nutrition post-transplant (White et al., 2008).

## 2.2 Overview of end stage kidney disease in Africa

There are inconsistent updates and/or inaccessibility of registries in most African countries, thus leading to unreliable estimates of ESKD. However, there is a general belief that like the major public health problems such as HIV/AIDS and tuberculosis, renal disease is 3-4 times more severe in Africa compared to the western world (Naicker, 2009). Kidney disease imposes a disastrous economic burden and human suffering in Africa. The onset of ESKD in Africa is at around 20 years of age compared to 45 to 63 years of age in developed countries. The number of cases of ESKD in Africa increase annually at 6-8% per year (Ojo, 2014). ESKD is considered

a "death sentence" in Africa because less than 2% of patients receive RRT (Ojo, 2014). Moosa and Kidd (2006) considered ESKD a major public health challenge in South Africa because only a minority of patients enjoy access to RRT. Due to limited access to RRT in South Africa, the Department of Health has set up formal guidelines to select potential patients for RRT such as patients'age and health status. The annual cost of dialysis is estimated at USD 2500 to 20,000 per patient in sub-Saharan Africa. Current projections have shown that none of the sub-Saharan African countries can afford the cost of treatment for patients with ESKD (Ojo, 2014). Thus urgent intervention in the sub-Saharan regions of Africa is paramount.

The principal cause of CKD in sub-Saharan Africa includes hypertension and diabetes. Veriava et al. (1990) had reported hypertension to be the cause of ESKD in 34.6% of black, 4.3% of white, 13.8% of Indian and 20.9% of mixed race groups based on statistics from the South African Dialysis and Transplant Registry (SADTR). However, estimates from the registry reflects only the total number of patients selected for RRT because the prevalence of ESKD in South Africa is still not accurately known.

## 2.3 Kidney transplantation

Improved survival, quality of life and substantial cost-savings are associated with kidney transplantation compared to dialysis. Studies supporting this view, which are based on the outcomes of kidney transplant studies, conclude that transplantation is the best treatment choice for patients with ESKD (Pitcher et al., 2006). However, this procedure is daunting in developing countries because it involves complex and multidisciplinary interventions. The agenda in many developed countries is to move all patients requiring RRT from dialysis to kidney transplantation (White et al., 2008). The obstruction to this goal is the low rate of kidney donation and thus the resulting shortage of donor kidneys. The need for donor kidneys has necessitated expanding the potential donor pool. These include the increased use of cadaveric or deceased kidneys, elderly donor kidneys, living relatives and unrelated donor kidneys.

In addition to a shortage of donor organs, costs associated with transplantation are another hindrance to kidney transplantation, because transplantation is unaffordable to most patients. The transplant rate in sub-Saharan Africa has been estimated to be four patients per million population (pmp) and the South Africa transplant rate is 9.2 patients pmp, which constitute

mainly non-black patients due to factors including socio-economic status. Disparity in access to renal transplants have been recognised globally with regards to ethnicity, socio-economic factors, gender and region (Schold et al., 2005). For instance, in United State of America (USA), white patients awaiting kidney transplant are two times more likely to receive a kidney transplant compared to their black counterparts (Locke et al., 2008).

After a successful kidney transplant, the graft requires a lifetime of constant maintenance in order to prevent rejection of the transplanted kidney. This is achievable through lifestyle modifications and immunosuppressive chemotherapy. Additionally, innovation in surgical techniques and improvement in immunosuppressive regimens have improve the success of kidney transplantation. The conventional maintenance immunosuppression regimen used after kidney transplant included azathioprine and cortisone until 1983, the use of cyclosporine in combination with other therapy began after 1983. From 2001, other immunosuppressive drugs including sirolimus and everolimus were added as part of the organ transplantation immunosuppressive regimen (Pitcher et al., 2006).

## 2.4 A brief overview of factors that influence graft survival

Kidney transplant studies focus mainly on ST graft survival time period and studies have shown significant improvement in ST graft survival outcomes (Hariharan et al., 2000; Irish et al., 2010). As a result of this, most kidney transplant studies have shifted focus to longer follow-up periods as well as factors that could impact on LT graft survival outcomes. The five year graft survival rate has been reported to be in the region of 82-87% (Wafa et al., 2011; Ghoneim et al., 2013; Fabian et al., 2016). The 10 year graft survival rate has been reported to be in the range of 50% (Opelz, 2000). However, recent studies done by Ghoneim et al. (2013) and Fabian et al. (2016), have shown that overall the 10 year graft survival rate after kidney transplantation is in the region of 65.5% and 66.8% respectively. Wafa et al. (2011) has shown the 15 year graft survival rate to be in the range of 40%.

Several prognostic factors influence graft survival rate after kidney transplantation. Identification of these factors is important to public health because it will enable a more effective transplant surgery, recovery and maintenance of the graft after transplant. Prognostic factors captured in the study database are listed in Table 2.2. Discussion of these factors in this

study is limited to statistical perspectives and not medical etiology perspectives. In context with this study, the factors may be grouped into four, but overlapping, categories. Citations under the 'influence' column reference are those studies that showed the corresponding factor influences graft survival, based on survival model-based techniques. While citations under the "no influence" column showed that the factors have no influence on graft survival.

**Table 2.2:** Study variables based on reviewed literature

| Category | Factor | Influence | No influence |
|---|---|---|---|
| **Recipient** | Age | Morris et al. (1999)<br>Moosa (2003) | McGee et al. (2010)<br>Jalalzadeh et al. (2015) |
| | Diabetes | Hariharan et al. (2002)<br>Morales et al. (2012) | Kim and Cheigh (2001) |
| | ESKD | Courtney et al. (2008) | Hariharan et al. (2002)<br>Wafa et al. (2011) |
| | Ethnicity | Malek et al. (2011)<br>Fabian et al. (2016) | Butkus et al. (1992)<br>Moosa (2003) |
| **Donor** | Age | Morris et al. (1999)<br>González-Molina et al. (2014) | Emiroğlu et al. (2005)<br>Jalalzadeh et al. (2015) |
| | Ethnicity | Locke et al. (2008)<br>Callender et al. (2009) | |
| | Type | Nemati et al. (2014)<br>Fabian et al. (2016) | McGee et al. (2010) |
| **Donor-recipient** | Blood group | Takahashi et al. (2004)<br>Montgomery et al. (2012) | El-Husseini et al. (2005)<br>Wafa et al. (2011) |
| | Gender | McGee et al. (2010)<br>Tan et al. (2012) | |
| **Transplantation** | Surgical complication | Ghoneim et al. (2013) | |
| | Acute rejection | Żukowski et al. (2014)<br>Koo et al. (2015) | |
| | Delayed graft function | Hariharan et al. (2002)<br>González-Molina et al. (2014) | Boom et al. (2000) |

Factors associated with the recipient, include age, diabetes at transplant, ethnicity and the cause of ESKD. In this study, causes of ESKD include renal disease, nephrectomy and hypertension. Donor factors are those factors that are directly associated with the characteristics of the kidney donor. The type of the kidney donated can be either a living or a cadaveric kidney. The donor-recipient category describe factors that require the donor and the recipient characteristics to be matched for transplantation. Donor-recipient blood group match and gender match have been previously studied as possible prognostic factors that influence the survivability of a graft after transplant. Lastly, prognostic factors associated with transplantation include complications as a result of surgery, acute rejection of the graft and delay in the function of the grafted kidney. Some examples of surgical complication (within the context of this study) are nephrectomy, wound sepsis and ureteric. An acute rejection episode

post-transplant could be clinical or histological.

Conventionally, survival analysis techniques are used to assess or predict risk factors of kidney graft survival after transplantation. Factors listed in this literature review are the variables used in this study. Based on the literature reviewed in Section 2.4, the impact of these factors on graft survival remains controversial. For example, studies done by González-Molina et al. (2014) and Jalalzadeh et al. (2015) resulted in contradictory findings with respect to the influence of donor age on graft survival. The common survival analysis techniques used in all the reviewed literature are the KM and Cox PH model. The assessment of linearity and PH assumptions were not reported in most of these studies. Evaluation of interaction between risk factors was also not reported in these studies. Alternative survival models such as parametric survival models were also not considered in all these studies. In all the literatures reviewed in this chapter, few of the authors considered a subset of their study variables in the adjusted Cox PH model through variable selection, while most of them included all the study variables in the multivariable Cox PH model. The various controversies surrounding the findings may be associated to differences in data analysis techniques or the duration of the follow-up. Hence; it is not unexpected that there are conflicting reports on the impact these factors have on graft survival. Therefore, the need to robustly assess the impact of these factors by employing variable selection methods, assessing the linearity and PH assumption and modelling the risk factors using parametric survival models may be vital in describing the impact of these factors on graft survival.

# Chapter 3

# Theoretical review of survival analysis

This chapter presents the theoretical background of survival analysis techniques used in this study. Basic quantities of interest and non-parametric methods are first presented in Section 3.1 before going into details of survival methods. The Cox regression model, which is the most commonly used method in analysing risk factors of graft survival as presented in Section 3.2. Extension of the Cox regression model (when the PH assumption is not tenable) is presented in Section 3.3. Acceleration failure time models, which assume a specific distribution for the survival time, are discussed in Section 3.4. The maximum likelihood method for parameter estimation in survival models is presented in Section 3.5. Sections 3.6 through 3.8 include the methods used for model development, assessment of model adequacy and comparison.

## 3.1 Basic concept and notation

### 3.1.1 Censoring

The key feature of time-to-event data is censoring of the survival times, i.e. incomplete observation of the survival times. There are different scenarios that could result in censored data, which includes Type I, Type II and Random censoring. In Type I censoring, the study duration is fixed but the number of failures is random. In this instance, subjects are followed simultaneously and failure is observed only if it occurs before the study ends, otherwise the subject is censored. For Type II censoring, the study duration is random but the number

of failures is fixed. For example, a sample of $n$ subjects is followed simultaneously until a predetermined number of failures $r$ among the subjects has occurred ($r < n$). In random censoring, subjects enter the study at random times, both the failure and censoring times are random.

On the basis of the previously discussed scenarios that could lead to censoring in a time-to-event data, censoring of observation could be right, left or interval. Right censoring occur when a patient's information is not complete at the right tail of the follow-up time axis. This could be because the patient withdraws from the study before an event occurs, the patient died as a result of other unrelated causes or the event did not occur by the end of the study. Left censoring occurs when a patient has experienced the event of interest before being enrolled in a study, i.e. the event is known to have occurred before the patient's enrolment but the exact event time is unknown. When the event time is known to have occurred within an interval but the exact time is not known, interval censoring is said to occur. In this study, the patients were not enrolled at the same time and observations were right censored. Right censoring is illustrated in Figure 3.1. Some of the patients did not experience graft failure at the end of the study (patients 3 and 8). Patients 2 and 9 were lost to follow up or withdrawn from the study. Different times of entry in the study is also shown in this figure.

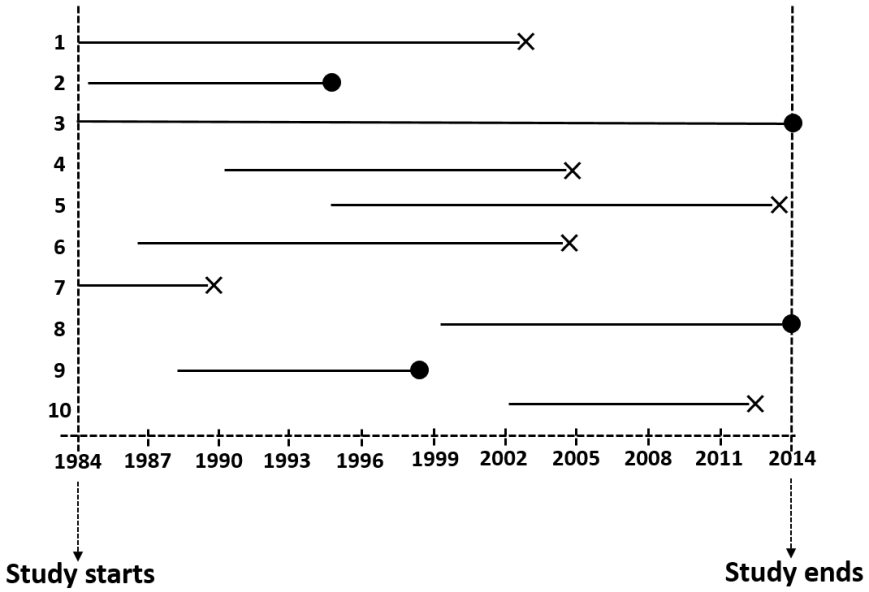


**Figure 3.1:** Illustration of right censoring features in a study to determine for example graft survival post-transplant. (•) indicates that the graft of the patient did not fail and (×) is indicative of graft failure.

### 3.1.2 Survival time functions

Let $T$ be a non-negative random variable associated with graft survival time (in context of this study, it is time from transplant until graft failure), assuming time is a continuous variable. Let the failure indicator $(\delta_j)$ be a random variable $(0, 1)$ , which is indicative of censorship or failure. $\delta = 0$ if a graft did not fail up until the study ends or a patient died as a result of other causes or the patient was removed from the study, and $\delta = 1$ if the graft failed during the follow up period. The distribution of $T$ is usually characterised by some functions, namely, the survival function, hazard function, probability density function and mean residual life at time $t$ (Collett, 2003; Klein and Moeschberger, 2005). In modelling survival data, one or more of these functions are used to illustrate the survival distribution pattern. The distribution function of $T$ is given by

$$F(t) = P(T \leq t),$$

which denotes the probability that the graft survival time is less than or equal to some specified value of time, $t$.

**Survival function**

One of the basic quantities used to describe survival data is the survival function $(S(t))$; the probability of graft surviving beyond time $t$.

$$S(t) = 1 - F(t) = Pr\,(T > t) = \int_t^{\infty} f(u)du, \tag{3.1}$$

where $f(.)$ is a density function. Thus,

$$f(t) = -\frac{dS(t)}{dt}, \tag{3.2}$$

Different types of survival curves can be estimated from survival data but they all have common properties. $S(t)$ is monotonic, non-increasing function with

$$S(t) = \begin{cases} 1 & \text{for } t \to 0 \\ 0 & \text{for } t \to \infty, \end{cases} \tag{3.3}$$

The probability of graft surviving is equal to one at time zero and equal to zero at infinite time. A survival function graph is referred to as a survival curve, the rate at which the curve declines depends on the risks associated with the event of interest. An example of a survival curve is shown in Figure 3.3, which was used to estimate the median survival time, although, other quantities such as the percentiles can be estimated as well. Assuming there was no censoring in this study, the survival function would be estimated as proportion of graft survival beyond time $t$

$$\widehat{S}(t) = \frac{\text{number of grafts surviving beyond time } t}{\text{total number of grafts at risk}}. \tag{3.4}$$

The survival function was estimated with a KM product limit estimator because there are censored observations in this study. The KM estimator is similar to a non-parametric likelihood estimator and is based on the product of a series of estimated probabilities. Suppose $t_1, t_2, t_3 \ldots$ denote the observed graft failure times, such that $t_1 < t_2 < t_3$. Let $d_1, d_2, d_3 \ldots$ denote the number of graft failures that occurred in the study and let $n_1, n_2, n_3 \ldots$ be the number of patients' grafts still at risk in the study. Assuming there are $r$ graft failure times among the patients (where $r \leq n$), we denote the $j^{th}$ ordered graft survival time (in ascending order) as $t_j$, for $j = 1, 2, \ldots, r$. We also denote $n_j$ $(j = 1, 2, \ldots, r)$ as the number of graft still at risk at time $t_j$ and $d_j$ $(j = 1, 2, \ldots, r)$ as the number of graft failures at time $t_j$. The constructed time intervals is illustrated in Figure 3.2.

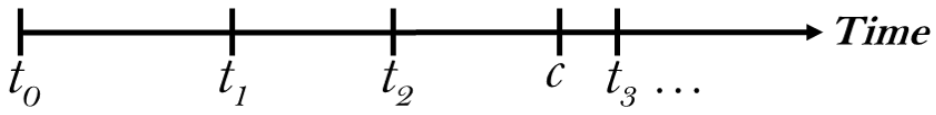


**Figure 3.2:** Illustrating different graft failure and censoring times.

$t_0$ denotes the time origin, which ends just before $t_1$. The first constructed interval begins at time $t_1$ (time of the first graft failure) and ends just before $t_2$. The figure also shows the second interval $(t_2 - t_3)$ and the censored time $c$. The KM estimator of the survival function at any time $t$, in the $k^{th}$ constructed time interval ($t_{(k)}$ to $t_{(k+1)}$) is the estimated probability of surviving through the interval and all the preceding intervals. This leads to KM estimates

of survival function, which is given by

$$\widehat{S}(t) = \prod_{t_j=1}^{k} \left( \frac{n_j - d_j}{n_j} \right),$$

for $t_{(k)} \leq t < t_{(k+1)}$, $k = 1, 2, ..., r$, with $\widehat{S}(t) = 1$ for $t < t_{(1)}$ and where $t_{(r+1)}$ is taken to $\infty$. Graphically, the KM curve is obtained by plotting the survival proportion against time. The KM survival curves for two or more groups are used to gain insight in the survival differences between the groups. The log-rank test (Mantel, 1967) is mainly used to test the null hypothesis of no difference i.e. $H_0 : S_1(t) = S_2(t)$ in the estimated survival functions while the alternative hypothesis states the opposite i.e. $H_a : S_1(t) \neq S_2(t)$.

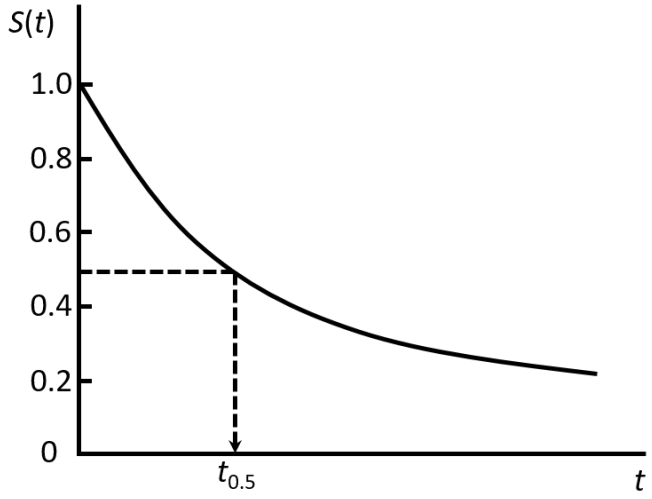


**Figure 3.3:** A typical survival function, showing the probability of graft failing at any time $t$. The graft median survival time is denoted by $t_{0.5}$.

### Hazard function

The hazard function or the instantaneous rate of failure is the chance of graft failure occurring in the next instant of time, given that the graft has survived up to time $t$. Hazard function $(h(t))$ is given as

$$h(t) = \lim_{\Delta t \to 0} \left\{ \frac{Pr\left(t \leq T < t + \Delta t | T \geq t\right)}{\Delta t} \right\}. \tag{3.5}$$

The relationship between equation (3.1),(3.2) and (3.5) can be expressed in the form

$$h(t) = \frac{f(t)}{S(t)} = \frac{f(t)}{1 - F(t)} = \frac{-d \log S(t)}{dt},$$

where

$$S(t) = \exp(-H(t)) = \exp\left[-\int_0^t h(u)du\right].$$

The quantity

$$H(t) = \int_0^t h(u)du = -\log S(t), \tag{3.6}$$

is the cumulative hazard function, which ranges from zero to infinity. Note when $t = 0, H(t) = 0$ and $S(t) = 1$ and when $t = \infty, H(t) = \infty$ and $S(t) = 0$. The slope of the $H(t)$ was used to understand the shape of the hazard function and identify the most appropriate survival model in this study. The KM estimator was used to estimate $H(t)$ in this study and the relationship is shown in equation (3.6). The hazard function can take several shapes (Figure 3.4). For example, one may assume that the hazard function for graft failure after kidney transplant is constant (black dot line), decreasing (black line), increasing (green line), bathtub-shape (red line) or hump-shape (blue line).

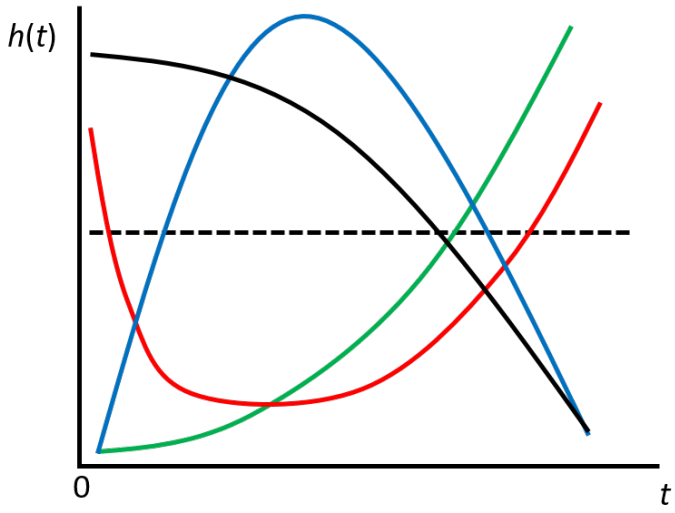


**Figure 3.4:** Illustrating several shapes of hazard function.

**Mean and median lifetime**

Let $\mu$ denote the mean or the expected value of graft survival time $T$, by definition $\mu$ is the integral of survival function, that is

$$\mu = E(T) = \int_0^\infty S(t)dt.$$

The median survival time is the time when 50% of the patients under study are expected to survive. In order words, the chance of surviving beyond this time is 50% (Figure 3.3). This is given by the value $t_{0.5}$, so that

$$S(t_{0.5}) = 0.5$$

In practice, the median survival time may not fall at exactly 0.5. In such a situation, the estimated median survival time ($\hat{t}(50)$) is the smallest time for which the estimated survival function value is less than $t_{0.5}$. So that

$$\hat{t}(50) = \min\left\{t \mid \hat{S}(t) < 0.5\right\},$$

where $t$ is the observed survival time. The median survival time is preferred to the mean because the mean survival time is usually affected by censoring in the data.

## 3.2 The Cox proportional hazard model

Modelling survival data enables the study of the effects of different covariates on the hazard function, as well as the extent to which other confounding factors affect the underlying hazard function. The semi-parametric Cox proportional (PH) or regression model introduced by D.R. Cox (David, 1972) is widely used in modelling survival data and is expressed as

$$h(t, \boldsymbol{X}) = h_0(t) \exp\left(\beta_1 X_1 + \beta_2 X_2 + ... + \beta_p X_p\right) = h_0(t) \exp(\boldsymbol{\beta}^{'} \boldsymbol{X}), \tag{3.7}$$

where $h_0(t)$ is the baseline hazard function and $\boldsymbol{\beta}$ is a vector of regression coefficients expressing quantitatively the effect of each of the explanatory variables in $\boldsymbol{X}$. The hazard function at a specific time depends on the values of $p$ explanatory variables $(X_1, X_2, \cdots, X_p)$, whose effect is measured by the respective values of the estimated coefficients $(\beta_1, \beta_2, \cdots, \beta_p)$. The baseline

hazard represents the hazard value when all the explanatory variables are equal to zero. Cox proposed a multiple linear regression model, in which the explanatory variables are connected to the hazard through a log transformation with the term $h_0(t)$ being the model intercept that changes over time. The non-parametric part of the model assumes no particular form for $h_0(t)$ but makes assumptions regarding the effect of the explanatory variables on the hazard, which is the parametric part of the model.

Other quantities such as the survival function can be obtained from the Cox PH model. The survival function is informative but underused in the Cox regression model. It is used in the Cox PH model survival probability predictions and in full parametric survival models (Bradburn et al., 2003). The survival function under the Cox PH model is

$$S(t, \boldsymbol{X}) = \{S_0(t)\}^{\exp(\boldsymbol{\beta}^{'} \boldsymbol{X})},$$

where $S_0(t)$ is the baseline survival function. Survival probability prediction for patients with covariates $(X_1, X_2, \cdots, X_p)$ are estimated easily once the baseline survival value at any given point in time is obtained.

The Cox regression model is similar to the logistic regression model in the sense that the effect of the explanatory variables acts multiplicatively on the baseline hazard function at any specific period (Vittinghoff et al., 2011). This leads to the Cox PH model key assumption, which is that the hazards of any two individuals are in constant proportion. The assumptions of proportionality between two subjects can be expressed in the form:

$$\text{HR} = \frac{h(t, \boldsymbol{X}_i)}{h(t, \boldsymbol{X}_j)} = \frac{h_0(t) \exp(\boldsymbol{\beta}^{'} \boldsymbol{X}_i)}{h_0(t) \exp(\boldsymbol{\beta}^{'} \boldsymbol{X}_j)} = \frac{\exp(\boldsymbol{\beta}^{'} \boldsymbol{X}_i)}{\exp(\boldsymbol{\beta}^{'} \boldsymbol{X}_j)} = \exp[\boldsymbol{\beta}^{'} (\boldsymbol{X}_i - \boldsymbol{X}_j)],$$

where $\boldsymbol{X}_i$ and $\boldsymbol{X}_j$ denote the covariates vectors for the two subjects. This implies that the hazard ratio (HR) for two subjects with sets of predictors is independent of the survival time, but dependent on the predictor values. The proportionality in this assumption is the hazard ratio $\exp(\boldsymbol{\beta})$.

## 3.3 Extension of the Cox proportional hazard model

In the Cox PH model defined in equation (3.7), we assume that all the covariates under study have a constant effect over time. The rationale for considering an extension of the Cox PH (Cox regression) model is when graphical statistical tests indicate that the PH assumption is violated for any or some of the study covariates, whose influence on the outcome variable is significant (Kleinbaum and Klein, 2006). The methods used in this extension are the stratified Cox regression model and Cox regression model with time by covariate interaction.

### 3.3.1 The stratified Cox regression model

In the stratified Cox regression model, the estimate of the covariate effect on the outcome variable is considered not to be the primary interest. That is the covariate is stratified-on and the Cox regression model is employed within stratum using other covariates that satisfied the PH assumption. It should be noted that controlling a variable that does not satisfy the PH assumption by stratification automatically excludes the variable from a set of predictors. This means that its effect on the outcome cannot be directly estimated in the stratified model. However, its effect is incorporated within stratum-specific baseline hazard functions. The hazard function for the stratified Cox regression model with no-interaction is given by:

$$h_g(t, \boldsymbol{X}) = h_{0g}(t) \exp(\boldsymbol{\beta}' \boldsymbol{X}),$$

where $g$=1, 2, ..., $G$ strata defined from the variable used for stratification. The baseline hazard function $h_{0g}(t)$ differs across the strata, indicating that the survival curve for each stratum will be different. The $\boldsymbol{\beta}$ is a vector of regression coefficients. Under the stratified Cox regression model, the proportional hazard assumption still holds for patients in the same $g^{th}$ stratum because they have the same baseline hazard function. On the other hand, the hazards between patients from different strata may not be proportional because their baseline hazard may not be the same. The estimated coefficients of the predictors are assumed to have common values for each stratum $g$ (no-interaction between the predictors and the stratified variable). To illustrate this, assuming a predictor 'gender' violates the PH assumption and another predictor 'age' satisfies the PH assumption. The coefficient $\beta$ for age is expected to be the same for each of

the gender strata (male and female) if the assumption of no-interaction is feasible. To verify this assumption, the interaction model

$$h_g(t, \boldsymbol{X}) = h_{0g}(t) \exp\{\beta_{1g} X_1 + \beta_{2g} X_2 + ... + \beta_{pg} X_p\}$$

needs to be fitted. The subscript $g$ in each of the regression coefficients indicates that the regression coefficients vary across the strata. The likelihood ratio (LR) test is used to confirm the no-interaction assumption by comparing the log-likelihood (LL) statistics for the interaction and no-interaction models.

$$\text{LR} = -2LL_{\text{no interaction}} - (-2LL_{\text{interaction}}).$$

Although the stratification model is more straight forward in controlling for non-proportionality, this model is associated with some drawbacks i.e. loss of power due to its construction and the effect of the stratified covariate on the outcome is not estimated.

### 3.3.2 Cox regression model with time-varying covariate effect

A covariate is said to have a time-varying effect if the HR varies over time, i.e. the effect of being a male may strongly affect graft survival immediately after kidney transplantation but decreases afterwards. This is different from time-varying covariates (covariate with non-fixed value), i.e. a patient's blood pressure level post-kidney transplant could fluctuate below or above 140 mmHg. However, a study variable may exhibit both time varying and non-constant effect over time. More details on time-varying effect or time-dependent covariate is described in Hosmer Jr and Lemeshow (1999). In this extension of the Cox regression model, we focused on time-independent covariates with non-proportional hazard or time-varying covariate effects because of all the explanatory variable values in this study are fixed over time. Assuming two covariates $X_1$ and $X_2$, with $X_2$ being the covariate with time-varying effect, equation 3.7 can be expressed in the form:

$$h(t, \boldsymbol{X}(t)) = h_0(t) \exp\{\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_2 g(t)\},$$

where the product term involving the covariate with a time-varying effect and some function

of time is defined by $x_2 g(t)$, and $g(t)$ is some function of time for the time-varying covariate effect. In this modification, the function of time $g(t)$ for the covariate that does not satisfy the PH assumption takes on the value $t$. This indicates that for the time-independent covariate that violates the PH assumption, its main effect and interaction with $t$ are included in the model. Further, the Heaviside function can be introduced in the Cox model e.g. $g(t) = 1$, if graft survival time is at or greater than a specified survival time, otherwise $g(t) = 0$. Inclusion of the product term of the non-proportional hazard covariate with time is used to check the PH assumption, assess the effect of the non-proportional covariate and aids in understanding how the HR changes over time.

## 3.4 Parametric survival models

Sections 3.2 and 3.3 focused on the discussion of the semi-parametric survival model. The rationale for employing this model was to avoid compete specification of the hazard function. Sometimes, the survival time distribution through previous research or exploratory data analysis is known to follow a particular parametric distribution, which imposes a specific parametric form on the baseline hazard ($h_0(t)$). In such a scenario, addressing the objective of the analysis using a full parametric form may provide estimates that are more clinically meaningful. In this section, the use of parametric models in survival analysis is presented. A parametric survival model assumes a specific distribution for the survival time and the regression coefficients are estimated with the method of full maximum likelihood. Once the $f(t)$ for the survival time is specified, the hazard function and the corresponding survival function can be obtained. Parametric models such exponential, Weibull, log-normal, log-logistic and generalised gamma distribution are discussed in this section. These models are presented in the accelerated failure time metric (AFT). AFT model is an alternative to the Cox regression model, especially when the PH assumption is not tenable.

In the semi-parametric model, the effect of the covariates is proportional and act multiplicatively on the hazards and the covariates increase or decrease the hazards. In contrast, the effect of covariates in an AFT model is constant and act multiplicatively on the survival times, and the covariates accelerate or decelerate the occurrence of events of interest (Klein and Moeschberger, 2005). Suppose $X_1, X_2, ..., X_p$ denote the $p$ explanatory variables for each patient in the study, the AFT model assumes that

$$S(t, \boldsymbol{X}) = S_0 \left\{ t/\exp(\eta) \right\}, \tag{3.8}$$

where $S_0(t)$ represents the baseline survival function and $\eta$ is the linear component of the AFT model, which is given as $\eta = \alpha_1 X_1 + \alpha_2 X_2 + ... + \alpha_p X_p$. The factor $\exp(\eta)$ indicates the time scale can only change from the baseline time scale if there is change in the values of the explanatory variables. It is known as the measure of association, as it helps to evaluate the relationship between the explanatory variables and the survival times. In terms of the random variables associated with two individuals survival times, the AFT assumption can be written as $T_1 = \eta T_2$. The hazard function under this model is given by:

$$h(t, \boldsymbol{X}) = e^{-\eta} h_0(t/e^{\eta}). \tag{3.9}$$

The AFT model assumes the relationship between the explanatory variable and the log of survival time is linear. A plausible way to represent this relationship is through the equation

$$Y = \log T = \mu + \alpha_1 X_1 + \alpha_2 X_2 + ... + \alpha_p X_p + \sigma\epsilon = \mu + \boldsymbol{\alpha}^{'} \boldsymbol{X} + \sigma\epsilon, \tag{3.10}$$

where $\mu$ is the model intercept, $\boldsymbol{\alpha}$ is a vector of regression coefficients quantitatively expressing the impact of each explanatory variable on the survival time. A negative value of $\boldsymbol{\alpha}$ indicates that survival time increases with decreasing value of the explanatory variable, and vice versa. The $\exp\left(\boldsymbol{\alpha}^{'} \boldsymbol{X}\right)$ is usually referred to as the acceleration factor. $\sigma$ is the scale parameter and $\epsilon$ is the error term, which is assumed to have a specific distribution such as a logistics, extreme value or normal distribution. The deviation of $\log T$ from linearity is modelled by the error term. The distribution $T$ is based on probability distribution of $\epsilon$, and the survival function of $T$ can be obtained from the survival function of the distribution of $\epsilon$.

$$S(t) = P(T > t) = P(\log T > \log t),$$

from equation (3.10)

$$\begin{aligned} S(t) &= P(\mu + \boldsymbol{\alpha}^{'}\boldsymbol{X} + \sigma\epsilon > \log t), \\ &= P\left(\epsilon > \frac{\log t - \mu - \boldsymbol{\alpha}^{'}\boldsymbol{X}}{\sigma}\right), \\ &= S_{\epsilon}\left(\frac{\log t - \mu - \boldsymbol{\alpha}^{'}\boldsymbol{X}}{\sigma}\right). \end{aligned} \tag{3.11}$$

The cumulative hazard function of $T$ based on the distribution of $\epsilon$ is given by:

$$\begin{aligned} H(t) &= -\log S_{\epsilon}\left(\frac{\log t - \mu - \boldsymbol{\alpha}^{'}\boldsymbol{X}}{\sigma}\right), \\ &= H_{\epsilon}\left(\frac{\log t - \mu - \boldsymbol{\alpha}^{'}\boldsymbol{X}}{\sigma}\right), \end{aligned}$$

where $H_{\epsilon}(\epsilon) = -\log S_{\epsilon}(\epsilon)$ is the cumulative hazard function of $\epsilon$. The $p^{th}$ percentile and the hazard function of the distribution of $\epsilon$ can also be obtained. The estimation of AFT model parameters is discussed in Section 3.5. For easy interpretation of the estimated coefficient from the AFT model, the estimated coefficient is exponentiated ($\exp(\boldsymbol{\alpha})$), which is known as the time ratio (TR). This time ratio is the effect size under AFT model and it is reported in a similar manner as the estimated hazard ratio (HR) under the PH model. For example, $TR > 1$ indicates the the covariate prolongs or slows down the time to graft failure and $TR < 1$ for a covariate, shows that an earlier occurrence of graft failure is more likely.

### 3.4.1 The exponential distribution

The exponential distribution is a one-parameter distribution and assumes that the hazard is constant with respect to time. In the context of this study, a constant hazard means that the hazard of graft failure at any time post-kidney transplant remains the same. Under the AFT model, the probability distribution function is

$$f(t) = \lambda \exp(-\lambda t),$$

for $\lambda > 0$, $t > 0$. The survival function is given by

$$S(t) = \int_0^\infty f(u)du = \exp(-\lambda t), \quad t > 0,$$

and the hazard function is

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

where $\lambda$ is a positive constant, which is estimated when the exponential model is fitted to an observed data. A constant hazard function relative to increasing survival time indicates a model based on the exponential distribution (Figure 3.4). Although Gore and Gore (1983) has noted that a constant hazard is improbable in graft failure post-kidney transplant, the exponential distribution is considered in this study because it is frequently employed as a parametric alternative to the Cox PH model in analysing survival data. This model is the simplest amongst parametric survival models. If the random variable $T$ has an exponential distribution then the random variable $\epsilon$ has an extreme value distribution.

### 3.4.2 The Weibull distribution

The Weibull distribution is a widely used distribution in survival analysis because of its relative simplicity and flexibility (Klein and Moeschberger, 2005). Although the Weibull model is reported in studies done by Montaseri et al. (2016) and Nikpour et al. (2016) as the best model in survival analysis of hamodialysis and gastric cancer patients, we considered the Weibull model in this study because of its flexibility in summarising survival data. Suppose $T$ in this study has a Weibull distribution with scale and shape parameters $\lambda$ and $\gamma$, then the survival, hazard and the density functions of a $W(\lambda, \gamma)$ distribution is given by:

$$S(t) = \exp(-\lambda t^\gamma), \quad h(t) = \lambda\gamma t^{\gamma-1}, \quad f(t) = \lambda\gamma t^{\gamma-1}\exp(-\lambda t^\gamma),$$

for $\gamma$, $\lambda > 0$, $t > 0$. The Weibull model is suitable enough to accommodate constant hazard ($\gamma = 1$), increasing hazard ($\gamma > 1$) and decreasing hazard function ($\gamma < 1$) as shown in Figure 3.4. Thus, the shape and the flexibility of the distribution depends solely on the values

of the shape parameter. The exponential distribution assumes a constant hazard, which is rarely tenable in practice. The hazard function of the Weibull distribution (which depends on two parameters) is more general than that of the exponential distribution. The exponential distribution is a special case of the Weibull distribution with $\gamma = 1$. Therefore, when $\gamma = 1$, the hazard function and the survival times of Weibull distribution have a constant value and an exponential distribution, respectively. The effect of the explanatory variables can be modelled either on the survival times or the hazard with the Weibull distribution. Assume $X_1, X_2, ..., X_p$ are the recorded explanatory variables for each of the $n$ patients; under the Cox PH model, the hazard of graft failure at time $t$ for the patients is

$$h(t) = \exp(\beta_1 X_1 + \beta_2 X_2 + ... + \beta_p X_p) h_0(t). \tag{3.12}$$

If the values of the explanatory variable are equal to zero, then $h(t) = h_0(t)$, and the baseline hazard function for these patients is $h_0 = \lambda\gamma t^{\gamma-1}$. Substituting the baseline hazard in equation (3.12), the hazard function under the Weibull PH model is

$$h(t) = \exp(\boldsymbol{\beta}^{'}\boldsymbol{X})\lambda\gamma t^{\gamma-1}, \tag{3.13}$$

where $\boldsymbol{\beta}^{'}\boldsymbol{X}$ represents $\beta_1 X_1 + \beta_2 X_2 + ... + \beta_p X_p$. Equation (3.13) shows that the graft survival time of these patients has a Weibull distribution with scale and shape parameters $\lambda \exp(\boldsymbol{\beta}^{'}\boldsymbol{X})$ and $\gamma$, respectively. The covariate effects in the model only alter the scale parameter of the Weibull distribution rather than the shape parameter. This shows the proportional property of the Weibull distribution and the survival function under PH model is given by

$$S(t) = \exp\left\{-\exp(\boldsymbol{\beta}^{'}\boldsymbol{X})\lambda t^{\gamma}\right\}. \tag{3.14}$$

Comparing equations (3.7) and (3.13), $h_0(t)$ is unspecified in equation (3.7) and the regression coefficients are the only parameters to estimate. In equation (3.13), apart from the regression coefficients, the scale and the shape parameters are estimated in the model, which fully specify

the hazard parametrically. Statistical software such as R, SAS and Stata fit the Weibull AFT model. But this model can be reparametrised to a PH model as shown below. If the baseline hazard $h_0(t) = \lambda\gamma t^{\gamma-1}$, then the hazard function of the Weibull distribution under AFT model (equation 3.9) is

$$h(t) = e^{-\eta}\lambda\gamma(e^{-\eta}t)^{\gamma-1} = (e^{-\eta})^{\gamma}\lambda\gamma t^{\gamma-1}, \tag{3.15}$$

where $\eta = \alpha_1 X_1 + \alpha_2 X_2 + ... + \alpha_p X_p$. If $h_0 = h(t)$, Then it follows that the graft survival times has a $W(\lambda e^{-\gamma\eta}, \gamma)$ or $W(\lambda\exp(-\gamma\boldsymbol{\alpha}^{'}\boldsymbol{X}), \gamma)$ distribution. This shows the AFT property of this distribution. Recall the survival times under the Weibull PH model is specified to have $W(\lambda\exp(\boldsymbol{\beta}^{'}\boldsymbol{X}), \gamma)$ distribution (equation 3.13). This indicates that when the estimated coefficient for the Weibull AFT model is multiplied by $-\gamma$, the corresponding $\beta$-coefficients under the Weibull PH model is obtained. If the survival time of a random variable $T$ has a Weibull distribution, then the random variable $\epsilon$ has an extreme value distribution (also known as Gumbel distribution). The survival function of the extreme value distribution is given by

$$S_{\epsilon}(\epsilon) = \exp(-e^{\epsilon}), -\infty < \epsilon < \infty.$$

From equation (3.11), the survival function of the random variable $T$ under Weibull AFT model is given by

$$\begin{aligned} S(t) &= \exp\left\{-\exp\left(\frac{\log t - \mu - \boldsymbol{\alpha}^{'}\boldsymbol{X}}{\sigma}\right)\right\}, \\ &= \exp\left(-\lambda t^{1/\sigma}\right). \end{aligned} \tag{3.16}$$

where $\lambda = \exp\left\{-(\mu + \boldsymbol{\alpha}^{'}\boldsymbol{X})/\sigma\right\}$. Other functions such as the hazard function and the cumulative hazard function can be obtained from the survival function. Comparing the survival functions under the Weibull PH (equation 3.14) and AFT model (equation 3.16), it is shown that

$$\lambda = \exp(-\mu/\sigma), \gamma = \sigma^{-1}, \boldsymbol{\beta} = -\boldsymbol{\alpha}/\sigma.$$

### 3.4.3 The log-normal distribution

A random variable $T$ associated with graft survival time is said to be log-normally distributed if $log(T)$ is normally distributed. The Log-normal distribution is characterised by two parameters, the mean ($\mu$) and standard deviation ($\sigma$). The log-normal distribution is popular in the analysis of time-to-event data because of its connection to the normal distribution (Klein and Moeschberger, 2005). The log-normal distribution among other parametric models was shown to be more efficient in describing kidney transplant data (Hashemian et al., 2013). In the log-normal distribution, the random variable takes only positive values and the shape of the distribution is skewed. The probability density function is

$$f(t) = \frac{\exp\left\{-\frac{1}{2}\left(\frac{\log t-\mu}{\sigma}\right)^2\right\}}{t(2\pi)^{1/2}\sigma} = \phi\left(\frac{\log t-\mu}{\sigma}\right)/t,$$

for $\sigma > 0$, $t > 0$, $\phi(.)$ is the density function of a standard normal variable. The survival function is

$$S(t) = 1 - \Phi\left(\frac{\log t-\mu}{\sigma}\right), \tag{3.17}$$

where $\Phi(.)$ is the cumulative distribution function of a standard normal distribution. The hazard function is

$$h(t) = \frac{\phi\left(\frac{\log t}{\sigma}\right)}{\sigma t\left\{1-\Phi\left(\frac{\log t}{\sigma}\right)\right\}}.$$

In the log-normal model, hazard is 0 at $t = 0$. It increases to a peak and then decreases towards 0 as $t$ becomes large (Figure 3.4). Assuming $T$ has a log-normal distribution, the

baseline survival function is $S_0(t) = 1 - \Phi\left(\frac{\log t - \mu}{\sigma}\right)$. The survival function under AFT model is given by

$$\begin{aligned} S(t) &= S_0(e^{-\eta}t) \\ &= 1 - \Phi\left(\frac{\log t - \eta - \mu}{\sigma}\right). \end{aligned}$$

Therefore, the graft survival times of these patients have log-normal distribution with parameters $\mu + \eta$ and $\sigma$. This shows the AFT property of the log-normal distribution but without a PH property. If $T$ is log-normally distributed, $\epsilon$ in equation (3.10) has a standard normal distribution. Thus the survival function of $\epsilon$ is given by $S_\epsilon(\epsilon) = 1 - \Phi(\epsilon)$. The cumulative hazard and other functions can be obtain from the survival functions.

### 3.4.4 The log-logistic distribution

The log-logistic distribution is an alternative model when the Weibull distribution does not give a satisfactory model fit for survival times. The hazard function for the log-logistic model is hump-shaped (Figure 3.4), which (in context of this study) shows that the hazard of graft failure for the patients in this study increases immediately after transplant, up to certain time and then decreases with time as the their body get used to the new organ (uni-modal hazard). The distribution is similar to the log-normal distribution, but the hazard function and the survival function of the log-logistic distribution have a closed form. Adelian et al. (2015) noted (although not a kidney transplant study) that log-logistic is a better model in identifying risk factors associated with survival post-liver transplantation. When a the random variable $T$ has a log-logistic distribution with scale ($\theta$) and shape ($k$) parameters, the $f(t)$ is given by

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

for $0 \leq t < \infty, k > 0$. The survival function

$$S(t) = \left\{1 + e^{\theta} t^{k}\right\}^{-1}, \tag{3.18}$$

and the hazard function corresponding to the survival function is given by

$$h(t) = \frac{e^{\theta} k t^{k-1}}{1 + e^{\theta} t^{k}}.$$

If $k \leq 1$, the hazard function of a log-logistic model decreases monotonically. Conversely, if $k > 1$, the hazard function at 0 time is equal to 0, then increases to a peak and decrease as time approaches infinity. If the baseline hazard follow a log-logistic distribution, the hazard function in equation (3.9) is

$$\begin{aligned} h(t) &= e^{-\eta} h_0(e^{-\eta} t) \\ &= \frac{e^{-\eta} e^{\theta} k (e^{-\eta} t)^{k-1}}{1 + e^{\theta} (e^{-\eta} t)^{k}} \\ &= \frac{e^{\theta - k\eta} k t^{k-1}}{1 + e^{\theta - k\eta} t^{k}}, \end{aligned}$$

where the linear combination of the p explanatory variables is denoted by $\eta$. This shows that the survival times has a log-logistic distribution with $\theta - k\eta$ and $k$ parameters. If $\epsilon$ has a logistic distribution, the survival function of $\epsilon$ is $S_{\epsilon}(\epsilon) = \frac{1}{1+e^{\epsilon}}$. The survival function of $T$ can be written using equation (3.11)

$$S(t) = \left\{1 + \exp\left(\frac{\log t - \mu - \boldsymbol{\alpha}' \boldsymbol{X}}{\sigma}\right)\right\}^{-1}. \tag{3.19}$$

Using equation (3.18) when $T$ has a log-logistic distribution, its survival function with $\theta - k\eta$ and $k$ parameters is

$$S(t) = \frac{1}{1 + e^{\theta - k\eta} t^{k}}. \tag{3.20}$$

The parameters $\mu$ and $\sigma$ in equation (3.19) can be expressed in terms of the parameters $\theta$ and $k$ in equation (3.20). Specifically, $\theta = -\mu/\sigma$, $k = \sigma^{-1}$. $\mu$ and $\sigma$ are usually the estimates produced in most statistical software. Other functions such as the hazard function and the cumulative hazard function can be obtained if $T$ has a log-logistic distribution (Collett, 2003).

There are only three equivalent ways to model the effect of the explanatory variables on survival with the log-logistic distribution. The first model is the linear model specified in equation (3.10). The second representation of a log-logistic model is to assume the effect of the explanatory variables act to increase or decrease the odds of survival by a proportional amount Another way is to represent the regression model as an AFT model (equation 3.8) with a log-logistic baseline survival function. The three representations show that log-logistic model can only be represented either as an AFT model or proportional odds model.

### 3.4.5 The gamma distribution

The gamma distribution considered in this study is the generalised gamma distribution. The *pdf* of the generalised gamma distribution with three parameters is given by

$$f(t) = \frac{\alpha\lambda^{\alpha\gamma}t^{\alpha\gamma-1}\exp[-(\lambda t)^{\alpha}]}{\Gamma(\gamma)},$$

for $t > 0$,$\gamma > 0$,$\lambda > 0$ and $\alpha > 0$. The survival and the hazard functions of this distribution do not have a closed form. The generalised gamma distribution is not commonly used in modelling lifetime data because of its complexity. However, this distribution can be appropriate in modelling lifetime data such as kidney transplant data because the Weibull and the log-normal distribution are special cases of gamma distribution. The exponential distribution is also a special case of this distribution (when $\alpha = \gamma = 1$). The generalised gamma distribution reduces to a Weibull distribution when $\gamma = 1$ and log-normal when $\gamma \to \infty$. Generally, this model is rarely used as the final model. However, it is used to select an appropriate model for the data. Assuming generalised gamma distribution is an appropriate model in this study, it can be used to discriminate between the exponential, Weibull and log-normal models because they are nested in the generalised gamma model.

## 3.5 Fitting the semi-parametric and parametric survival models

### 3.5.1 Estimation for the Cox regression model

In order to fit the Cox PH model specified (equation 3.7), we need to estimate the baseline hazard function $h_0(t)$ and $\boldsymbol{\beta}$-coeffients. The $\boldsymbol{\beta}'s$ are estimated first and are used to derive the estimates of $h_0(t)$. Suppose that $t_1, t_2, ..., t_n$ is the observed graft survival times for $n$ patients. We assume no ties between the observed graft survival times. Let $t_{(1)} < t_{(2)} < ... < t_{(r)}$ be the ordered graft failure times and $\boldsymbol{X}_j$ denotes the $p^{th}$ covariate associated with a patient whose graft failure time is $t_j$. The risk set $R(t_j)$ at time $t_j$ is defined as the set of patients whose grafts are still functioning and are not censored at a time just prior to $t_j$. Cox presented a method known as partial likelihood in estimating the unknown parameters of the Cox PH models (David, 1972; Cox, 1975). This method is based on the conditional likelihood of time to event of interest, which is independent of parameters that are not of interest and also works efficiently when the covariates in the model are time-dependent. Details of the computation of the partial likelihood are discussed in details in Collett (2003).

The partial likelihood can be written as

$$L(\beta) = \prod_{j=1}^{r} \left\{ \frac{h_0(t_{(j)}) \exp(\boldsymbol{\beta}' \boldsymbol{X}_j)}{\sum_{l \in R(t_j)}^{n_j} h_0(t_{(j)}) \exp(\boldsymbol{\beta}' \boldsymbol{X}_j)} \right\} = \prod_{j=1}^{r} \left\{ \frac{\exp(\boldsymbol{\beta}' \boldsymbol{X}_j)}{\sum_{l \in R(t_j)}^{n_j} \exp(\boldsymbol{\beta}' \boldsymbol{X}_l)} \right\}. \tag{3.21}$$

In the context of this study, the numerator of the likelihood function depends on patient information whose graft fails at time $t_j$ and the denominator comprises of all patients with functioning grafts who are still at risk of graft failure at time $t_j$. The LL function for equation (3.21) is given by

$$\log L(\boldsymbol{\beta}) = \sum_{j=1}^{r} \boldsymbol{\beta} \boldsymbol{X}_j - \sum_{j=1}^{r} ln \left( \sum_{l \in R(t_j)}^{n_j} \exp(\boldsymbol{\beta} \boldsymbol{X}_l) \right).$$

Maximising equation (3.21) gives the maximum likelihood estimates in the Cox PH models.

Kalbfleisch and Prentice (2011) suggested a number of approaches for modifying the partial likelihood function method to take tied observations into account. The regression coefficient $\boldsymbol{\beta}$ in the extended Cox models are also obtained using the partial likelihood function. This is identical to the partial likelihood defined in equation (3.21) i.e. for the stratified model the partial likelihood $L = L_1 \times L_2 \times, ..., \times L_G$, the product of each stratum partial likelihood. That is $L(\beta) = \prod_{g=1}^{G} L_g(\beta)$.

### 3.5.2 Estimation for the parametric models

Under non-informative censoring, all parametric distribution models can be fitted using the appropriate maximum likelihood method of estimation (Klein and Moeschberger, 2005). For example, the contribution of patient $i$ with graft failure at time $t_j$ to the likelihood function is the product of hazard and survival function

$$L_j = f(t_j) = S(t_j)h(t_j),$$

where $f(t_j)$ is the density function from the start of the observation to the graft failure time. For a patient with a functioning graft up until the end of the study (censored patient), its contribution to the likelihood function is

$$L_j = S(t_j),$$

which is the probability of the event $P(T > t)$. The two expressions for both patients with graft failure and censored graft can be written in a single expression

$$L = \prod_{j=1}^{n} \{f(t_j)\}^{\delta_j} \{S(t_j)\}^{1-\delta_j} = \prod_{j=1}^{n} \{h(t_j)\}^{\delta_j} S(t_j), \tag{3.22}$$

where $\delta_j$ denotes an indicator variable, which takes the value zero if the graft survival is censored or unity if the graft survival time is not censored. The LL is given by

$$l = \sum_{j=1}^{n} \{\delta_j \log h(t_j) - H(t_j)\}, \tag{3.23}$$

where $H(t)$ is the cumulative hazard. The unknown parameters are estimated by maximising equation (3.23). The likelihood function in fitting the AFT model is best derived from the

log-linear AFT model. From equation (3.11), let $z_j = (\log t_j - \mu - \boldsymbol{\alpha}' \boldsymbol{X})$, then $S(t_j) = S_{\epsilon_j}(z_j)$. After differentiating with respect to $t$, the likelihood function in equation (3.22) can be written under the AFT model as

$$L(\boldsymbol{\alpha}, \mu, \sigma) = \prod_{j=1}^{n} (\sigma t_j)^{-\delta_j} \left\{ f_{\epsilon_j}(z_j) \right\}^{\delta_j} \left\{ S_{\epsilon_j}(z_j) \right\}^{1-\delta_j}.$$

The LL function is

$$l(\boldsymbol{\alpha}, \mu, \sigma) = \sum_{j=1}^{n} \left\{ -\delta_j \log(\sigma t_j) + \delta_j \log f_{\epsilon_j}(z_j) + (1 - \delta_j) \log S_{\epsilon_j}(z_j) \right\}.$$

Methods such as the Newton-Raphson procedure is used to maximise the LL function in order to obtain the maximum likelihood estimates of the unknown parameters $\mu, \sigma$ and $\boldsymbol{\alpha}$.

### 3.5.3 Hypothesis testing and confidence interval

Wald test, likelihood ratio test and score test are usually employed to test the hypothesis of no effect for any predictor variable in the model, holding other terms fixed. For example, the null and alternative hypotheses for the Cox PH model are

$$H_0 : \beta = 0, \quad H_1 : \beta \neq 0$$

A Wald test statistic is given as

$$z^2 = \left( \frac{\hat{\beta}}{se(\hat{\beta})} \right)^2, \tag{3.24}$$

where $z^2 \sim \chi^2_1$, if $H_0$ is true. The parameter of interest in the Cox PH model is the $HR = exp(\hat{\beta})$ and the standard error of the estimated parameter as specified in equation (3.24) is used to construct a 95% confidence interval (CI) for the true estimated $HR$.

$$[L, U] = \left( \exp\left\{ \hat{\beta} - 1.96 se(\hat{\beta}) \right\}, \exp\left\{ \hat{\beta} + 1.96 se(\hat{\beta}) \right\} \right).$$

Similar to the Cox PH model, the value of the Wald test statistic is also used to test the null hypothesis that $\alpha = 0$ in parametric models. The standard error of the estimated parameters

($\hat{\alpha}$) in parametric models is also used to obtain 95% CI for the unknown $\alpha$-parameters in parametric models.

## 3.6 Model development

A model building procedure reduces the number of covariates until the most parsimonious model is achieved. This procedure summarises the data and results, with respect to statistical significance, confounding factors and important factors (Bursac et al., 2008). Among the statistical procedures of model building, variable selection is a key procedure that serves to efficiently select the best subset of pre-specified covariates that describe the study data or graft survival in the simplest way. This procedure tends to identify covariates on which the hazard function depends, remove redundant covariates (which could add noise to the estimated quantities of interest), reduce cost of modelling unnecessary predictors and check for collinearity among the covariates.

Several approaches have been proposed to select predictors for inclusion in a model. Most of these procedures are mechanical (e.g. forward and stepwise method of variable selection) and have few limitations. Studies including Mundry and Nunn (2009) demonstrated the weakness of using a stepwise procedure in model building. From the result of a simple simulation study, the authors concluded that the null hypothesis testing method based on a stepwise procedure inflates the rate of Type I error (the probability of rejecting null hypothesis, when it is true). Mazerolle (2006) reported on the superiority of using Akaike's information criterion (AIC) in model selection (variable selection) over stepwise procedure. Collett (2003) described the use of automatic procedures, such as the stepwise procedure, is usually driven by large number of predictors.

Most modern penalisation procedures such as Lasso and ridge regression have been extended from linear regression to survival analysis (Tibshirani et al., 1997; Gui and Li, 2005). These procedures add a penalty term to the log-likelihood function to control for over-fitting. Hosmer Jr and Lemeshow (1999) considered the purposeful variable selection method (why studying survival data), within which the data analyst have complete control at each step of the model building. The purposeful method is comparable with the penalised procedures (such as Lasso) because they provide prediction accuracy and the most parsimonious model that describes the study data. However, the Lasso procedure automatically selects significant

covariates and shrinks the coefficients of non-significant covariates to exactly zero. Lasso method also performs better when covariates number $p$ is greater than the patient size $n$. Unlike the Lasso procedure, the purposeful method gives the analyst the opportunity to carefully scrutinise the resulting model (at each stage of model building procedure) prior to reporting the final best model. In addition, the purposeful method starts with univariable analysis and retains important confounding covariates in the final model. However, the model building procedure becomes more complex with the purposeful method when there are too many predictors. The purposeful method has been applied in several survival studies (Dicken et al., 2006; Thabut et al., 2008; Assassi et al., 2009), and Bursac et al. (2008) comparatively showed that this procedure leads to significant variables, confounding factors and a richer model.

Generally, several strategies for model building are reported in literature with the rationale being to select as less number of covariates as possible. However, studies have debated that model building procedure involves a combination of "science, statistical methods, experience and common sense". These studies also showed that no method of variable selection is better than any other; hence, their results are comparable. (Murtaugh, 2009; Hosmer Jr et al., 2013; Zhang, 2016)

## 3.7 Semi-parametric and parametric survival model adequacy assessments

To draw a valid inference from any fitted model, the adequacy of the model can be evaluated using both graphical and residual-based methods. These methods are used to identify possible problems with the model fit. A number of residual-based procedures for verifying model adequacy are discussed in Hosmer Jr and Lemeshow (1999) and Collett (2003).

### 3.7.1 The cumulative hazard plot

Checking the assumptions of PH is important prior to the use of a Cox PH model and its parameter interpretations. Once the PH assumptions are met, the statistical estimates are consistently comparable (Wilson, 2014). Studies describing the assessment of the PH assumptions have provided guidance on how to use methods such as the cumulative hazard plot also known as the $\log[-\log(survival)]$ or the log-log plot (Bradburn et al., 2003). The

$\log[-\log(survival)]$ plots is preferred to other hazard plots, because the plot gives a definitive pattern that enables a logical conclusion on the proportionality assumption (Bradburn et al., 2003). Recall the Cox PH model (equation 3.7), the assumption of proportionality under this model also implies that

$$H(t) = H_0(t)\exp(\boldsymbol{\beta}^{'}\boldsymbol{X}), \tag{3.25}$$

where the quantity $H(t)$ and $H_0(t)$ denote the cumulative hazard and the cumulative baseline hazard functions, respectively. The assumption also holds when the logarithm of equation (3.25) is taken.

$$\log H(t) = \log H_0(t) + \boldsymbol{\beta}^{'}\boldsymbol{X}. \tag{3.26}$$

Using equation (3.6), equation (3.26) can be expressed as $\log[-\log S(t)] = \log[-\log S_0(t)] + \boldsymbol{\beta}^{'}\boldsymbol{X}$. If the Cox PH model is the appropriate model, the plot of $\log \hat{H}(t)$ or equivalently $\log[-\log \hat{S}(t)]$ against $\log(t)$ should be roughly parallel. The proportionality confirmed with the cumulative hazard plot may not be valid when adjusting for other predictors because the cumulative hazard plot is a univariate method. Hence, other statistical methods could be used.

### 3.7.2 The scaled Schoenfeld residuals

Grambsch and Therneau (1994) proposed a scaled version of Schoenfeld residuals, which is symmetrical around zero, detects departure from the fitted model, is more effective and straight forward with respect to computation. For the $i^{th}$ patient, the vector of Schoenfeld residuals is $\boldsymbol{r}_{Pi} = (r_{P1i}, r_{P2i}, ..., r_{Ppi})'$ and the component of this vector is the scaled Schoenfeld residuals denoted by

$$r^*_{Pi} = r\text{var}(\hat{\boldsymbol{\beta}})\boldsymbol{r}_{Pi}$$

where (in context of this study) $r$ could be defined as the number of graft failures among the $n$ patients, the quantity $\text{var}(\hat{\boldsymbol{\beta}})$ is the estimated variance for the model parameter. The null hypothesis of this test is that the scaled Schoenfeld residuals are uncorrelated (independent of time) and the $p$-value is based on a chi-squared test. All covariates in the model are evaluated and the proportional assumption is rejected if, for any covariate, $p < 0.05$. A graph of the residuals for each covariate can be plotted for additional verification.

### 3.7.3 The Cox-Snell residuals

The Cox-Snell residual is widely used in survival data analysis to evaluate the overall fit of a model (Klein and Moeschberger, 2005). For the $i^{th}$ patient with observed survival time $t_i$, the Cox-Snell residual for the Cox regression model is defined by

$$r_{Ci} = \exp(\boldsymbol{\beta}^{'} \boldsymbol{X}_i)\hat{H}_0(t_i) = \hat{H}_i(t_i) = -\log \hat{S}_i(t_i), \tag{3.27}$$

where the quantity $\hat{H}_0$ denotes the estimated baseline cumulative hazard function for the fitted Cox PH model, $\hat{H}_i$ is the estimated cumulative hazard and $\hat{S}_i(t)$ is the estimated survival function for $i^{th}$ patient at time $t_i$.

The Cox-Snell residuals defined in equation 3.27 is virtually similar to the Cox-Snell residuals used in assessment of parametric model fit. The only difference is that the survival function and the hazard function depend on a particular parametric distribution. The Cox-Snell residuals can be used to check the overall fit of a parametric model, for a parametric model, the Cox-Snell residual for $i^{th}$ patient in the study is given by

$$r_{Ci} = \hat{H}_i(t) = -\log \hat{S}_i(t).$$

Where $\hat{H}_i(t)$ is the estimated cumulative hazard function, which is the Cox-Snell residuals. According to Klein and Moeschberger (2005), the Cox-Snell residuals for the four parametric models considered in this study are defined as

$$\begin{aligned}
\text{Exponential} \quad & r_{Ci} = \exp(\hat{\boldsymbol{\beta}}^{'} \boldsymbol{X}_i)\hat{\lambda}t, \\
\text{Weibull} \quad & r_{Ci} = \exp(\hat{\boldsymbol{\beta}}^{'} \boldsymbol{X}_i)\hat{\lambda}t^{\hat{\gamma}}, \\
\text{Log-normal} \quad & r_{Ci} = \log\left[1 - \Phi\left(\frac{\log T - \hat{\mu} - \hat{\boldsymbol{\alpha}}^{'} \boldsymbol{X}_i}{\hat{\sigma}}\right)\right], \\
\text{Log-logistic} \quad & r_{Ci} = \log\left[\frac{1}{1 + \exp(\hat{\boldsymbol{\beta}}^{'} \boldsymbol{X}_i)\hat{\lambda}t^{\hat{\gamma}}}\right].
\end{aligned}$$

The Cox-Snell residuals was used in this study to assess the overall fit of the parametric and the semi-parametric models. The Cox-Snells residuals correlate with survival time, are

asymmetrically distributed, have exponential distribution with the mean and the variance is equal to unity. The cumulative or the log cumulative hazard plot of Cox-Snell residuals should result in an approximately straight line through the origin with unit slope, if the model fit the data.

### 3.7.4 The martingale and deviance residuals

Under right censoring and time independent covariates, the martingale residual is given by

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

where $\delta_i$ is defined in equation (3.1) and $r_{Ci}$ is the Cox-Snell residual in equations (3.27). The residual compares the observed graft failure for patient $i$ between the time interval $(0, t_i)$ and the expected graft failure based on the model estimation. The residual values ranges from $-\infty$ to 1, they are approximately uncorrelated with one another in large samples and have a mean of zero (Therneau et al., 1990). The deviance residual is defined by

$$r_{Di} = \text{sign}(r_{Mi}) \left[-2 \left\{r_{Mi} + \delta_i \log(\delta_i - r_{Mi})\right\}\right]^{1/2},$$

where the quantity $r_{Mi}$ is the martingale residual, the sign function defined by sign(.) takes the value $-1$ or $+1$ if its argument is negative or positive, respectively. The deviance residuals are normalised transformations of the martingale residuals and have a mean of zero. If the model is valid, the $r_{Di}$ are more symmetrically distributed around zero compared to $r_{Mi}$. The martingale and the deviance residuals used to assess the fit of the Cox regression model can also be used to check the adequacy of the parametric models.

### 3.7.5 The delta-beta statistic

The delta-beta statistic denoted by $\Delta_i\hat{\beta}$ ($\Delta_i\hat{\beta} \approx \hat{\beta}_j - \hat{\beta}_{j(i)}$), is an approximation to the real change in the estimated parameter, when any influential observation is deleted from the fit. The value of this statistic is used to determine observations that strongly influence the parameter estimates. Any observation with a delta-beta statistic value greater than 1 (in absolute value) is seen as an overly influential observation (Cohen et al., 2003; Van der Meer et al., 2010; Sarkar et al., 2011).

## 3.8 Model comparison

The problems of selecting the best possible model from a group of competing models is a usual challenge faced in statistical modelling. Various procedures for choosing an appropriate model have been proposed, but the AIC is a popular model selection tool in statistical modelling. It is an extension of the principle of the conventional maximum likelihood. The AIC is defined by the expression.

$$AIC = -2l + 2k, \tag{3.28}$$

where $l$ is the LL of the model and $k$ is the total number of parameters in the model. The quantity $-2l$ is known as the goodness of fit and the quantity $2k$ is the bias correction, which is referred to as penalty term. Any model that conforms to the observe data should adequately lead to a smaller AIC. According to Shibata (1980), AIC is asymptotically efficient and yet inconsistent; in other words, high dimensional models are favoured during the model selection (this means that the true model is overestimated). The LR defined in Section 3.3 is used to compare nested models. The LR statistic follows $\chi^2$ distribution with degree of freedom equal to number of predictor variables excluded from the model. The null hypothesis is that the true model is the reduced model (model without the excluded predictor) while the alternative is that the full model is the true model. If the $p$-value of the test is significant ($p$ <0.05), the $H_0$ is rejected, otherwise we fail to reject the null hypothesis and conclude that the reduced model is more reasonable than the full model.

# Chapter 4

# Data and Methods

## 4.1 Introduction

In this chapter, the details of the retrospective study of adult kidney transplants in CMJAH and the application of the statistical methods reviewed in Chapter 3 are presented. This chapter begins with the dataset description and the exploratory data analysis techniques, model building based on Cox PH model, the extension of Cox PH model, parametric models and ends with simulation study. Figure 4.1 illustrates the overview of the study design.

## 4.2 Description of the dataset

The kidney transplant study for the Johannesburg region comprised of 2404 living and cadaveric donor kidney transplants carried out between 1966 and 2013. Within this period of time, there have been several innovations in medical practices, especially in the use of immunosuppressive drugs to prevent transplant rejection. Between 1966 and 1983, known as the pre-cyclosporine era (pre-CYA), patients received an immunosuppressive regimen that included mainly azathioprine and prednisone after kidney transplantation. Between 1984 and 2000, cyclosporine (CYA) became the major immunosuppressant used in combination with azathioprine and prednisone to prevent transplant rejection. Therefore, this period is known as the CYA era. From 2001 to 2014 (when the study ended), a new generation of immunosuppressive regimens was introduced to treat patients after kidney transplantation.

Some drugs in use in this era (new generation era) are sirolimus, mycophenolate and tacrolimus in combination with aforementioned drugs used in the previous two eras. Therefore, the study was subdivided into three different eras based on the immunosuppressive regimen used post-transplant, namely: Pre-CYA, CYA and New generation.[1]

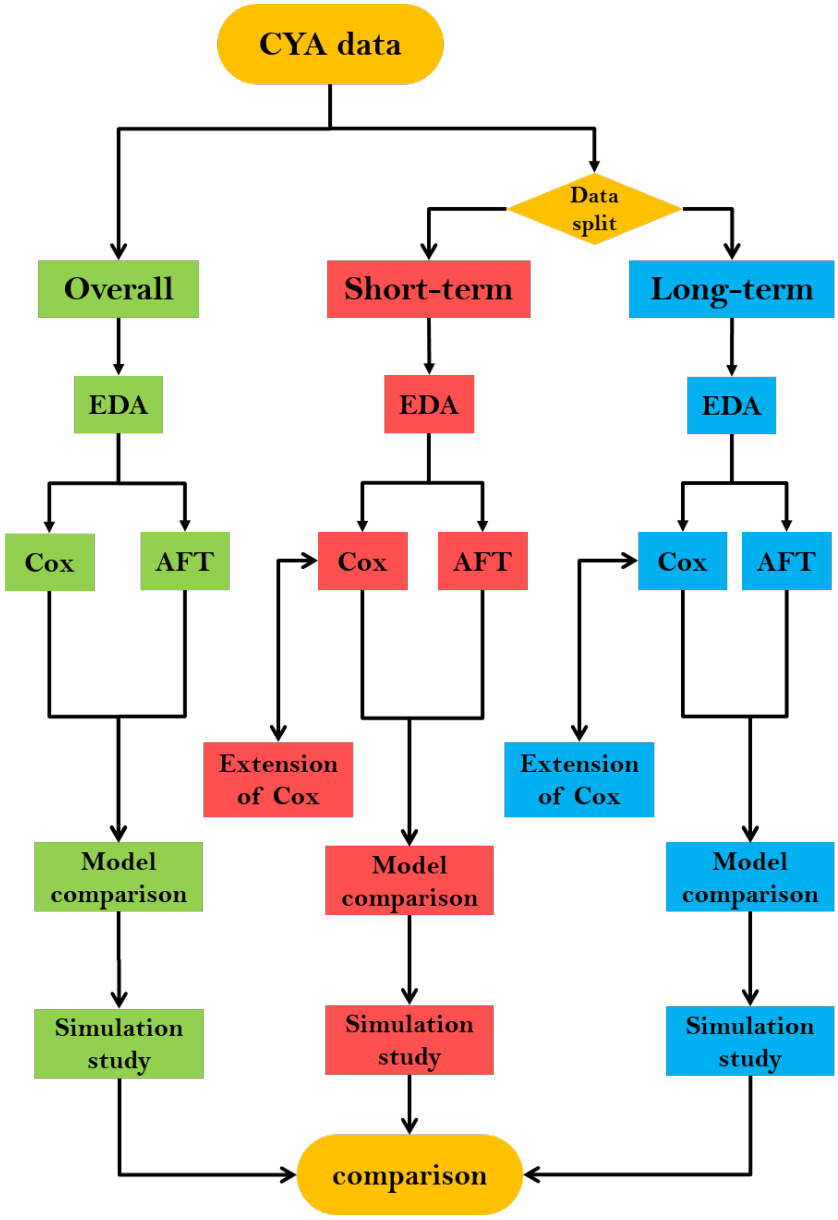


**Figure 4.1:** Graphical illustration of the study design approach.

[1]Ethical clearance required to carry out this study (under the title 'Kidney transplant outcomes study for the Johannesburg region') was approved for Dr June Fabian by the Wits Human Research Ethics Committee (medical clearance certificate number: M121186)

Most patients had only one kidney transplant, performed in Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). Each patient's file was archived after the transplant and a series of measurements detailing the patient characteristics, donor characteristics, transplant and post-transplant follow-up information were recorded. The observed information pertaining to a patient was continuously updated in the files until the patient's death or loss to follow-up. A database was created (Harris et al., 2009) for capturing the data. Other available sources containing data for the patients were retrieved and compared during data capturing. These included ward admission registers, transplant registers, patient records, work-up files and laboratory reports.

Simple descriptive statistics and graphical techniques were used to detect and correct inaccurate or problematic observations (illustrated in Figure 4.2), this was done with the knowledge of the study co-investigator. This retrospective study involves three eras. We analysed a subset of this study by restricting the study to include only adult kidney transplant in CMJAH during the CYA era (because the CYA era contains fewer missing cases compared to other eras). We further limited the study to focus on transplants done in CMJAH; hence, patients that did not receive kidney transplant in CMJAH were excluded. Patients below the age of 18 years and patients that had more than one transplant were also excluded from the data. Cases with missing date of transplant, which is the variable used for estimation of survival time were removed from the study. Patients with missing age at transplant were subsequently excluded, because these cases cannot be classified as adults or pediatric patients. Figure 4.2 describes how the study population was obtained, which includes the 751 patients used in the study .

The period between diagnosis of ESKD and date of transplant (waiting period) was not captured in this data. Graft failure time (graft survival time) is the outcome of interest in this study, which is defined as the period between a kidney transplant and a graft failure. Death with a functioning graft was not considered in this study. In other words, a patient who died with a functioning graft was not captured in the data. Figure 4.3 shows that none of the patients' deaths occurred before graft failures. 43% of the patients experienced graft failure, while 57% of the patients were censored either due to lost to follow up or graft failure not occurring by the end of the study. The censoring in this study is assumed to be non-informative because there is no information in the study data that indicates why patients were censored. Moreover, death with a functioning graft is not part of this study.

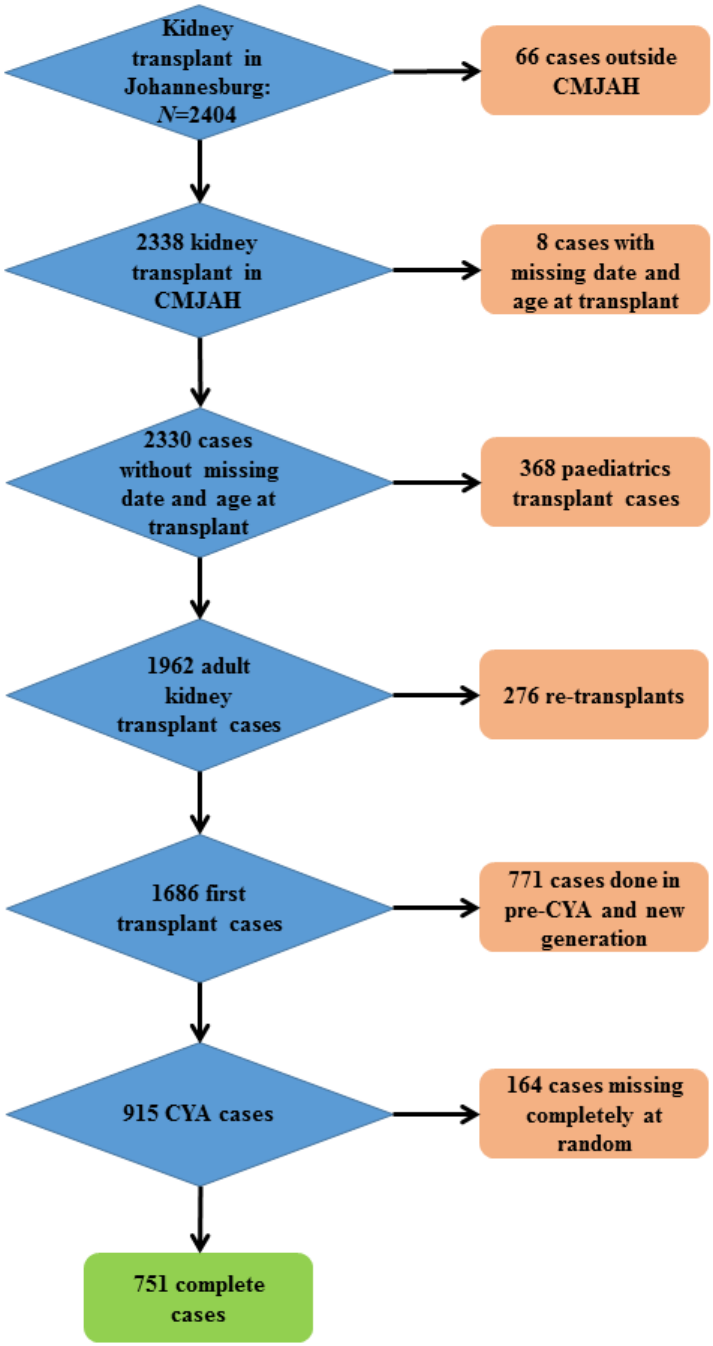


**Figure 4.2:** Flowchart of data extraction and cleaning steps for kidney transplant data used in this study. Panels on the right-hand side represent cases that were excluded from the study. Little's MCAR test was used to assess the mechanism of missingness in the 915 CYA cases (see Table C.3 on page 132).

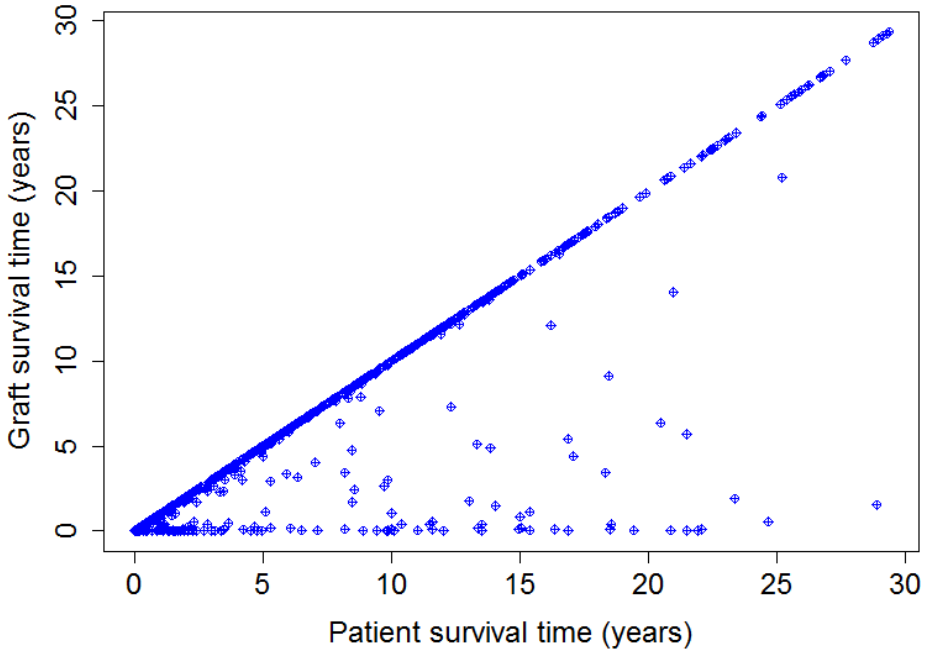


**Figure 4.3:** Scatter plot of graft survival time versus patient survival time for the 915 CYA era cases.

The choice of variables for this study is based on the known risk factors affecting graft survival after kidney transplant as discussed in Section 2.4. All variables were recoded and labelled to prepare the data for analysis and to have more descriptive variable names/values. Recipient and donor gender variables were combined into one variable (which describes donor-recipient gender match) with four categories named 'new_gender'. For instance, a case with a male donor and a female recipient was recoded to 'male-female'. Recipient and donor blood group variables were combined to one variable (called new_bloodgroup) with two categories. Also, recipient ethnicity variable was collapsed into two categories (white and non-white) due to reasons to be discussed. All the covariates included in this study are not time-dependent because they were only measured at the start of the study. The demographic and clinical information of the 751 patients included in this study is summarised in Table 4.1.

**Table 4.1:** Summary of the data and characteristics of the patients that received first kidney transplant in CMJAH between 1984 and 2000 ($N$=751). Variables with * are surgical complication variables

| **Variables** | **Description** | **Information** |
|---|---|---|
| recip_age | Recipient age | 18-68 yrs (mean=38.1 years, SD=10.9) |
| dnr_age | Donor age | 1-65 yrs (mean=28.4 years, SD=13.9) |
| new_gender | Donor-recipient gender | ff 87(11.6%), fm 198 (26.4%), mf 158 (21.0%) and mm 308 (41.0%) |
| new_bloodgroup | Donor-recipient blood group | matched 674 (89.7%), mismatched 77 (10.3%) |
| ethnicity | Recipient ethnicity | white 436 (58.1%) and non-white 315 (41.9%) |
| dnr_type | Donor type | cadaveric 643(85.6%) and living 105 (14.4%) |
| delayed_gf | Delayed graft function | no 474 (63.1%) and yes 277 (36.9%) |
| diabetes | Diabetes at transplant | no 703 (93.6%) and yes 48 (6.4%) |
| renal_disease | Renal disease ESKD | no 423 (56.3%) and yes 328 (43.7%) |
| hypertension | Hypertension ESKD | no 512 (68.2%) and yes 239 (31.8%) |
| urological | Urological ESKD | no 695 (92.5%) and yes 56 (7.5%) |
| inherited | Inherited ESKD | no 682 (90.8%) and yes 69 (90.2%) |
| nephrectomy | Nephrectomy* | no 699 (93.1%) and yes 52 (6.9%) |
| wound_sepsis | Wound sepsis* | no 664 (88.4%) and yes 87 (11.6%) |
| wound_haematoma | Wound haematoma* | no 699 (93.1%) and yes 52 (6.9%) |
| ureteric | Ureteric* | no 710 (94.5%) and yes 41 (5.5%) |
| no_complication | No complication* | no 260 (34.6%) and yes 491 (65.4%) |
| AR_clinical | Clinical acute rejection | no 283 (37.7%) and yes 468 (62.3%) |
| AR_histological | Histological acute rejection | no 626 (83.4%) and yes 125 (16.6%) |

The variable "nephrectomy" describes surgical complication as a result of removal of a native (failed) kidney (i.e. "surgical complication due to nephrectomy") before transplantation.

## 4.3 Exploratory data analysis

Graphical illustrations based on the histogram, survival function, hazard function and cumulative hazard function were used to gain insight into the survival and hazard function distributions. It is understood that the pattern of the estimated hazard function with the KM method may not be regular. The kernel smoothed estimate was used to smooth the estimated hazard function in order to have a clear pattern of its distribution. The shape of the hazard function plot will give an idea as to the suitability of the parametric assumptions prior to fitting the parametric models. For example, a constant hazard over time indicates that an exponential distribution model may provide a good fit, and a uni-modal hazard could suggest a model based on the log-logistic distribution.

## 4.4 Model building based on the Cox PH model

To assess the performance of the Cox PH and AFT models in modelling graft survival post-transplant, our first approach was to use the purposeful method of variable selection in the model building procedure to identify the covariates in which the hazard function depends on (Hosmer Jr and Lemeshow, 1999). The purposeful method proceeds as follow:

**Step 1**: Univariate association between each of the categorical variables and graft survival were evaluated using the KM estimator and survival differences were assessed with the log-rank test. Also, the univariate relationship between the continuous variables and graft survival were assessed using the Cox regression model or Cox PH model. All the variables significant at the 25% level at this stage of variable selection were selected as candidates to fit the initial multivariable Cox PH model.

**Step 2**: The multivariable Cox PH model was fitted. The possibility of multicollinearity among the variables were assessed using the variance inflation factor (VIF). According to Craney and Surles (2002), VIF $\geq$5 or $\geq$10 are usually used to indicate strong collinearity. At this stage, variables that are not significant at the 10% level or confounders were dropped from the model (one at a time). For example, the variable with the largest non-significant $p$-value was deleted from the model and the likelihood ratio test was conducted. The model without the omitted covariate is considered more appropriate if the $p$-value of this test is insignificant at the 5% level. Further, if omitting the variable results in a 15% change (or more) in the estimated

parameter of any of the remaining covariates in the reduced model as compared to the full model, the variable is considered as an important confounder. The interactive procedure of dropping, refitting and assessing significant and confounding factors continued up until the model contains only the important covariates.

**Step 3**: Some variables may not be significantly associated with graft survival individually, but may have influence on graft survival when adjusted for other covariates. Hence, variables that were not significant in the univariable analysis were added in the Cox PH multivariable analysis one at a time. Their significant impact on graft survival (at the 10% level of significance) and their impact on the estimated parameters of other variables in the model were assessed. If they are not significant based on these two criteria, these variables are deleted from further analysis. Finally, variables that are not significant at 5% level of significance were subsequently dropped from the model (one at a time). Their importance to the model were evaluated using the likelihood ratio test and percent change in the parameters of the remaining variables. If the test is insignificant and the change in the parameters (of the remaining variable) are not 15% or greater, these variables are excluded from the analysis. Multicollinearity was re-assessed for all the selected variables, to check whether any significant variable added at this stage could correlate with the variables in the model.

**Step 4**: Under the Cox PH model, a continuous covariate is assumed to have a log-linear relationship with the log-hazard. Sometimes the effect of a continuous covariate may not be linear in the log-hazard. Consequently, assuming a linear effect when the non-linear effect is applicable results in mis-specification. This could have an impact in the estimated parameter and standard error. The functional form of the continuous covariate was diagnosed using (i) martingale residuals plot from a null model, (ii) cumulative sums of martingale residuals plot and (iii) smoothing spline fit based on the Cox PH model. There is strong evidence to avoid fitting a linear term of any covariate in the Cox PH model if (i) the martingale residuals plot shows a non-linear trend, (ii) the observed process is not typical with simulated realisation in the cumulative martingale residuals plot or (iii) the non-linear term of the variable in the smoothing spline fit model is significant at the 5% level.

**Step 5**: If there is an interaction among the predictor variables (i.e. interaction between two covariates in equation 3.7), the expression of the hazard function will be $h(t, X) = h_0(t) \exp(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2)$. Inclusion of an interaction term in a regression model, especially based on clinical perspectives, can lead to better or conclusive inferences needed to develop public health policies and improve clinical practices. Two-way interaction between

the covariates were assessed and inclusion in the model was based on statistical and clinical significance. The significance of any interaction included in the model was confirmed with the $p$-value of the partial likelihood ratio test.

**Step 6**: The proportional hazard assumption was assessed at this stage of model building. $p$-values based on scaled Schoenfeld residuals, cumulative martingale residuals and inclusion of covariates by time interactions in the Cox PH model were used to verify the validity of the PH assumption. If the $p$-values of these tests are significant at the 5% level for any covariate, then the assumption of proportionality is violated for that covariate and such a covariate may affect the fit of the Cox PH model. At this stage we have obtained both the main and the interaction effects, which complete the main procedure of our model building based on the Cox PH model.

### 4.4.1 Extension of Cox proportional hazard model

It is well-understood that the estimated hazard and the effect of some covariates may not be constant over a long period of time. To address the issue of the non-proportional hazard of some covariates in this study, we divided the follow-up period into short-term (ST) and long-term (LT). Exploratory data analysis (EDA) and the procedure of model building described in Sections 4.3 and 4.4 were applied to the ST and LT analyses. Delayed graft function (DGF) and ethnicity variables violated the PH assumption in ST and LT analyses, respectively. The first option was to incorporate a stratified model in both analyses. It was assumed that there was no interaction between the stratified covariate and other covariates in the models. To verify this assumption, the interaction models were fitted in both analyses and the LR test was used to confirm the no-interaction assumption. The PH assumption was also tested for all the covariates in the model. The stratified models were used to plot the adjusted survival curves and the cumulative hazard function. Further, the Cox regression model was extended to include a product term of the non-proportional hazard covariate with time. The Heaviside (HV) function was introduced in the extended Cox regression model to identify where the effect of the covariate that violated the PH assumption is not proportional. Based on the adjusted survival curve and the cumulative hazard function plots from the stratified models, we let the function of time to take HV1 if survival time is less than 6.6 months (HV1<6.6 months), otherwise HV2 (if survival time is greater than 6.6 months) for ST analysis. The same condition was repeated in LT analysis where HV1<10 years survival time and HV2≥10 years. The fits of the extended Cox regression model were compared with the standard Cox PH model both in ST and LT analyses.

## 4.5 Parametric models

Variables fitted in the Cox PH model (for the ST, LT and overall data analyses) were used to fit parametric models. The shape of the baseline hazard function from the EDA helped to identify the suitable AFT models to use in this study. We let the baseline take a parametric AFT form such as log-normal, log-logistic or Weibull distribution. However, we included the exponential distribution because it is a special case of the Weibull distribution and a common distribution used in many studies. Also, the generalised gamma distribution was included because exponential, Weibull and log-normal distributions are its special cases. The Cox-Snell residuals and AIC were used to compare the fit of the AFT models to the Cox PH models. We further assessed outlying and influential observations using the deviance residuals and the delta-beta statistic in the best model.

## 4.6 Simulation of simple survival data

To evaluate the estimation of the appropriate models in the analyses, we mimicked a realistic population. This was done by designing a simulation study based on the distribution observed in the kidney transplant cohort, the covariate profiles and the effect of these covariates on graft survival. The event and the censoring time distributions were modelled in the analyses. The R-package 'survsim' (Moriña and Navarro, 2014) used for simulation of cohort survival data such as simple and complex survival analysis was used for the simulation study. The function 'simple.surv.sim' in this package is of interest to this study data. This function simulates survival cohort data for standard survival analysis. The details of the 'simple.surv.sim' function is found in the R-cran repository. The size of the cohort (depending on the number of observations in each analyses) to be simulated, the maximum follow-up period (depending on the analysis in question), the event and the censoring time distribution with their parameters, the relationship between each covariates and graft survival, and each covariate profile were all imputed in this function in order to simulate a survival cohort comparable to the kidney transplant study. The simulated survival data was used to re-estimate the parameter values based on the distribution the simulated data was built-on and the goodness-of-fit of the reasonable models in this study were assessed with the simulated data.

## 4.7 Software

Data cleaning was performed using SAS Version 9.4. All data analyses were done using statistical software R (version 3.2.3) and SAS (version 9.4). A significance level of $p<0.05$ was considered as significant level unless otherwise specified.

# Chapter 5

# Results

## 5.1 Introduction

This chapter presents the results of this study. The analysis is divided into three sections. The results from the overall graft survival analysis are presented in Section 5.2. The results of the ST graft survival analysis are presented in Section 5.3. The LT graft survival analysis results are reported in Section 5.4. Some of the results described in Sections 5.3 and 5.4 are in Appendixes A and B. The reference category used for each categorical predictor is the category with higher number of graft failures except, in the ST graft survival analysis where diabetic patients' category was used as the reference category.

## 5.2 Overall graft survival analysis

### 5.2.1 Exploratory data analysis for overall graft survival

The graphical illustration of graft survival experienced post-kidney transplant in the overall data analysis is presented in Figure 5.1 (page 54). This is used to understand some important features of the data or to gain insight into the underlying distribution of the graft survival time. As expected, the shape of the histogram (Figure 5.1A) is positively skewed, indicating that most of the graft survival times observed are clustered at the left-side of this plot.

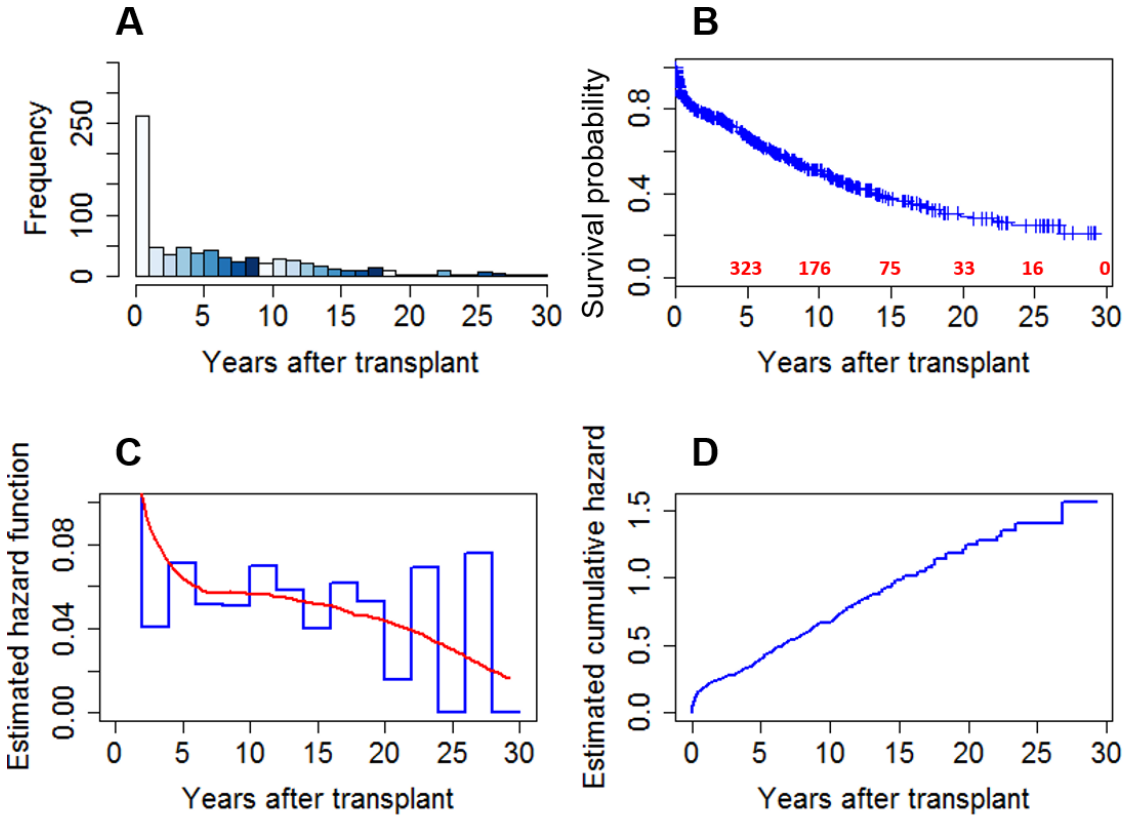


**Figure 5.1:** Exploratory data analysis of the overall transplant data showing (A) histogram of the underlying frequency distribution of the graft survival time variable, (B) KM estimate of the survival function, (+) indicates censoring and the numbers in red show grafts at risk at each 5 year interval. (C) KM estimate of a kernel-smoothed hazard function and (D) KM estimate of the cumulative hazard function for the overall data analysis ($N$=751).

The histogram shows that the graft survival times spread from about zero to about 29.25 years and the peak of graft failure occurred within the first year post-transplant. In other words, the risk of graft failure is high within the first year of kidney transplant. The histogram correlates with the profile of the survival function (Figure 5.1B). The graft survival curve shows a steep drop at the beginning of the study (highest hazard of graft failure is experienced within this period), gradually decreases as the follow-up time increases and flattens towards the end of the follow-up. This indicates that the longest observed survival time (29.25 years) is censored because the curve did not go down to zero. Figure 5.1B shows that as the follow up time increases, the number of grafts at risk decreases. The median graft survival time after kidney transplant is approximately 10 years. The estimated graft survival rate is 82%, 67%, 51%, 37%,

29% and 25% for 1, 5, 10, 15, 20 and 25 years, respectively. Figure 5.1B indicates that there are several censored observations. The estimated hazard of graft failure shows a solid step function (Figure 5.1C). It is clear that the true shape of the hazard experienced by the grafts is not visible. With the help of the kernel smoother, the hazard function plot also shows that the hazard of graft failure is high at the beginning of the study, which subsequently declines until it levels off at about 6 years and stays roughly constant to about 12 years then decreases gradually as the follow-up time increases. The accumulation of the hazard experienced by the patients' grafts is shown in Figure 5.1D. The cumulative plot shows a sharp rise at the beginning of the follow-up, indicating a high hazard of graft failure during that period. It is apparent that the hazard of graft failure experienced in this study is not constant because the gradient of the cumulative hazard ($\hat{H}(t)$) plot is not equal. The curvature seen in the $\hat{H}(t)$ plot is in the reverse direction to that shown in the survival function estimates (Figure 5.1B). Thus, a sharp rise in $\hat{H}(t)$ is associated with a sharp fall in $\hat{S}(t)$.

### 5.2.2 Model development for overall graft survival

All explanatory variables significant in the univariable analyses (Table 5.1, page 56) at the 25% level of significance were incorporated in the multivariable Cox proportional hazard model. The result of the analysis is shown in Table 5.2 (page 57). The maximum $p$-value is observed for 'wound sepsis' ($p$=0.864), therefore this predictor was deleted from Model 1. Omitting 'wound sepsis' and refitting the multivariable model (Model 2) resulted in a LR of 0.029, which is not statistically significant ($p$=0.864). This indicates no improvement over the full model by excluding this variable. Furthermore, the change in coefficients ($\Delta\hat{\beta}$) for each covariate remaining in Model 2 was compared with Model 1. The result shows that 'wound sepsis' is neither a significant predictor of graft survival nor a confounder. Omitting 'hypertension' (which has the highest $p$-value in Model 2) in Model 3, made no difference in the model ($p$=0.469), rather it changed the parameter estimates for 'renal disease' by more than 15%. However, 'renal disease' is also not a significant predictor of graft failure at the 10% level of significance as shown in Model 3. Therefore, it is reasonable not to retain the two variables (hypertension and renal disease) in the model as 'hypertension' is not an important confounder. The change in $-2LL(\hat{\beta})$ on deleting 'urological' and 'no_complication' from Models 4 and 5 are 0.329 and 0.189, respectively. The deletion of these variables did not confound the relationship of any of the remaining predictor variables and graft survival. Hence, these variables were excluded from Model 6 (which contains variables associated with graft survival at the 10% level of significance).

**Table 5.1:** Univariable analysis of the relationship between the study variables and overall graft survival. $p$-values for the categorical variables and the continuous variables* were estimated based on log-rank test and the Cox PH model results, respectively.

| Variable | $p$-value |
|---|---|
| dnr_type | <0.001 |
| renal_disease | 0.063 |
| hypertension | <0.001 |
| urological | 0.095 |
| inherited | 0.069 |
| nephrectomy | 0.290 |
| wound_sepsis | 0.131 |
| wound_haematoma | 0.621 |
| ureteric | 0.356 |
| no_complication | 0.059 |
| delayed_gf | 0.003 |
| diabetes | 0.371 |
| AR_clinical | 0.809 |
| AR_histological | 0.323 |
| new_gender | 0.990 |
| new_bloodgroup | 0.304 |
| ethnicity | <0.001 |
| dnr_age* | 0.260 |
| recip_age* | <0.001 |

At this stage, variables that were initially set aside because they were insignificant at the 25% level in the univariable analyses were reconsidered one at a time in the multivariable model (Table 5.3, page 58). None of these variables caused a significant change in the value of $-2LL(\hat{\beta})$ of Model 6 (except 'diabetes') when added and none confounded the relationship of any of the predictors with graft survival when deleted. Therefore, these variables (except 'diabetes') did not make it back in the multivariable model and were excluded from the study. The inclusion of 'diabetes' in Model 6 changed the $p$-value of 'inherited' to more than the 10% level of significance ($p$=0.108); hence, 'inherited' was removed and its exclusion from Model 6 (model with 'diabetes') did not cause a significant change in the value of $-2LL(\hat{\beta})$. Also the deletion of 'inherited' only caused an 8.2% change in the estimated coefficients of the remaining variables in the model. 'Recipient age', 'donor type', 'recipient ethnicity', DGF and 'diabetes' are the only selected variables at this stage of model building and there is no multi-collinearity among these variables (Table C.4, page 132).

The functional form of 'recipient age' using martingale residuals, cumulative martingale residuals and smoothing spline fit was assessed. Figure 5.2 (page 59) shows a plot of the martingale residuals from a null model and the cumulative martingale residuals. The plot of

**Table 5.2:** Multivariable Cox regression model of the overall transplant data containing significant covariates at the 25% level in the univariable analysis (Model 1). Partial likelihood ratio test (with $p$-value*) indicating the effect of deleting non-significant covariates from the multivariable analyses (Models 2-6) and their impact in the coefficient change for the covariates in the resulting (reduced) model. The variable in bold font was deleted in the succeeding model.

| Model | Variable | $p$-value | %Δ | -2LL | -2LLΔ | $p$-value* |
|---|---|---|---|---|---|---|
| 1 | recip_age | <0.001 | | 3648.825 | | |
| | dnr_type | 0.027 | | | | |
| | ethnicity | 0.010 | | | | |
| | hypertension | 0.469 | | | | |
| | delayed_gf | 0.028 | | | | |
| | no_complication | 0.288 | | | | |
| | renal_disease | 0.287 | | | | |
| | inherited | 0.044 | | | | |
| | urological | 0.198 | | | | |
| | **wound_sepsis** | 0.864 | | | | |
| 2 | recip_age | <0.001 | 0.3 | 3648.796 | 0.029 | 0.864 |
| | dnr_type | 0.027 | 0.5 | | | |
| | ethnicity | 0.009 | 0.7 | | | |
| | **hypertension** | 0.468 | 0.3 | | | |
| | delayed_gf | 0.029 | 0.4 | | | |
| | no_complication | 0.175 | 8.4 | | | |
| | renal_disease | 0.289 | 0.3 | | | |
| | inherited | 0.044 | 0.1 | | | |
| | urological | 0.199 | 0.2 | | | |
| 3 | recip_age | <0.001 | 0.8 | 3649.349 | 0.524 | 0.469 |
| | dnr_type | 0.028 | 0.3 | | | |
| | ethnicity | 0.012 | 9.5 | | | |
| | delayed_gf | 0.026 | 1.7 | | | |
| | no_complication | 0.198 | 5.7 | | | |
| | **renal_disease** | 0.430 | 36.4 | | | |
| | inherited | 0.061 | 13.8 | | | |
| | urological | 0.251 | 12.7 | | | |
| 4 | recip_age | <0.001 | | 3649.972 | | |
| | dnr_type | 0.025 | | | | |
| | ethnicity | 0.001 | | | | |
| | delayed_gf | 0.028 | | | | |
| | no_complication | 0.200 | | | | |
| | inherited | 0.089 | | | | |
| | **urological** | 0.345 | | | | |
| 5 | recip_age | <0.001 | 0.6 | 3650.926 | 0.953 | 0.329 |
| | dnr_type | 0.025 | 0.4 | | | |
| | ethnicity | <0.001 | 4.7 | | | |
| | delayed_gf | 0.028 | 0.2 | | | |
| | **no_complication** | 0.186 | 3.3 | | | |
| | inherited | 0.108 | 6.0 | | | |
| 6 | recip_age | <0.001 | 0.5 | 3652.648 | 1.722 | 0.189 |
| | dnr_type | 0.024 | 0.7 | | | |
| | ethnicity | <0.001 | 0.4 | | | |
| | delayed_gf | 0.024 | 2.8 | | | |
| | inherited | 0.090 | 5.3 | | | |

**Table 5.3:** Results of adding covariates that were not significant in the univariable analysis of overall graft survival (Table 5.1) to the multivariable Model 6. The $p$-value with * is for the partial likelihood ratio test, %Δ is the highest change in the estimated coefficients of other variables in the model.

| Model | $p$-value | -2LL | -2LLΔ | $p$-value* | %Δ |
|---|---|---|---|---|---|
| Model 6 | 0.189 | 3652.648 | 0.000 | | |
| Model 6 + dnr_age | 0.919 | 3652.638 | 0.010 | 0.919 | 1.0 |
| Model 6 + nephrectomy | 0.489 | 3652.141 | 0.507 | 0.477 | 0.5 |
| Model 6 + wound_haematoma | 0.866 | 3652.620 | 0.028 | 0.866 | 0.2 |
| Model 6 + ureteric | 0.411 | 3651.928 | 0.720 | 0.396 | 4.5 |
| Model 6 + diabetes | 0.044 | 3648.980 | 3.668 | 0.055 | 6.2 |
| Model 6 + diabetes + AR_clinical | 0.795 | 3648.912 | 0.068 | 0.794 | 0.6 |
| Model 6 + diabetes + AR_histological | 0.370 | 3648.203 | 0.777 | 0.378 | 7.1 |
| Model 6 + diabetes + new_bloodgroup | 0.970 | 3648.979 | 0.001 | 0.970 | 0.2 |
| Model 6 + diabetes + new_gender | | 3645.845 | 3.135 | 0.077 | 12.9 |
| ff | 0.875 | | | | |
| mf | 0.827 | | | | |
| mm | 0.205 | | | | |
| (Model 6 + diabetes) - inherited | 0.108 | 3651.776 | 2.796 | 0.095 | 8.2 |

*ff* (female to female), *mf* (male to female) and *mm* (male to male).

the martingale residuals from a null model is expected to be a straight line, if a linear term is needed for this variable. The Lowess smoothed line in Figure 5.2A is approximately straight, suggesting a linear term of 'recipient age' is appropriate in the model. Also the observed process for 'recipient age' is expected to be within the simulated realisation in the cumulative martingale residuals plot if a linear term is needed for 'recipient age'. It is obvious that the observed process for 'recipient age' is more typical with the simulated realisations from the null distribution (Figure 5.2B); except for slight departures from the linear fit at both the right- and left-hand tail of the cumulative martingale residuals plot, which is not a significant departure ($p$=0.097). To objectively conclude on the functional form of 'recipient age', the smoothing spline fit based on the Cox regression model was fitted (Table 5.4, page 59). The non-linear term of this variable is expected to be significant at the 5% level if a non-linear term is appropriate in the model. The non-linear term of 'recipient age' in the spline fit is not significant ($p$=0.167), as shown in Table 5.4. Hence, the linear term of 'recipient age' is reasonable in the model. Possible interaction terms were assessed in the Cox regression model. The Wald test $p$-value shows no significant interaction between the predictors at the 5% level.

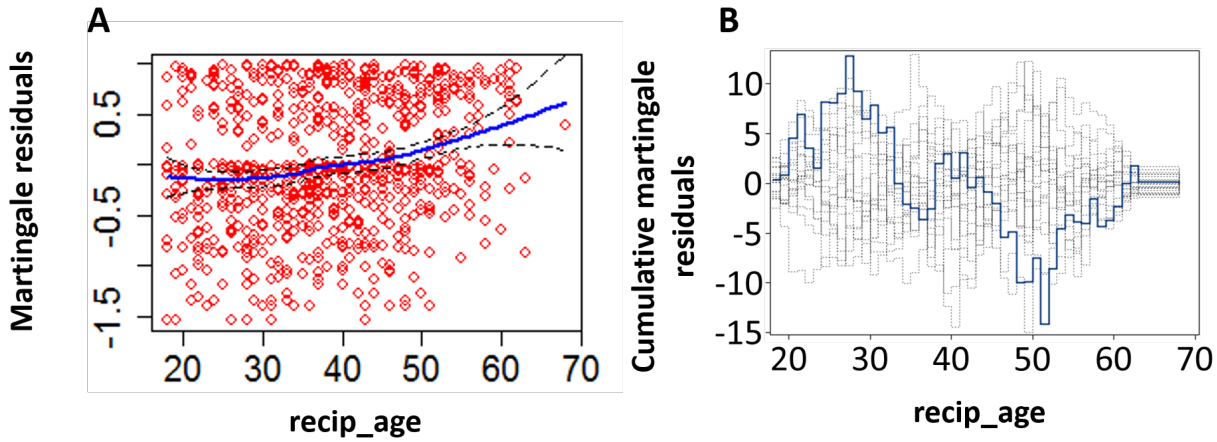


**Figure 5.2:** Linearity assumption assessment for overall graft survival analysis. Plot of (A) smoothed martingale residuals from a null Cox regression model versus 'recipient age' and (B) cumulative martingale residual versus 'recipient age' ($p$=0.097), the bold line represents the observed process and the dotted lines represent the simulated processes.

**Table 5.4:** Smoothing spline fit result (based on the Cox regression model) for assessing the linearity assumption of the continuous variable (recipient age) in overall graft survival analysis.

| Variable | Coefficient | SE | $p$-value |
|---|---|---|---|
| recip_age-linear | 0.032 | 0.0 | <0.001 |
| recip_age-nonlinear | | | 0.167 |
| dnr_type | -0.445 | 0.2 | 0.032 |
| ethnicity | 0.515 | 0.1 | <0.001 |
| delayed_gf | 0.313 | 0.1 | 0.010 |
| diabetes | 0.475 | 0.2 | 0.019 |

The KM and log cumulative hazard plots were used to assess the PH assumption for the categorical variables (Figure 5.3 and Figure 5.4, page 60 and 61). The rule is that the KM plot should drift apart steadily and the log cumulative hazard plot should not exhibit a non-constant group difference. The survival curves for 'donor type' show no crossing lines and these curves drifted apart steadily, which is an indication of proportionality. However, there is a large separation between the categories, which could be as a result of few number of recipients of live donor kidney (with graft failure) surviving more than ten years. KM survival curves for 'recipient ethnicity', DGF and 'diabetes' indicate violation of the PH assumption, more especially the obvious crossing-lines seen in the survival curve for 'diabetes'. Looking at the log-log plots of all the variables, the PH assumption seems to be violated for all the variables because of non-constant group differences.

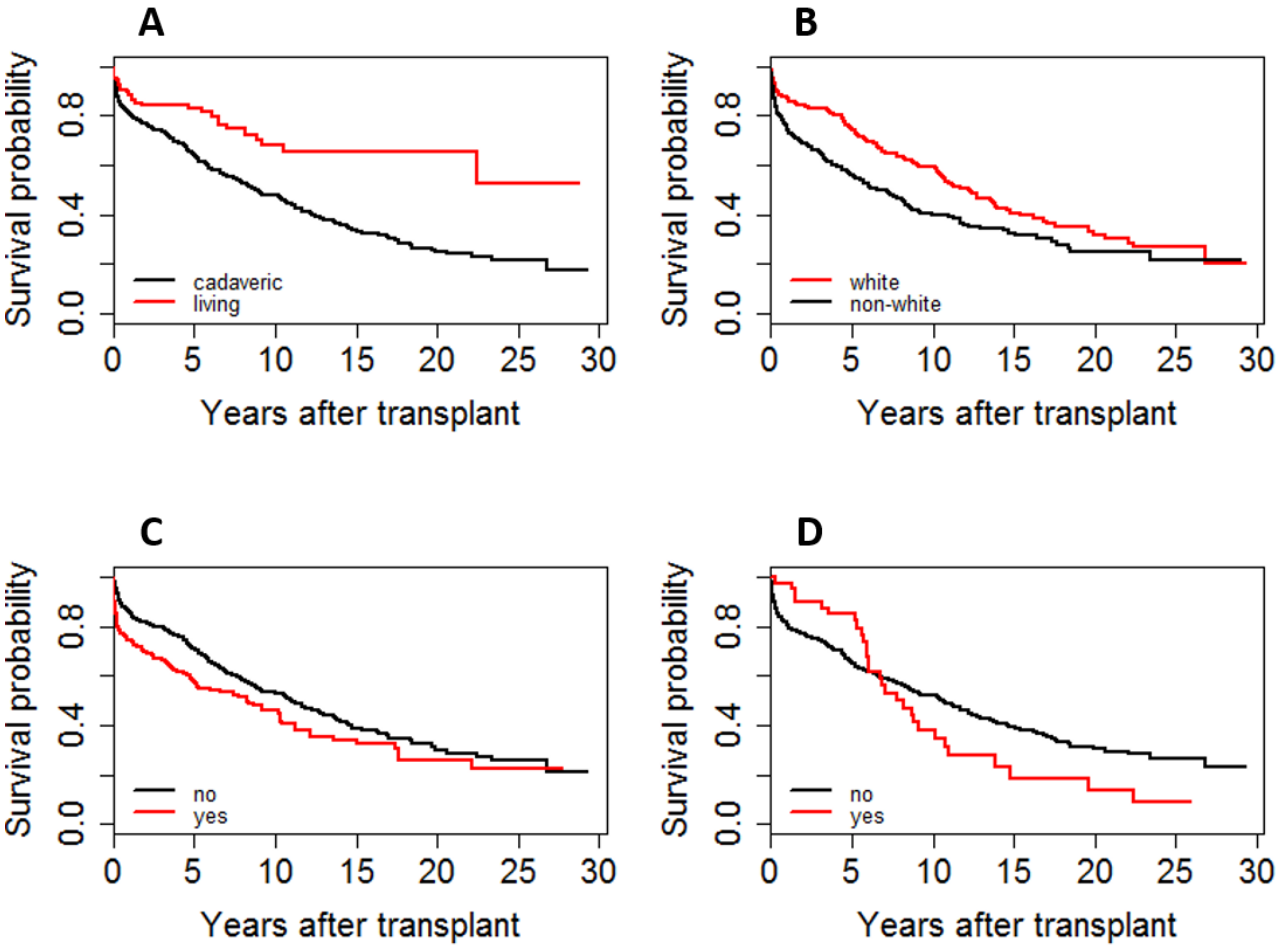


**Figure 5.3:** Graphs of KM estimates of survival function for the selected predictors (A) donor type, (B) ethnicity, (C) delayed graft function and (D) diabetes.

However, for 'donor type', the non-parallel lines could also be a result of small sample size of graft failures observed in recipients of live donor kidney compared to recipients of cadaveric donor. In practice, the log-log plot may not be perfectly parallel and there is no statistical test to assess the significance of log-log plot lines. Hence, a formal test based on the scaled Schoenfeld and the cumulative martingale residuals with statistical significance was employed to assess departure from proportionality.

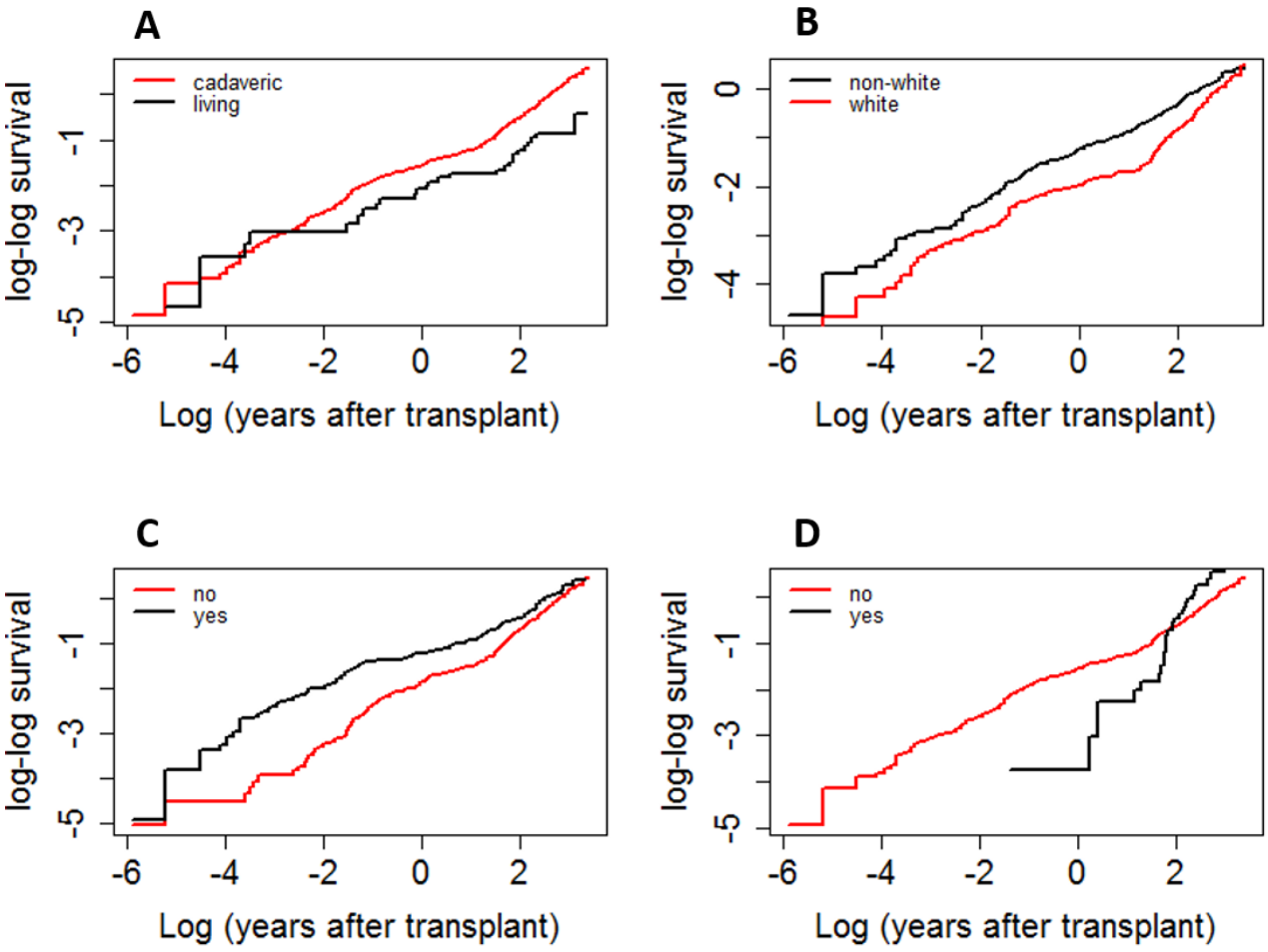


**Figure 5.4:** Plots of log cumulative hazards for the selected predictors (A) donor type, (B) ethnicity, (C) delayed graft function and (D) diabetes.

Table 5.5 (page 62) shows the $p$-values of tests based on the scaled Schoenfeld and cumulative residuals for non-proportional hazard assessment. The results of the two tests suggest evidence of deviation from the proportionality assumption for all the variables except 'donor type'. The results of the two tests are graphically illustrated for each of the predictors in the Cox regression model (Figure 5.5, page 63). Under common definition, the Lowess line in the scaled Schoenfeld residual plot is expected to have a zero slope, otherwise the PH assumption is not valid for that predictor. Also, the observed test processes is expected to be within the simulated processes, if PH assumption is valid. This figure also suggest a non-constant effect over time for 'donor type' alone.

The final Cox regression model (Table 5.6, page 62) concluded that all these predictors are significantly associated with graft survival at the 5% level of significance but only 'donor type' satisfied the PH assumption in this model. Thus, there is evidence of lack of model-fit for the Cox PH model.

**Table 5.5:** Non-proportionality test in the Cox regression model, $p$-values for scaled Schoenfeld residuals and cumulative residuals (*) tests.

| **Variable** | **rho** | **chisq** | ***p*-value** | ***p*-value*** |
|---|---|---|---|---|
| recip_age | 0.113 | 4.630 | 0.032 | 0.035 |
| dnr_type | -0.074 | 1.750 | 0.186 | 0.168 |
| ethnicity | -0.104 | 3.410 | 0.050 | 0.003 |
| delayed_gf | -0.143 | 6.470 | 0.011 | 0.001 |
| diabetes | 0.180 | 10.000 | 0.002 | <0.001 |
| GLOBAL | | 32.670 | <0.001 | |

**Table 5.6:** Analysis of risk factors associated with overall graft survival on fitting the multivariable Cox regression model ($N$=751).

| **Variable** | **Coefficient** | **HR** | **(95% CI)** | **SE** | ***p*-value** |
|---|---|---|---|---|---|
| recip_age | 0.032 | 1.03 | (1.02-1.04) | 0.006 | <0.001 |
| dnr_type | -0.459 | 0.63 | (0.42-0.95) | 0.207 | 0.027 |
| ethnicity | 0.478 | 1.61 | (1.29-2.02) | 0.115 | <0.001 |
| delayed_gf | 0.315 | 1.37 | (1.08-1.74) | 0.120 | 0.009 |
| diabetes | 0.421 | 1.52 | (1.03-2.25) | 0.200 | 0.035 |

Reference category: dnr_type (cadaveric), ethnicity (white), delayed_gf (no) and diabetes (no).

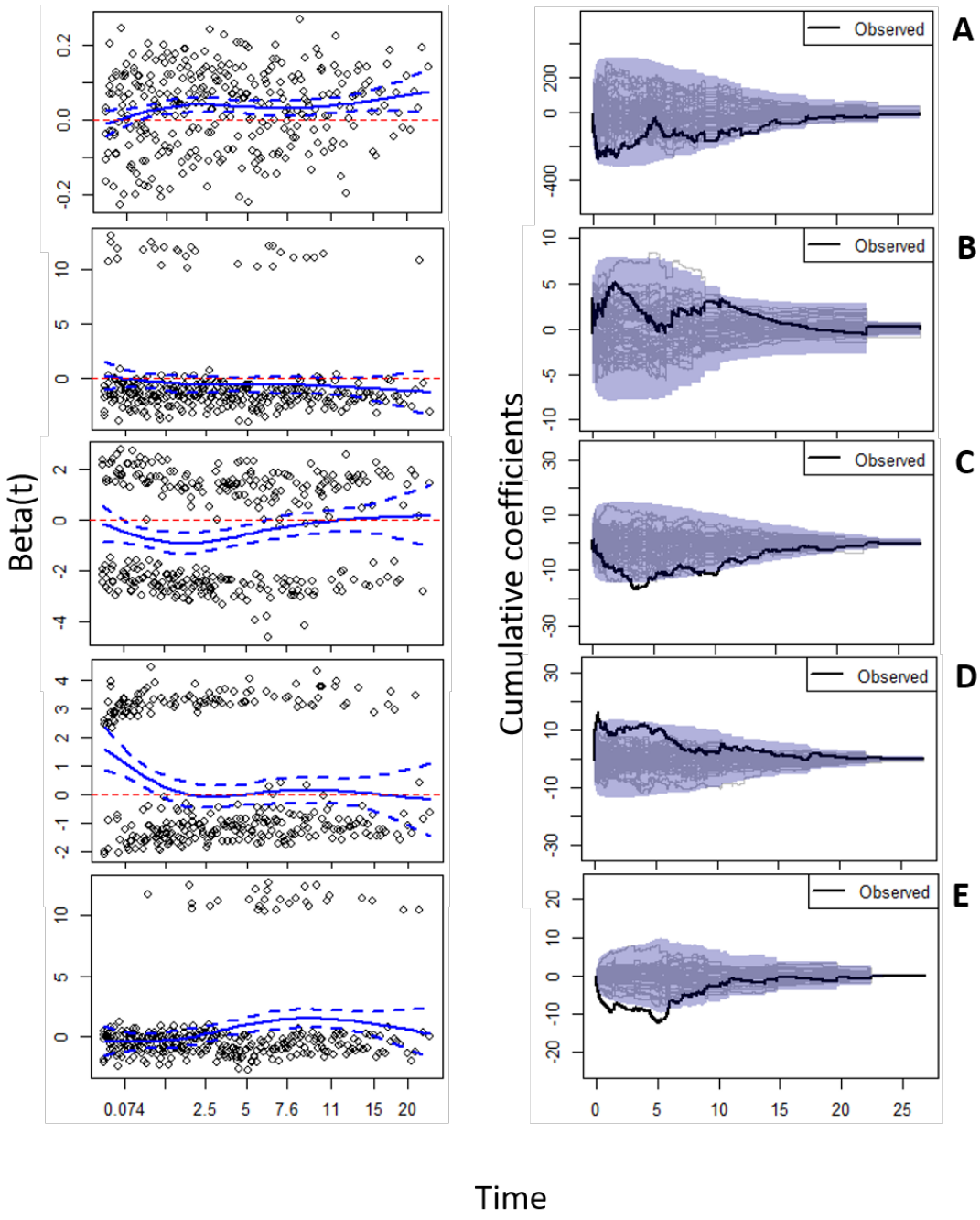


**Figure 5.5:** Assessing the PH assumption. Left-panel: graphs of the scaled Schoenfeld residuals versus transformed time for each predictor in the Cox regression model. The solid and the broken lines represent the smoothing spline fit and the ±2 standard error for the fit. Right-panel: graphs of observed test processes with 50 simulated processes for each predictor in the Cox regression model. The solid black profile signifies the observed pattern. (A) recipient age, (B) donor type, (C) ethnicity (D) delayed graft function and (E) diabetes.

### 5.2.3 Accelerated failure time models for overall data graft survival

Variables in Table 5.6 (page 62) were used to fit parametric AFT models. These models (with the exception of log-normal and log-logistic) suggest that all the predictors are significantly associated with overall graft survival at the 5% level (Table 5.7, page 65). Nonetheless, the $p$-values for 'diabetes' in the exponential and Weibull models are marginally significant based on the 5% level of significance. The lowest AIC is observed for the gamma model followed by the Weibull model, and the criterion indicates that parametric models out-performed the Cox PH model in modelling the overall kidney transplant data (Table 5.8, page 66).

The Cox-Snell residuals plot was used as a diagnostic tool to graphically assess the goodness-of-fit for these models. The closer the plotted points are to the 45° line (referent line), the better the fit of the model to the observed data. Figure 5.6 (page 67) represents the plot of the estimated cumulative hazard function against the Cox-Snell residuals for the five models. This figure indicates that the estimated cumulative hazards approximately follow the referent line for the Cox PH and gamma models (excluding few deviations observed at large values of the models' cumulative hazard). Most of the plotted points in the log-normal and log-logistics fits are not close to the referent line, indicating a bad fit. Based on the rule of the Cox-Snell residuals plot, it would appear that the Cox regression model fit is more reasonable compared to the other models. This is not a reflection of the information criterion assessment (Table 5.8, page 66). Therefore, we based our conclusion on the AIC values because the Cox-Snell residuals could result in a straight line even when the model is not appropriate.

Since the gamma model provides a reasonable fit according to AIC and exponential, Weibull and log-normal models are nested within the gamma model, the LR test was conducted to test against the gamma distribution. The LR test indicates that the Weibull model is equally appropriate (Table 5.9, page 67). We conclude that the Weibull fit is also reasonable because it is a special case of the generalised gamma. The Weibull model (with the significant predictors) is given by

$$\begin{aligned} LogT = 5.317 - 0.051 recip\_age + 0.789 dnr\_type - 0.797 ethnicity - 0.526 delayed\_gf \\ - 0.662 diabetes + 1.662. \end{aligned}$$

**Table 5.7:** Analysis of risk factors associated with the overall graft survival on fitting multivariable parametric accelerated failure time models ($N$=751).

| Model | Factor | Coeffient | TR | (95%CI) | SE | $p$-value |
|---|---|---|---|---|---|---|
| **Exponential** | Intercept | 4.307 | | | | |
| | recip_age | -0.035 | 0.97 | (0.95-0.98) | 0.006 | <0.001 |
| | dnr_type | 0.460 | 1.58 | (1.06-2.37) | 0.207 | 0.026 |
| | ethnicity | -0.523 | 0.59 | (0.47-0.74) | 0.115 | <0.001 |
| | delayed_gf | -0.379 | 0.68 | (0.54-0.87) | 0.120 | 0.002 |
| | diabetes | -0.409 | 0.66 | (0.45-0.98) | 0.200 | 0.040 |
| | Scale | 1.000 | | | | |
| | Shape | 1.000 | | | | |
| **Weibull** | Intercept | 5.317 | | | | |
| | recip_age | -0.051 | 0.95 | (0.93-0.97) | 0.009 | <0.001 |
| | dnr_type | 0.789 | 2.20 | (1.12-4.34) | 0.346 | 0.023 |
| | ethnicity | -0.797 | 0.45 | (0.31-0.66) | 0.193 | <0.001 |
| | delayed_gf | -0.526 | 0.59 | (0.40-0.87) | 0.200 | 0.009 |
| | diabetes | -0.662 | 0.52 | (0.27-0.99) | 0.333 | 0.047 |
| | Scale | 1.662 | | | | |
| | Shape | 0.602 | | | | |
| **Log-normal** | Intercept | 4.721 | | | | |
| | recip_age | -0.045 | 0.96 | (0.94-0.98) | 0.011 | <0.001 |
| | dnr_type | 0.680 | 1.97 | (0.95-4.11) | 0.375 | 0.069 |
| | ethnicity | -1.006 | 0.37 | (0.23-0.59) | 0.243 | <0.001 |
| | delayed_gf | -1.015 | 0.36 | (0.22-0.59) | 0.253 | <0.001 |
| | diabetes | -0.278 | 0.76 | (0.31-1.87) | 0.463 | 0.548 |
| | Scale | 2.658 | | | | |
| **Log-logistic** | Intercept | 4.781 | | | | |
| | recip_age | -0.048 | 0.95 | (0.93-0.97) | 0.011 | <0.001 |
| | dnr_type | 0.696 | 2.01 | (0.99-4.08) | 0.362 | 0.054 |
| | ethnicity | -1.003 | 0.37 | (0.24-0.57) | 0.224 | <0.001 |
| | delayed_gf | -0.799 | 0.45 | (0.28-0.72) | 0.239 | <0.001 |
| | diabetes | -0.470 | 0.63 | (0.29-1.34) | 0.387 | 0.225 |
| | Scale | 1.421 | | | | |
| **Gamma** | Intercept | 5.293 | | | | |
| | recip_age | -0.046 | 0.96 | (0.94-0.97) | 0.008 | <0.001 |
| | dnr_type | 0.820 | 2.27 | (1.17-4.41) | 0.339 | 0.016 |
| | ethnicity | -0.539 | 0.58 | (0.41-0.82) | 0.174 | 0.002 |
| | delayed_gf | -0.336 | 0.71 | (0.52-0.98) | 0.159 | 0.035 |
| | diabetes | -0.608 | 0.54 | (0.33-0.90) | 0.255 | 0.017 |
| | Scale | 1.019 | | | | |
| | Shape | 1.991 | | | | |

Reference category: dnr_type (cadaveric), ethnicity (white), delayed_gf (no) and diabetes (no).

The acceleration factors (TR) in Table 5.7 were calculated by exponentiating the coefficients i.e. $e^{-0.051} = 0.95$ for recipient age variable. The confidence interval calculated for this predictor was also obtained by $\exp\{-0.051 \pm 1.96(0.009)\}=(0.93 - 0.97)$.

The index plot of the deviance residuals for the Weibull model shows no observed peculiar pattern (Figure 5.7, page 68). The deviance residual distribution of this plot is mostly within the range of $\pm 3$ and observations 6, 114 and 665 are slightly outside this bound. However, these points were not considered outlying observations because they are not totally withdrawn from the other points in the plot. Also Figure 5.8 (page 68) shows that there was no patient observation with undue influence on the model regression estimates, which could affect the inference made from Weibull fit. The highest change in the estimated coefficients for the predictors in the model is 0.12, which is less than one for influential observation in a small dataset.

**Table 5.8:** AIC values signifying the performance of the respective models in fitting the overall graft survival models.

| **Model** | **Cox** | **Exponential** | **Weibull** | **Log-normal** | **Log-logistic** | **Gamma** |
|---|---|---|---|---|---|---|
| AIC | 3661.961 | 2250.257 | 2104.688 | 2155.208 | 2133.513 | 2093.357 |

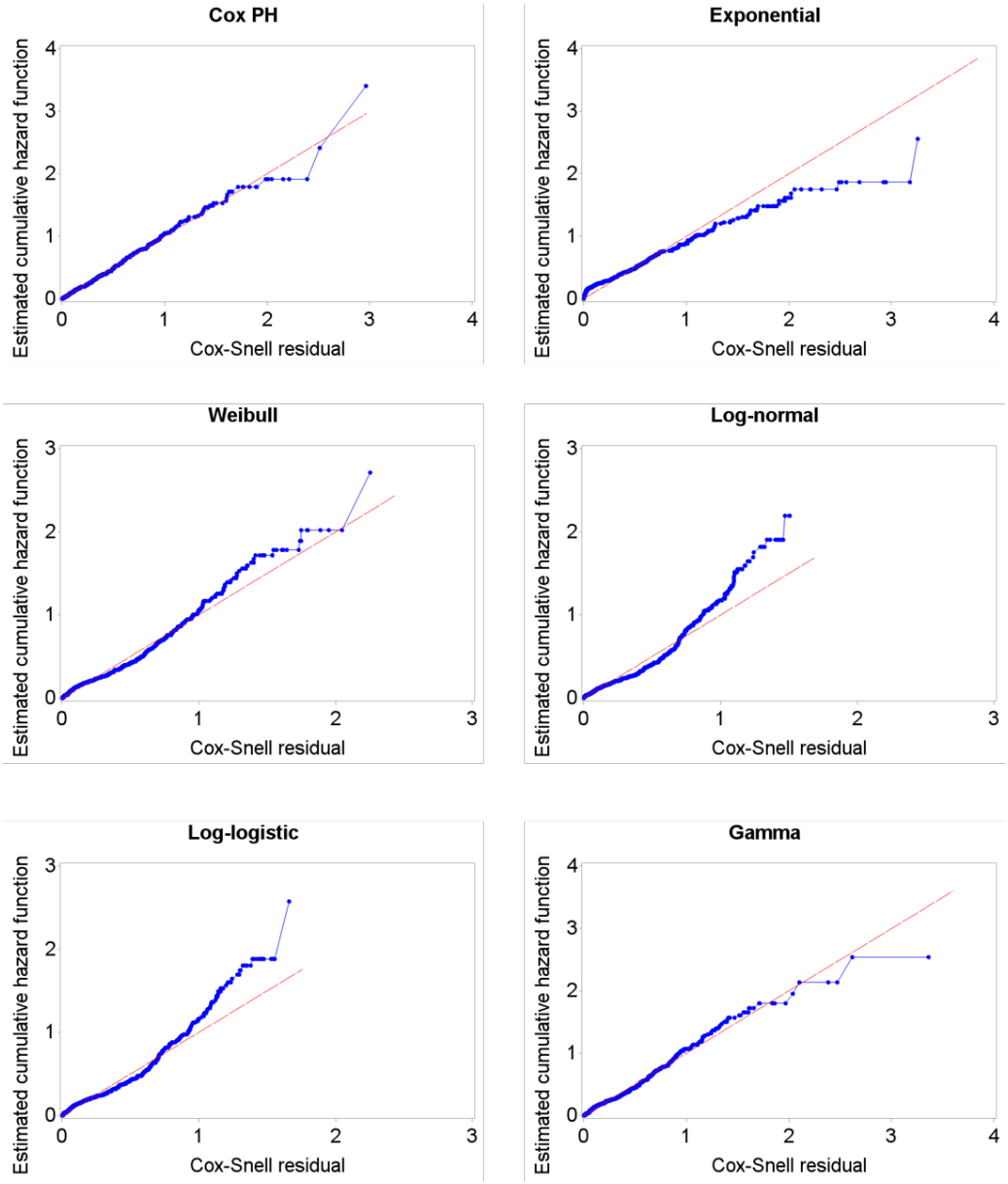


**Figure 5.6:** Assessment of goodness-of-fit using the Cox-Snell residuals. The dashed lines represent the reference with a unit slope and zero intercept.

**Table 5.9:** Likelihood ratio test for comparing nested models

| Distribution | Number of parameters | -2LL | -2LLΔ |
|---|---|---|---|
| Gamma | 3 | 2077.382 | |
| Exponential | 1 | 2238.251 | 160.872 |
| Weibull | 2 | 2090.800 | 13.418 |
| Log-normal | 2 | 2141.200 | 63.818 |

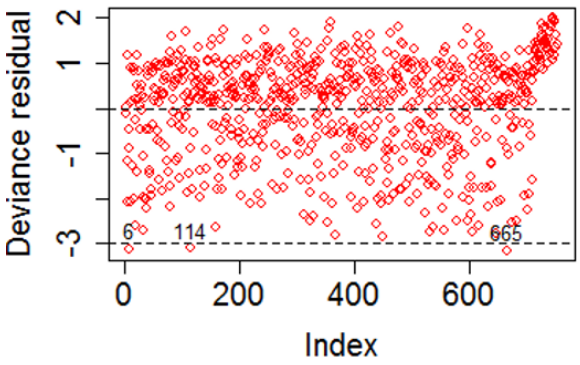


**Figure 5.7:** Assessment of goodness-of-fit using an index plot of the deviance residual for the Weibull model in overall graft survival analysis. The numbers 6, 114 and 665 are observations slightly outside the boundary.

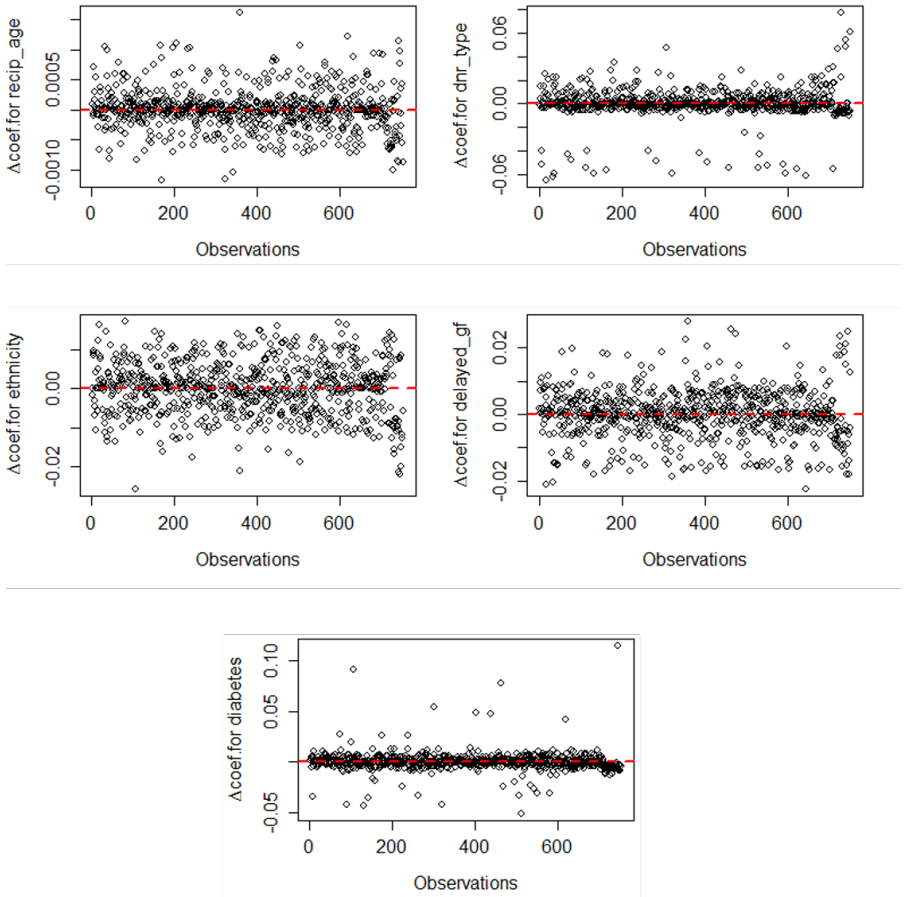


**Figure 5.8:** Graphs of the dfbeta residuals for the overall graft survival analysis illustrating the diagnostics on the estimated regression coefficients for all the predictors in the Weibull model.

### 5.2.4 Assessing goodness-of-fit of the Weibull model through simulation

To further assess the goodness-of-fit of the Weibull model, the parameters estimated from the Weibull model using the real data (Table 5.7) were used for simulating a comparable cohort. The predictors with their respective effect size, distribution and proportion for the non-reference categories (or mean and variance for the continuous variable) are detailed in Table 5.10. The event and censorship times are based on the Weibull distribution. The scale of the time to event (1.66), scale of the time to censorship (1.63), as well as their intercepts (5.3167 and 1.7210) were imputed for the simulation process. Using a sample size of 751 with a follow-up time of 29.25 years, we performed a simulation, setting the random number seed at 180 (for reproducible results). The simulated data was used to refit a Weibull model. The result of the Weibull model based on the simulated data seems to approximate the result from the real data (Table 5.11, page 70), suggesting that the Weibull model is reasonable to use in this analysis. In addition, the Cox-Snell residuals plot of the Weibull model based on the simulated data is more typical with the referent line than what is observed in the real data for the Weibull model (Figure 5.9, page 70).

**Table 5.10:** Details of the predictors used for the simulation of a 751 cohort based on the Weibull model.

| Factor | Coefficient | Distribution | probability or mean (var) |
|---|---|---|---|
| recip_age | -0.051 | Normal | 38.13582(119.1682) |
| dnr_type(living) | 0.789 | Bernoulli | 0.14380825570 |
| ethnicity(white) | -0.797 | Bernoulli | 0.41944074570 |
| delayed_gf(yes) | -0.526 | Bernoulli | 0.36884154460 |
| diabetes(yes) | -0.662 | Bernoulli | 0.06391478029 |

**Table 5.11:** Goodness-of-fit assessment for the overall transplant data using simulation-based method. The table shows the comparison between the Weibull models for the real (Real) and simulated (Sim) data in context of the parameter estimates, time ratios, 95% confidence interval and $p$-values.

| Variable | Coefficient | | TR | | (95% CI) | | $p$-value | |
|---|---|---|---|---|---|---|---|---|
| | Real | Sim | Real | Sim | Real | Sim | Real | Sim |
| Intercept | 5.317 | 5.486 | | | | | | |
| recip_age | -0.051 | -0.052 | 0.95 | 0.95 | (0.93-0.97) | (0.95-0.95) | <0.001 | <0.001 |
| dnr_type | 0.789 | 0.785 | 2.20 | 2.19 | (1.12-4.34) | (1.76-2.73) | 0.023 | <0.001 |
| ethnicity | -0.797 | -0.793 | 0.45 | 0.45 | (0.31-0.66) | (0.40-0.52) | <0.001 | <0.001 |
| delayed_gf | -0.526 | -0.562 | 0.59 | 0.57 | (0.40-0.87) | (0.50-0.65) | 0.009 | <0.001 |
| diabetes | -0.662 | -0.572 | 0.52 | 0.56 | (0.27-0.99) | (0.42-0.75) | 0.047 | <0.001 |

Reference category: dnr_type (cadaveric), ethnicity (white), delayed_gf (no) and diabetes (no).

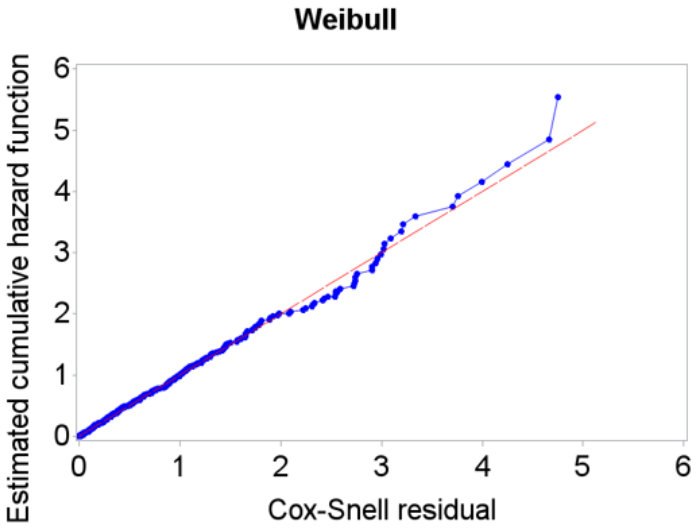


**Figure 5.9:** Cox-Snell residuals obtained from fitting the Weibull survival model to the simulated data in the overall graft survival analysis. The dashed line represents the reference with a unit slope and zero intercept.

## 5.3 Short-term graft survival analysis

### 5.3.1 Exploratory data analysis for short-term graft survival

A graphical representation of graft survival time distribution within the first year post-transplant is shown in Figure 5.10 (page 71). The histogram indicates that the risk of graft failure is highest within one month of transplant and tappers off with time (Figure 5.10A).

The survival rate within this first year of transplant (Figure 5.10B) is about 90%. The survival plot also shows that at the $12^{th}$ month of follow-up, about 65% of grafts are still at risk. The hazard of graft failure (Figure 5.10C) is highest at the beginning of the study and gradually decreases as the follow-up time increases. This figure shows that the hazard of graft failure at the beginning of the study is about seven times higher than the hazard at the $12^{th}$ month of the study. There is a sharp rise in the cumulative hazard plot (Figure 5.10D) and the slope shown in the plot is not unity, indicating that the hazard rates are higher at the beginning and not constant within the first year of kidney transplant.

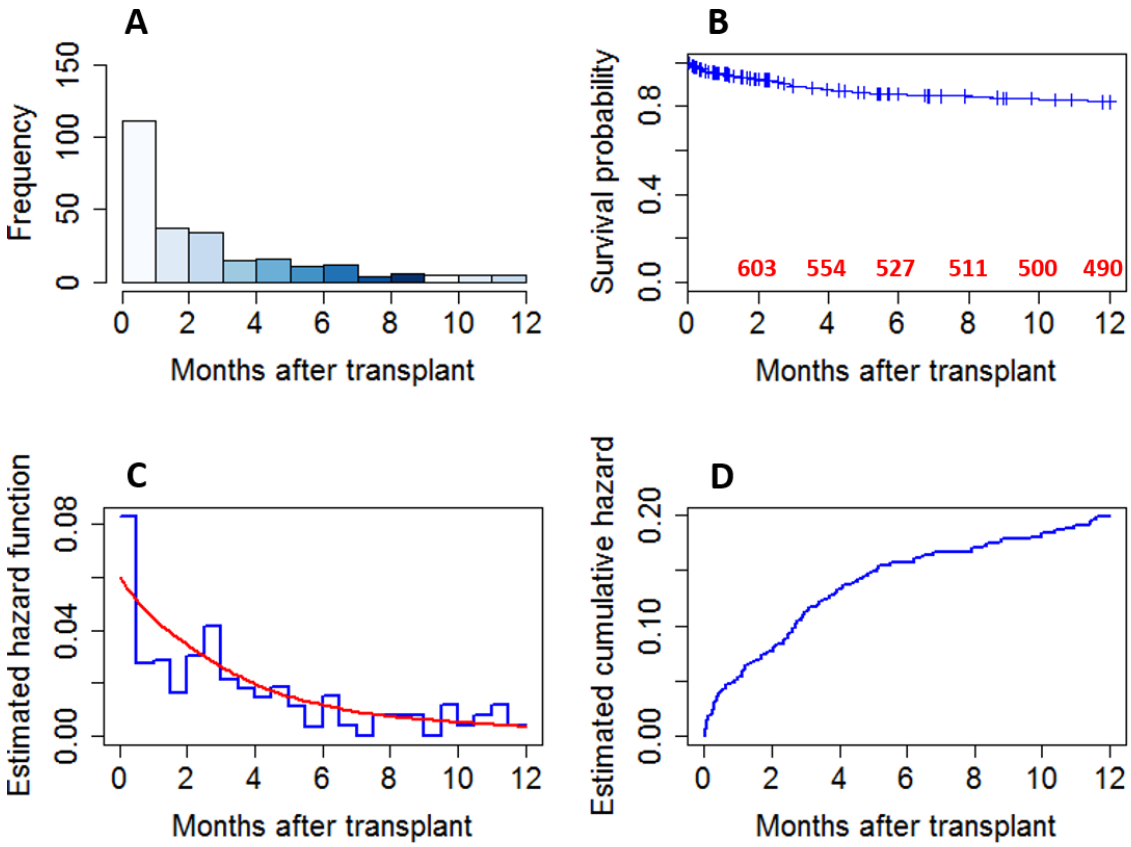


**Figure 5.10:** Exploratory data analysis for ST graft survival. (A) histogram of the underlying frequency distribution of the graft survival time variable, (B) KM estimate of the survival function, the + signs indicates censoring and the numbers in red show grafts at risk at each 2 month interval. (C) KM estimate of a kernel-smoothed hazard function and (D) KM estimate of the cumulative hazard function for the overall data analysis ($N$=751).

### 5.3.2 Model development for short-term graft survival

Similar to the model building procedure used in the overall data analysis, the multivariable Cox PH model containing all significant covariates in Table A.1 (page 116) was fitted (Table A.2, page 117). In order to simplify the model, $p$-values of the variables (based on the Wald test) were examined. The one degree of freedom of the LR test with a $p$-value of 0.909 shows that the model without 'wound haematoma' (Model 2) is not statistically different from the model with 'wound haematoma' (Model 1). The exclusion of this variable has no influence on other variables parameters. Also, deletion of 'hypertension' from Model 2 made no difference in the model, rather it influenced the parameter estimate of 'renal disease'. Since 'renal disease' is not significant, both variables ('hypertension' and 'renal disease') were excluded from the model. Further sequential exclusion of 'donor type' and 'inherited' from Models 5 and 6 had no effect on the models and the estimated parameters. Variables previously set aside in Model 1 because they were not significant at the 25% level in Table A.1 (page 116) were reconsidered in Model 6 (Table A.3, page 118), only 'ureteric' (among the variables) made it back into the multivariable model at the 10% level. 'Recipient age' and 'AR-histological' were over the 5% level of significance; Hence, the model was further optimised by excluding these variables one at a time. Deletion of 'recipient age' and 'AR-histological' made no significant impact in the model and the estimated parameters (Table A.3). The best subset of the predictors selected are 'nephrectomy', 'no_complication', DGF, 'diabetes', 'ethnicity' and 'ureteric'.

There was no need to test the assumption of linearity in the ST data analysis because all the selected predictors are categorical. All possible two-way interaction between the covariates were analysed and none of the interactions is significant at the 5% level. The assessment of the PH assumption for the sub-variables selected in the ST analysis is shown in Figure A.1 (page 119). There is no line-crossing observed in the survival profiles of these variables. The survival curves shown in Figure A.1A, B, D, E and F drifted apart gradually. The fewer number of graft failures observed in patients with nephrectomy complications, diabetes and ureteric complications possibly caused the flattening of the curves, especially for the survival plots of 'nephrectomy' and 'diabetes' (Figure A.1A, D and F). The PH assumption seems to be violated with respect to DGF (Figure A.1C), because the curves show larger differences at the beginning than later. The log-log plots of these variables are comparable with the KM profiles. The log-log profiles of 'no_complication' and 'ethnicity' appear approximately parallel (Figure A.2B and E, page 120). There is an indication that the PH assumption is violated in Figure A.2C. Again, the log-log plot profile for 'nephrectomy' and 'diabetes' (which has fewer

number of graft failures in one of the categories) are not properly defined because the time post-transplant is in log-scale.

The global test of the scaled Schoenfeld residuals (Table 5.12, page 73) suggests evidence of non-proportionality ($p$=0.026). DGF contributes to this non-proportionality observed in the global test. The cumulative residuals test also supports the violation of assumption only for DGF ($p$=0.002). The graphical output of these tests is shown in Figure A.3 (page 121). The departure from the zero line observed in the scaled Schoenfeld residuals plots (Figure A.3, left-panel) is only significant for DGF (Table 5.12, page 73). Figure A.3 (left-panel) also shows that the observed test process for DGF is not within the simulated process (Figure A.3C, right-panel). Hence, DGF violated the PH assumption in the ST analysis.

The final Cox regression model suggests all these predictors are significantly associated with graft survival at the 5% level of significance and only DGF violated the PH assumption in this model. The standard error and coefficient for 'diabetes' are large, which definitely affects the width of the confidence interval. This could be as a result of the reference category used and fewer number of graft failure observed in diabetic patients.

**Table 5.12:** Non-proportionality test in the Cox regression model for ST graft survival, $p$-values for scaled Schoenfeld residuals and cumulative residuals (*) tests.

| Variable | rho | chisq | $p$-value | $p$-value* |
|---|---|---|---|---|
| nephrectomy | -0.098 | 1.150 | 0.284 | 0.471 |
| no_complication | 0.103 | 1.260 | 0.261 | 0.443 |
| delayed_gf | -0.307 | 11.400 | 0.001 | 0.002 |
| diabetes | -0.019 | 0.041 | 0.840 | 0.330 |
| ethnicity | 0.123 | 1.870 | 0.171 | 0.362 |
| ureteric | 0.000 | 0.000 | 0.997 | 0.659 |
| GLOBAL | NA | 14.300 | 0.026 | |

### 5.3.3 Extension of the Cox PH model for short-term graft survival

The stratified Cox model was fitted to control for DGF by stratification because the PH assumption was not met for this predictor. Table 5.14 (page 75) shows the result of the stratified Cox model, which indicates that all the variables (except the one being stratified-on) were included in the model and they all satisfied the PH assumption (Table A.4, page 122). Only 'ureteric' is not significantly associated to ST graft survival at the 5% level of significance.

**Table 5.13:** Analysis of risk factors associated to ST graft survival on fitting multivariable Cox regression model ($N$=751).

| Variable | coefficient | HR | (95% CI) | SE | $p$-value |
|---|---|---|---|---|---|
| nephrectomy | -1.614 | 0.20 | (0.05-0.82) | 0.722 | 0.025 |
| no_complication | 0.668 | 1.95 | (1.33-2.86) | 0.196 | 0.001 |
| delayed_gf | 0.619 | 1.86 | (1.29-2.68) | 0.188 | 0.001 |
| diabetes | 2.043 | 7.72 | (1.07-55.44) | 1.006 | 0.042 |
| ethnicity | 0.553 | 1.74 | (1.20-2.52) | 0.189 | 0.003 |
| ureteric | -0.930 | 0.40 | (0.16-1.00) | 0.473 | 0.049 |

Reference category: nephrectomy (no), no_complication (yes), delayed_gf (no), diabetes (yes), ethnicity (white) and ureteric (no).

This model assumes no interaction between DGF and any of the predictors in the model. To confirm this, an interaction model that includes interaction of DGF and each of the predictors was fitted. There was no significant interaction observed between DGF and any of the predictors. The result of the LR test of the no-interaction model ($-2LL_{\text{no-interaction}} = 1310.10$) and the interaction model ($-2LL_{\text{interaction}} = 1301.82$) shows no statistical significance between the two models ($p$=0.089). Hence, the no-interaction model is more appropriate than the interaction model. There is no large difference between the HR of the predictors in the stratified Cox regression model and in the standard Cox regression model. For example, the hazard of graft failure for patients with complication is 95% (standard Cox regression model) and 93% (stratified Cox regression model) higher than patients without complication immediately after transplantation. This shows the difference in performance between these two models. Interpretation of each of the effects for these predictors in the stratified model will account for adjusting for the other predictors in the model and DGF as the stratified variable.

Figure 5.11 (page 75) shows the adjusted survival function and cumulative hazard function for DGF. The survival plot indicates that patients who experienced instant functioning of the grafted kidneys consistently experience higher graft survival than those patients who experienced DGF. In addition, the cumulative hazard plot also affirms that patients that did not experience delayed graft function post-transplant had a lower risk of graft failure compared to patients that experienced delayed graft function at all time points.

**Table 5.14:** Result of the stratified Cox regression with no-interaction model for the ST graft survival analysis.

| Variable | Coefficient | HR | (95% CI) | SE | *p*-value |
|---|---|---|---|---|---|
| nephrectomy | -1.642 | 0.19 | (0.05-0.80) | 0.722 | 0.023 |
| no_complication | 0.660 | 1.93 | (1.31-2.82) | 0.196 | 0.001 |
| diabetes | 2.048 | 7.75 | (1.08-55.71) | 1.006 | 0.042 |
| ethnicity | 0.567 | 1.76 | (1.22-2.55) | 0.189 | 0.003 |
| ureteric | -0.878 | 0.42 | (0.16-1.05) | 0.473 | 0.064 |

Reference category: nephrectomy (no), no_complication (yes), diabetes (yes), ethnicity (white) and ureteric (no).

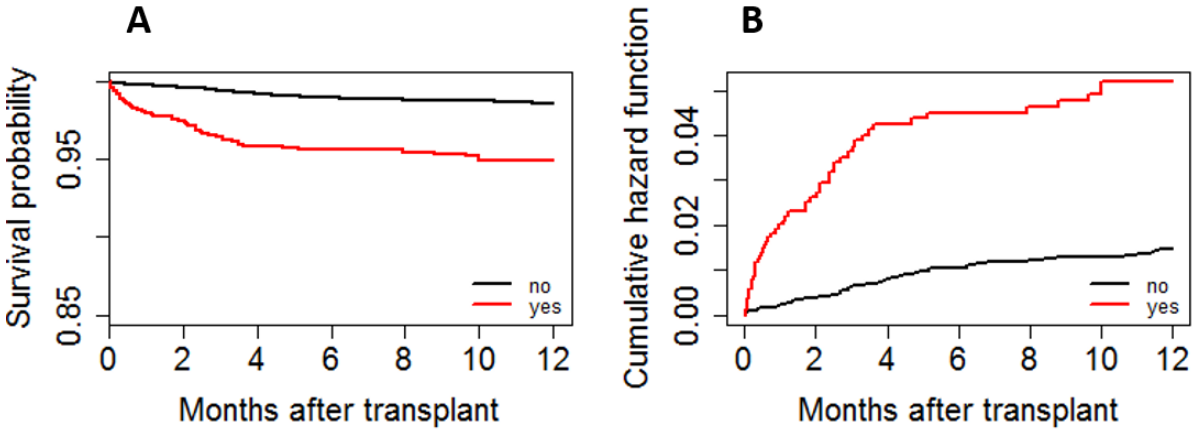


**Figure 5.11:** Graphs of KM estimates of adjusted (A) survival function and (B) cumulative hazard function from the stratified Cox regression model with no interaction for the ST graft survival analysis.

An extended Cox model that includes a product term for DGF with time, the main effect of DGF and the other predictors that satisfied the PH assumption were considered. Table 5.15 (page 76) shows that the $p$-value of the estimated coefficient for the product term is significant ($p$=0.008), suggesting that the PH assumption is not satisfied for DGF. This model indicates that the HR for DGF depends on the values of the estimated coefficient for the main and interaction effects for DGF. The effect of DGF on graft survival is expected to increase with survival time (Figure 5.12, page 77) because the coefficient value of the product term is positive. For example, the HR for DGF at 6 months post-transplant is $10.5[e^{(1.191+0.193(6))}]$, indicating a patient who experienced DGF is approximately 11 times more likely to experience graft failure compared to a patient that did not experience DGF at the $6^{th}$ month. Generally, Figure 5.12 supports that patients that did not experience DGF had better graft survival compared to patients that experienced DGF in this study.

To test the significance of the stratified model in comparison to the proportional hazard model (Table 5.13, page 74), the likelihood ratio test was conducted. Under the null hypothesis that the coefficient of the product term (DGF × time) is zero, the chi-square statistic with one degree of freedom yielded a $p$-value of 0.004. This provides evidence that the effect of DGF on graft survival is time-dependent. Therefore, it is necessary that the time variable values should be incorporated when interpreting the effect of DGF on graft survival. Hence, a model with the product term of DGF and time is preferred to one without the product term.

The model fitted in Table 5.15 (page 76) demonstrates how the effect of DGF on ST graft survival changes over time. Two Heaviside (HV) functions could be used to describe the effect of DGF on graft survival and assess the PH assumption of DGF. Based on Figure 5.11 (page 75), it can be said that after 6.6 months, the divergence in the survival curve minimised (this threshold results in minimum AIC value). Hence, the HV function describing the effect of DGF before and after the $6.6^{th}$ month (post-transplant) was included in the Cox regression model. The results show that the estimated HR for patients that experienced DGF versus patients that did not experience DGF is 2.02 ($p$=<0.001) before the $6.6^{th}$ month, while the HR after the $6.6^{th}$ month is 1.06 ($p$=0.906). This is indicative of assumption violation for DGF because the $p$-value of the hazard ratio after 6.6 months post-transplant is significant. In other words, the hazard for DGF differs at these two time periods.

**Table 5.15:** Result of the extended Cox regression model with main effect of delayed graft function and its interaction with time for ST graft survival analysis.

| Variable | Coefficient | HR | (95% CI) | SE | $p$-value |
|---|---|---|---|---|---|
| nephrectomy | -1.630 | 0.20 | (0.05-0.81) | 0.722 | 0.024 |
| no_complication | 0.659 | 1.93 | (1.32-2.83) | 0.196 | 0.001 |
| diabetes | 2.047 | 7.74 | (1.08-55.65) | 1.006 | 0.042 |
| ethnicity | 0.563 | 1.76 | (1.21-2.54) | 0.189 | 0.003 |
| ureteric | -0.889 | 0.41 | (0.16-1.04) | 0.473 | 0.060 |
| delayed_gf | 1.191 | 3.30 | (1.90-5.70) | 0.280 | <0.001 |
| delayed_gf×time | 0.193 | 1.21 | (1.05-1.40) | 0.072 | 0.008 |

Reference category: nephrectomy (no), no_complication (yes), delayed_gf (no), diabetes (yes), ethnicity (white) and ureteric (no).

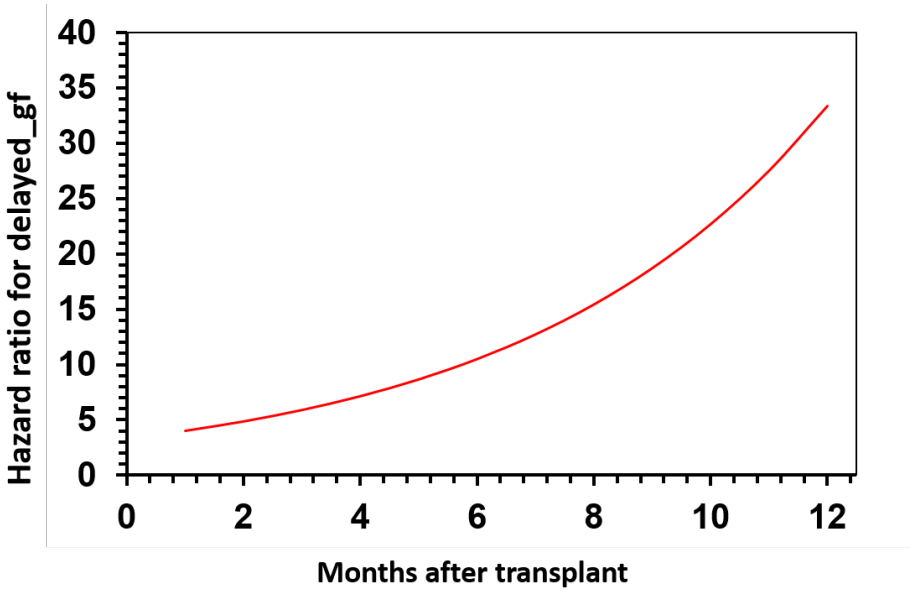


**Figure 5.12:** The plot of hazard ratio for delayed graft function versus time, illustrating the non-proportional effect of the covariate (delayed graft function) in the ST graft survival analysis.

**Table 5.16:** Result of the extended Cox regression model with Heaviside functions (HV1 and HV2) for assessing the PH assumption for delayed graft function in the ST graft survival analysis.

| Variable | Coefficient | HR | (95% CI) | SE | *p*-value |
|---|---|---|---|---|---|
| nephrectomy | -1.615 | 0.20 | (0.05-0.83) | 0.722 | 0.026 |
| no_complication | 0.659 | 1.95 | (1.33-2.85) | 0.196 | <0.001 |
| diabetes | 2.044 | 7.72 | (1.07-55.89) | 1.006 | 0.043 |
| ethnicity | 0.555 | 1.74 | (1.20-2.54) | 0.189 | 0.004 |
| ureteric | -0.921 | 0.40 | (0.15-1.03) | 0.473 | 0.058 |
| HV1 | 0.704 | 2.02 | (1.35-3.02) | 0.202 | <0.001 |
| HV2 | 0.062 | 1.06 | (0.38-3.02) | 0.534 | 0.906 |

Reference category: nephrectomy (no), no_complication (yes), delayed_gf (no), diabetes (yes), ethnicity (white) and ureteric (no).

### 5.3.4 Accelerated failure time models for short-term graft survival

Parametric AFT models were fitted using variables in Table 5.13 (page 74). These models (with exception of the exponential and log-logistic models) indicate that 'ureteric' is not a significant predictor of ST graft survival at the 5% level of significance (Table 5.17, page 79). The standard errors for 'nephrectomy', 'diabetes' and 'ureteric' are larger in all the models,

which could be as a result of fewer graft failures observed in patients with nephrectomy, ureteric or diabetes in ST analysis. These large standard errors could have resulted in broader widths of the confidence intervals observed for 'nephrectomy' and 'ureteric' in all the AFT models. Hence, this may suggest lack of accuracy in parameter estimates for these predictors. The log-normal model has the lowest value of AIC, indicating a more reasonable model compared to the other models (Table 5.18, page 80). The parametric models out-performed the Cox regression model according to the AIC. Based on the Cox-Snell residual plots (Figure 5.13, page 80), the assumption of a constant hazard appears not to be tenable, because the majority of the plotted points did not fall on (or closer to) the referent line for exponential model fit. The fit of the log-normal, log-logistic and gamma models are comparable, which corresponds to what is observed in Table 5.18. The index plot used to assess the adequacy of the most reasonable model (log-normal) in the analysis shows no peculiar pattern and outlying observation, as shown in Figure 5.14 (page 81). Also the dfbeta plots (Figure 5.15, page 81) show that none of the observations had undue influence on the parameter estimates, which could affect inferences made from the log-normal model. This figure shows that the highest change in the estimated coefficients is 0.87 (in absolute value), which is less than 1 for overly influential observations in a small dataset.

**Table 5.17:** Analysis of risk factors associated with the ST graft survival data on fitting multivariable parametric accelerated failure time models ($N$=751).

| Model | Factor | Coeffient | TR | (95%CI) | SE | $p$-value |
|---|---|---|---|---|---|---|
| Exponential | Intercept | 4.225 | | | | |
| | nephrectomy | 1.546 | 4.69 | (1.14-19.30) | 0.722 | 0.032 |
| | no_complication | -0.714 | 0.49 | (0.33-0.72) | 0.195 | <0.001 |
| | delayed_gf | -0.715 | 0.49 | (0.34-0.71) | 0.187 | <0.001 |
| | diabetes | -2.078 | 0.13 | (0.02-0.90) | 1.006 | 0.039 |
| | ethnicity | -0.561 | 0.57 | (0.39-0.83) | 0.189 | 0.003 |
| | ureteric | 1.028 | 2.80 | (1.11-7.07) | 0.474 | 0.030 |
| | Scale | 1.000 | | | | |
| | Shape | 1.000 | | | | |
| Weibull | Intercept | 7.623 | | | | |
| | nephrectomy | 2.901 | 18.18 | (1.35-244.94) | 1.327 | 0.029 |
| | no_complication | -1.210 | 0.30 | (0.15-0.61) | 0.363 | <0.001 |
| | delayed_gf | -1.120 | 0.33 | (0.17-0.64) | 0.343 | <0.001 |
| | diabetes | -3.696 | 0.03 | (0.00-0.91) | 1.839 | 0.044 |
| | ethnicity | -1.006 | 0.37 | (0.18-0.73) | 0.351 | 0.004 |
| | ureteric | 1.688 | 5.41 | (1.00-29.18) | 0.860 | 0.050 |
| | Scale | 1.803 | | | | |
| | Shape | 0.555 | | | | |
| Log-normal | Intercept | 7.256 | | | | |
| | nephrectomy | 2.758 | 15.76 | (1.72-144.71) | 1.131 | 0.015 |
| | no_complication | -1.210 | 0.30 | (0.13-0.67) | 0.414 | 0.004 |
| | delayed_gf | -1.447 | 0.24 | (0.11-0.49) | 0.375 | <0.001 |
| | diabetes | -3.165 | 0.04 | (0.00-0.60) | 1.356 | 0.020 |
| | ethnicity | -1.075 | 0.34 | (0.16-0.71) | 0.373 | 0.004 |
| | ureteric | 1.633 | 5.12 | (0.91-28.68) | 0.879 | 0.063 |
| | Scale | 3.272 | | | | |
| Log-logistic | Intercept | 7.148 | | | | |
| | nephrectomy | 2.872 | 17.67 | (1.46-214.39) | 1.273 | 0.024 |
| | no_complication | -1.217 | 0.30 | (0.14-0.63) | 0.383 | 0.002 |
| | delayed_gf | -1.268 | 0.28 | (0.14-0.57) | 0.357 | <0.001 |
| | diabetes | -3.577 | 0.03 | (0.00-0.83) | 1.730 | 0.039 |
| | ethnicity | -1.041 | 0.35 | (0.18-0.71) | 0.358 | 0.004 |
| | ureteric | 1.723 | 5.60 | (1.02-30.89) | 0.871 | 0.048 |
| | Scale | 1.670 | | | | |
| Gamma | Intercept | 7.171 | | | | |
| | nephrectomy | 2.740 | 15.48 | (1.74-137.54) | 1.115 | 0.014 |
| | no_complication | -1.200 | 0.30 | (0.13-0.69) | 0.422 | 0.004 |
| | delayed_gf | -1.476 | 0.23 | (0.11-0.49) | 0.390 | <0.001 |
| | diabetes | -3.110 | 0.05 | (0.00-0.60) | 1.322 | 0.019 |
| | ethnicity | -1.077 | 0.34 | (0.16-0.71) | 0.376 | 0.004 |
| | ureteric | 1.603 | 4.97 | (0.87-28.33) | 0.888 | 0.071 |
| | Scale | 3.461 | | | | |
| | Shape | -0.131 | | | | |

Reference category: nephrectomy (no), no_complication (yes), delayed_gf (no), diabetes (yes), ethnicity (white) and ureteric (no).

**Table 5.18:** AIC values signifying the performance of the respective models in fitting ST graft survival analysis.

| Model | Cox | Exponential | Weibull | Log-normal | Log-logistic | Gamma |
|---|---|---|---|---|---|---|
| AIC | 1469.557 | 552.658 | 493.803 | 487.339 | 491.430 | 489.253 |

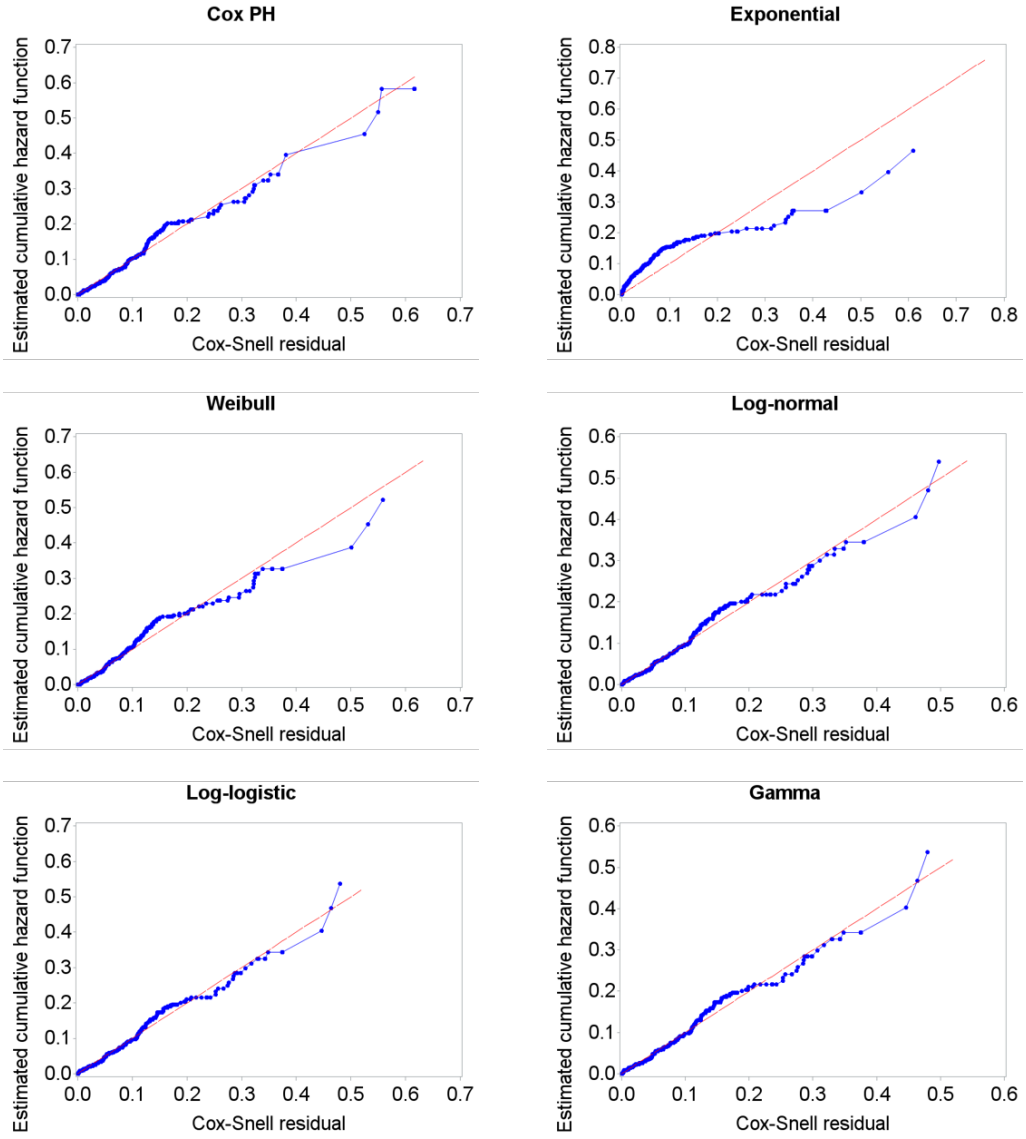


**Figure 5.13:** Cox-Snell residuals obtained from fitting the corresponding survival model to the ST graft survival analysis. The dashed lines represent the reference with a unit slope and zero intercept.

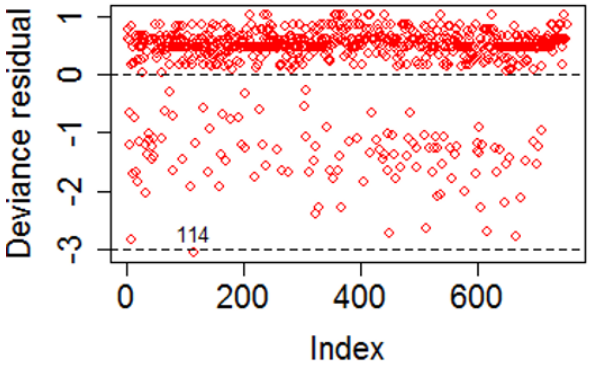


**Figure 5.14:** Assessment of goodness-of-fit using an index plot of the deviance residuals for the log-normal model in ST graft survival analysis.

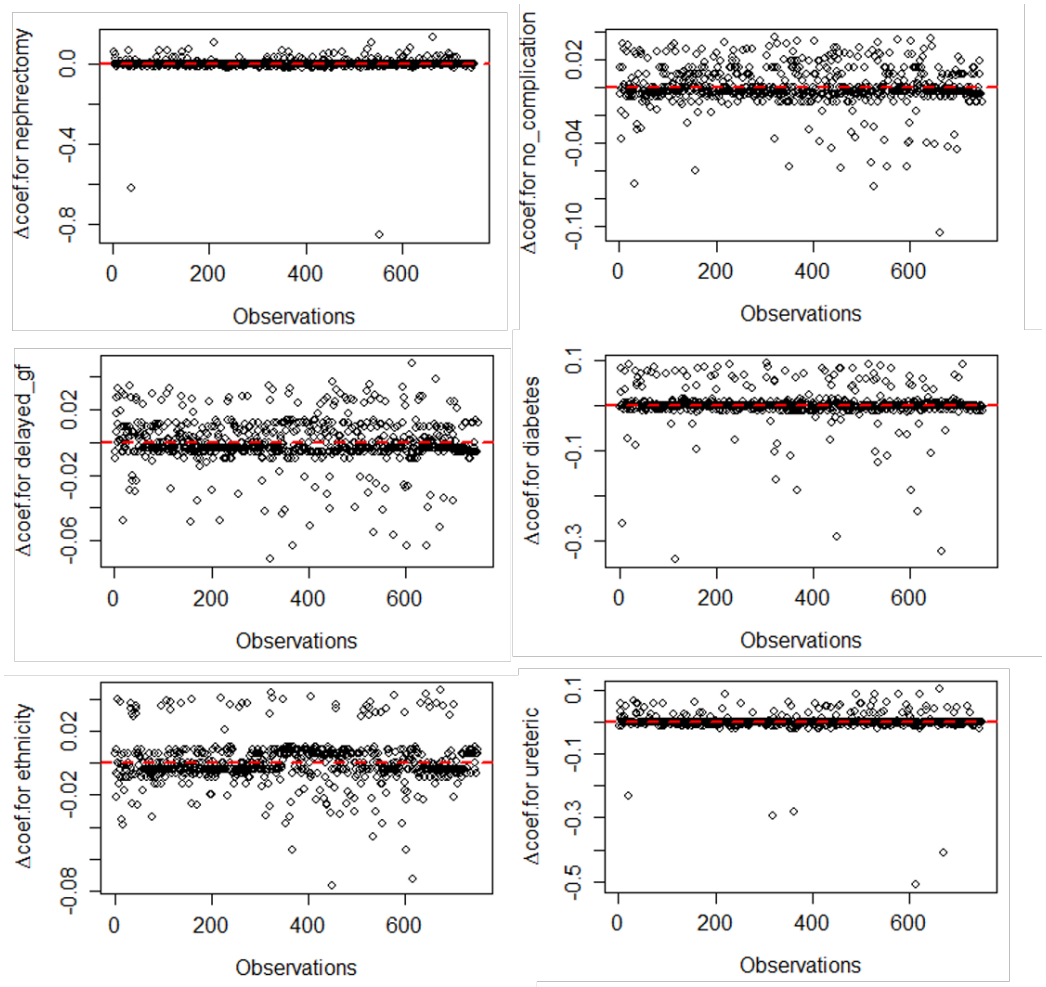


**Figure 5.15:** Graphs of the dfbeta statistic illustrating the diagnostics on the estimated regression coefficients for all the predictors in the log-normal model for ST graft survival analysis.

### 5.3.5 Assessing goodness-of-fit of the log-normal model through simulation

The parameters estimated from the log-normal model using the real data (Table 5.17), were used for simulating a comparable cohort. The predictors with their respective effect size, distribution and proportion for the non-reference categories are detailed in Table 5.19. The event and censorship times are based on the log-normal distribution. The scale of the time to event, scale of the time to censorship, as well as their intercepts are indicated in the table footnote. Using a sample size of 751, we set a random seed of 1000 and ran a simulation. Finally, the goodness-of-fit assessment based on simulation is shown in Table 5.20 (page 83). The log-normal model parameter estimates based on the simulated data is comparable with the log-normal parameter estimates based on the real data. The fit of the log-normal model seems to be better with the simulated data than the real data according to the Cox-Snell residual plot (Figure 5.16, page 83).

**Table 5.19:** Details of the predictors and input parameters used for the simulation of a 751 cohort based on the log-normal model for the ST analyses.

| Factors | Coefficient | Distribution | Probability |
|---|---|---|---|
| nephrectomy (yes) | 2.758 | Bernoulli | 0.06924101198 |
| no_complication (no) | -1.210 | Bernoulli | 0.34620505990 |
| delayed_gf (yes) | -1.447 | Bernoulli | 0.36884154460 |
| diabetes (no) | -3.167 | Bernoulli | 0.93608521970 |
| ethnicity (non-white) | -1.075 | Bernoulli | 0.41944074570 |
| ureteric (yes) | 1.633 | Bernoulli | 0.05459387483 |

seed=1000, n=751, foltime=1.05, anc.ev=3.27, beta0.ev=7.26, anc.cens= 1.2, beta0.cens=0.0463

**Table 5.20:** Goodness of fit assessment for ST graft survival analysis using the simulation-based method. The table shows the comparison between the estimated coefficients, the time ratios with a 95% confidence interval and $p$-values for the real (Real) and the log-normal-based simulated (Sim) data.

| Variable | Coefficient | | TR | | (95% CI) | | $p$-value | |
|---|---|---|---|---|---|---|---|---|
| | Real | Sim | Real | Sim | Real | Sim | Real | Sim |
| Intercept | 7.256 | 7.065 | | | | | | |
| nephrectomy | 2.758 | 2.076 | 15.76 | 7.97 | (1.72-144.71) | (1.57-40.50) | 0.015 | 0.012 |
| no_complication | -1.210 | -1.374 | 0.30 | 0.25 | (0.13-0.67) | (0.13-0.49) | 0.004 | <0.001 |
| delayed_gf | -1.447 | -0.977 | 0.24 | 0.38 | (0.11-0.49) | (0.19-0.73) | <0.001 | 0.004 |
| diabetes | -3.165 | -3.187 | 0.04 | 0.04 | (0.00-0.60) | (0.00-0.52) | 0.020 | 0.014 |
| ethnicity | -1.075 | -1.281 | 0.34 | 0.28 | (0.16-0.71) | (0.14-0.54) | 0.004 | <0.001 |
| ureteric | 1.633 | 1.956 | 5.12 | 7.07 | (0.91-28.68) | (0.83-60.09) | 0.063 | 0.073 |

Reference category: nephrectomy (no), no_complication (yes), delayed_gf (no), diabetes (yes), ethnicity (white) and ureteric (no).

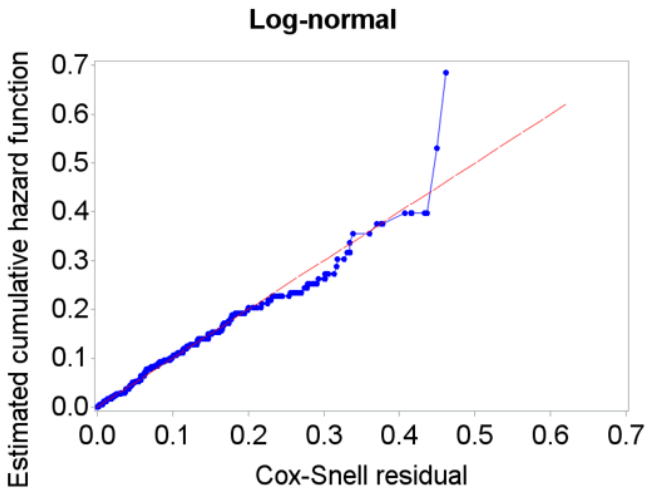


**Figure 5.16:** Cox-Snell residuals obtained from fitting a log-normal survival model to the simulated data in ST graft survival analysis. The dashed line represents the reference with a unit slope and zero intercept.

## 5.4 Long-term graft survival analysis

### 5.4.1 Exploratory data analysis for long-term graft survival

In the exploratory data analysis of the LT graft survival distribution (Figure 5.17, page 85), the histogram (Figure 5.17A) shows that most of graft failures occurred between 1 and 15

years post-transplant. The survival rate of grafts in the LT study is shown in Figure 5.17B. At about 12 years of follow-up, 50% of the grafts had failed. None of the grafts survived up to 30 years and about 60% of the grafts were censored. The baseline hazard (Figure 5.17C) shows a profile which increased and subsequently decreased with time post-transplant. The hazard increases to a peak at about 7 years of follow-up study and stay approximately constant and then decreases gradually towards zero from 12 years as time increases. There is a gradual rise in the cumulative hazard, indicating a lower hazard of graft failure at the beginning of LT graft survival. The noise observed towards the end of the cumulative hazard plot is also shown in Figure 5.1C. This could be as a result of the number of grafts at risk towards the end of the study.

### 5.4.2 Model development for long-term graft survival

The model building procedure detailed in the overall analysis was also employed in the LT analysis. Among the 19 variables evaluated for a relationship with graft survival in the univariable analysis, only 8 were significantly related with graft survival at the 25% level (Table B.1, page 123). The multivariable Cox regression model containing all significant variables in the univariable analysis was fitted (Table B.2, page 124). Omitting 'wound sepsis', 'urological' and 'hypertension' from Models 1, 2 and 3 respectively, made no significant impact in the model and the estimated coefficients. The final variables selected at this stage is shown in Model 4 (Table B.2).

In the next step, variables that were not significant in the univariable analysis were added one at time in Model 4 (Table B.3, page 125). These variables also did not show a significant relationship with graft survival and are also not confounders. Hence, they were excluded from the study. Lastly, the model was further optimised by dropping 'inherited' ($p$=0.064). Excluding this variable and refitting the model resulted in a LR with $p$=0.051, which is slightly above the threshold of 5% level of significance. Furthermore, the change in coefficients ($\Delta\hat{\beta}$) for each variable remaining in the model was compared with the original model. The highest change in coefficients is approximately 11% (Table B.3, page 125). Therefore, 'inherited' was subsequently dropped from the study.

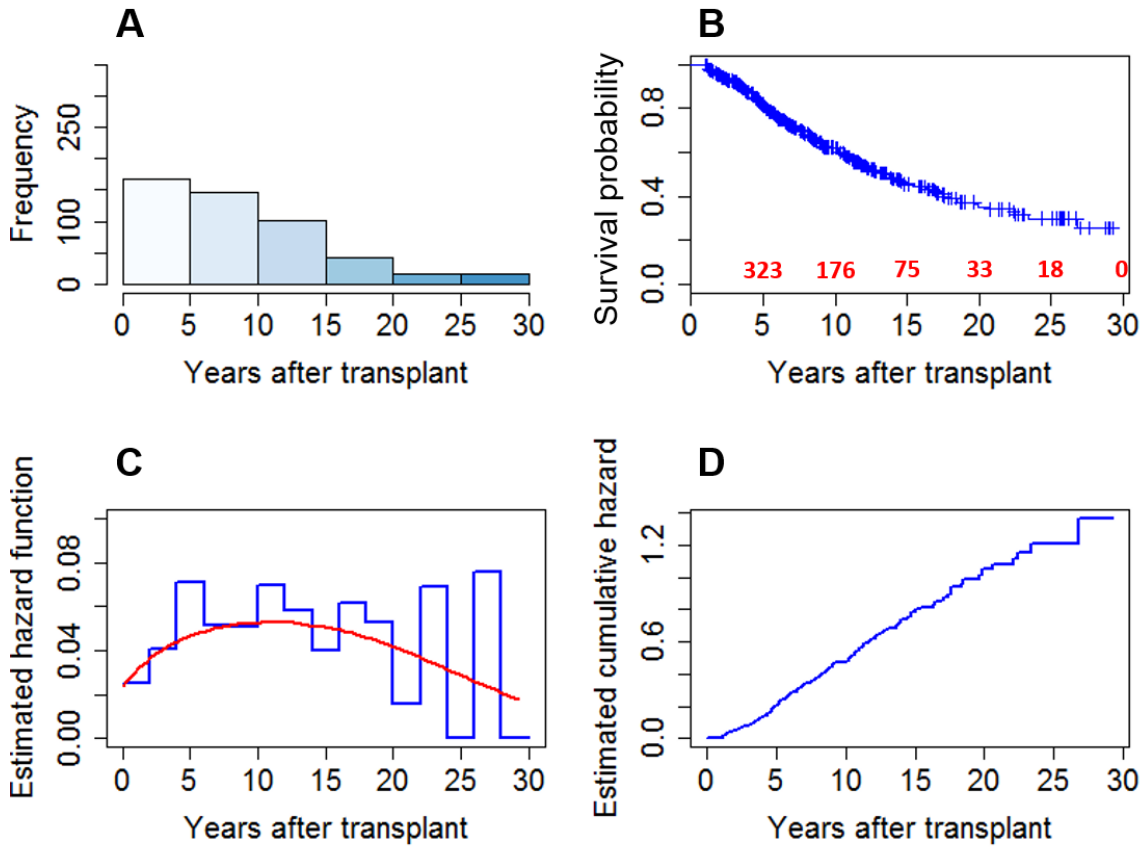


**Figure 5.17:** Exploratory data analysis for LT graft survival. (A) histogram of the underlying frequency distribution of the graft survival time variable, (B) KM estimate of the survival function, (+) indicates censoring and the numbers in red show grafts at risk at each 5 year interval. (C) KM estimate of a kernel-smoothed hazard function and (D) KM estimate of the cumulative hazard function for the overall data analysis ($N$=490).

The next step was to assess the scale of 'recipient age' as the only continuous variable selected. The Lowess smoothed line in Figure 5.18A (page 86) is approximately straight, suggesting a linear term for recipient age is appropriate in the model. The cumulative martingale residuals plot (Figure 5.18B, page 86) shows that the observed process of this variable is typical with the simulated process. The spline fit supports that 'recipient age' is related with graft survival in the log-hazard because the non-linear term in Table 5.21 (page 87) is not significant.

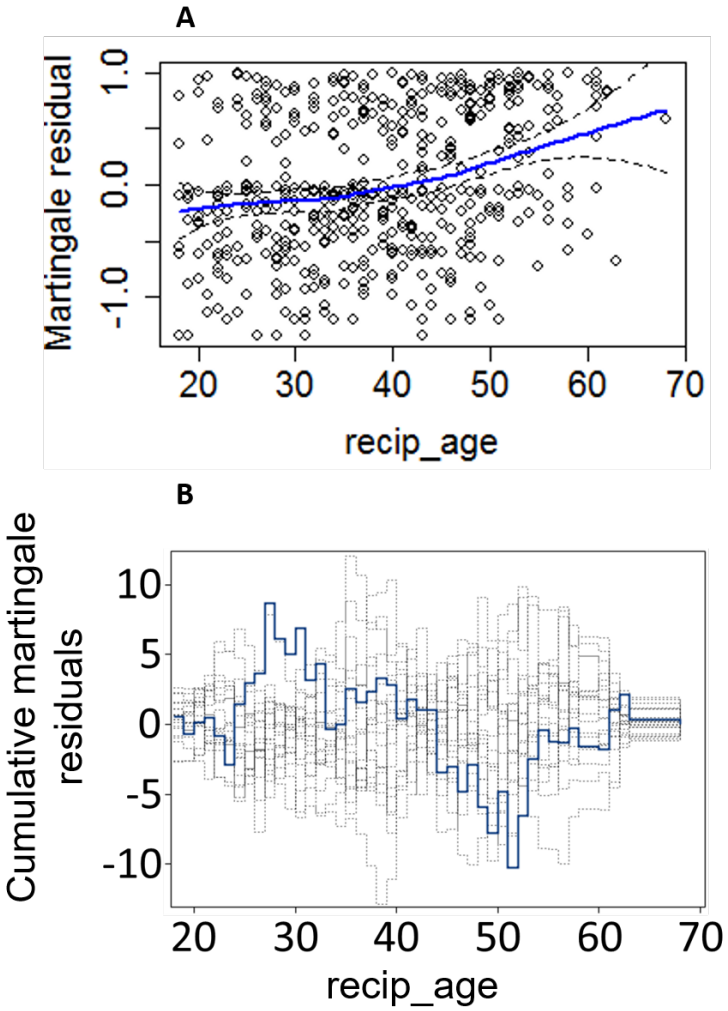


**Figure 5.18:** Linearity assumption assessment for LT graft survival analysis. Plot of (A) smoothed martingale residuals from a null Cox regression model versus recipient age and (B) cumulative martingale residual versus recipient age ($p$=0.148), the bold line represents the observed process and the dotted lines represent the simulated processes.

Finally, possible interactions between the predictors were assessed. The result shows a significant interaction between 'recipient age' and 'diabetes' (Table 5.23, page 89). This is statistically and clinical reasonable, indicating the effect of age differs between the two categories of 'diabetes'. Comparing the model with and without 'age-diabetes' interaction, the LR test (11.138, with 1 degree of freedom) is significant at the 5% level of significance ($p$<0.001). The $p$-values based on the Wald statistics show that all the terms in the model are significant.

**Table 5.21:** Smoothing spline fit result (based on the Cox regression model) for assessing the linearity assumption of the continuous variable (recipient age) in LT graft survival analysis.

| Variable | Coefficient | SE | *p*-value |
|---|---|---|---|
| dnr_type | -0.629 | 0.274 | 0.022 |
| diabetes | 0.870 | 0.215 | <0.001 |
| ethnicity | 0.458 | 0.149 | 0.002 |
| recip_age-linear | 0.042 | 0.007 | <0.001 |
| recip_age-nonlinear | | | 0.231 |

Reference category: dnr_type (cadaveric), diabetes (no) and ethnicity (white).

Figure B.1 (page 126) shows the assessment of the PH assumption for the categorical predictors using the KM and log-log plots. Only 'ethnicity' displays evidence of non-proportionality, though there is line-touching in the survival profile for 'diabetes' at the beginning, before the lines drifted apart. On the basis of the rule of parallel lines in PH assumption, there is suggestion that the proportionality assumption is not valid for all these variables. However, the line-touching observed in 'donor type' and 'diabetes' could be a result of a fewer graft failures observed in patients with diabetes or patients that received live donor kidney transplants. Table 5.22 (page 88) shows the $p$-values of tests based on scaled Schoenfeld and cumulative residuals for non-proportional hazard assessment. The result of the two tests suggests evidence of deviation from the proportionality for 'ethnicity'. The result of the two tests are graphically illustrated for each of the predictors in the Cox regression model (Figure B.2, page 127). The Lowess lines in Figure B.2 (left panel) approximately have a zero slope, except for 'ethnicity' (Figure B.2 C). The observed process in the cumulative martingale residual plot for 'ethnicity' is not distributed well-within the simulated process. This figure suggests a non-constant effect over time for ethnicity. The non-constant effect of 'ethnicity' indicates a lack of fit in the Cox regression model, which could lead to misleading parameter interpretation.

### 5.4.3 Extension of the Cox PH model for long-term survival

An extended Cox regression model (a more adequate model) was employed because the PH assumption was violated for 'ethnicity'. Table 5.24 (page 89) shows the result of the stratified model with no-interaction. An interaction model that includes ethnicity with the predictors was fitted. To conclude which model is more suitable, the LR test was conducted and the result $(-2LL_{\text{no-interaction}} - (-2LL_{\text{interaction}}) = 2.615)$ is not significant at the 5% level of significance. Thus, we conclude that the stratified model with no-interaction is more appropriate in this analysis. The estimated parameters in Table 5.23 (page 89) for the standard Cox regression

model is comparable with the parameter estimates for the stratified Cox regression model. Interpretation of the effect of each predictor in the stratified model will account for adjusting for other predictors in the model and 'ethnicity' as the stratified predictor. Figure 5.19 (page 89) shows the adjusted survival function and cumulative hazard function by 'ethnicity'. The survival plot indicates that graft survival experienced by white patients is consistently higher than graft survival experienced by non-white patients. In addition, the cumulative hazard plot also supports this finding.

Table 5.25 (page 90) shows the results of an extended Cox model with the product term of 'ethnicity' with time, the main effect of 'ethnicity' and the other predictors that satisfied the PH assumption. There is evidence to conclude on interaction of 'ethnicity' with time in the LT analysis, since the $p$-value of the estimated coefficient for the product term is significant ($p$=0.011). Based on Table 5.25, the estimated HR for 'ethnicity' at 5 years post-transplant is $3.51[e^{(0.876+0.076(5))}]$. This suggests that a non-white patient is approximately four times more likely to experience graft failure compared to a white patient (Figure 5.20). The LR used to test the significance of this model, compared to model without the interaction of 'ethnicity' with time (Table 5.23), is equal to 6.926 with $p$=0.008. This confirms that a model with the product term of 'ethnicity' and time is preferred to a model without the product term. The threshold used to create the two HV functions were based on Figure 5.19 (page 89). With this function, the effect of 'ethnicity' on graft survival before and after the $10^{th}$ year was assessed (we assumed the divergence in the survival curve minimised after this period). The result shown in Table 5.26 (page 90) indicates that the estimated HR for non-whites as compared to whites is 1.99 ($p$<0.001) before the $10^{th}$ year, while the HR after the $10^{th}$ year is 1.35 ($p$=0.286). This model with the HV function confirms a non-proportional effect of 'ethnicity' over time because the $p$-value of HV1 is significant.

**Table 5.22:** Non-proportionality test in the Cox regression model for LT graft survival, $p$-values for scaled Schoenfeld residuals and cumulative residuals (*) tests.

| **Variable** | **rho** | **chisq** | ***p*-value** | ***p*-value*** |
|---|---|---|---|---|
| dnr_type | -0.056 | 0.622 | 0.430 | 0.461 |
| diabetes | 0.080 | 1.323 | 0.250 | 0.072 |
| recip_age | 0.021 | 0.099 | 0.753 | 0.434 |
| ethnicity | 0.167 | 5.499 | 0.019 | 0.013 |
| diabetes×recip_age | 0.005 | 0.006 | 0.936 | 0.686 |
| GLOBAL | NA | 9.230 | 0.100 | |

**Table 5.23:** Analysis of risk factors associated with LT graft survival based on the multivariable Cox regression model ($N$=490).

| Variable | Coefficient | HR | 95% CI | SE | $p$-value |
|---|---|---|---|---|---|
| dnr_type | -0.698 | 0.50 | (0.29-0.85) | 0.273 | 0.011 |
| diabetes | 0.806 | 2.24 | (1.44-3.48) | 0.224 | <0.001 |
| recip_age | 0.135 | 1.14 | (1.08-1.21) | 0.029 | <0.001 |
| ethnicity | 0.435 | 1.54 | (1.16-2.06) | 0.147 | 0.003 |
| diabetes×recip_age | -0.086 | 0.92 | (0.87-0.97) | 0.027 | 0.001 |

Reference category: dnr_type (cadaveric), diabetes (no) and ethnicity (white).

**Table 5.24:** Results of the stratified Cox regression with no interaction model for LT graft survival analysis.

| Variable | Coefficient | HR | (95% CI) | SE | $p$-value |
|---|---|---|---|---|---|
| dnr_type | -0.655 | 0.52 | (0.30-0.89) | 0.275 | 0.017 |
| diabetes | 0.773 | 2.17 | (1.40-3.36) | 0.224 | 0.001 |
| recip_age | 0.136 | 1.15 | (1.08-1.22) | 0.029 | <0.001 |
| diabetes×recip_age | -0.087 | 0.92 | (0.87-0.97) | 0.027 | 0.001 |

Reference category: dnr_type (cadaveric) and diabetes (no).

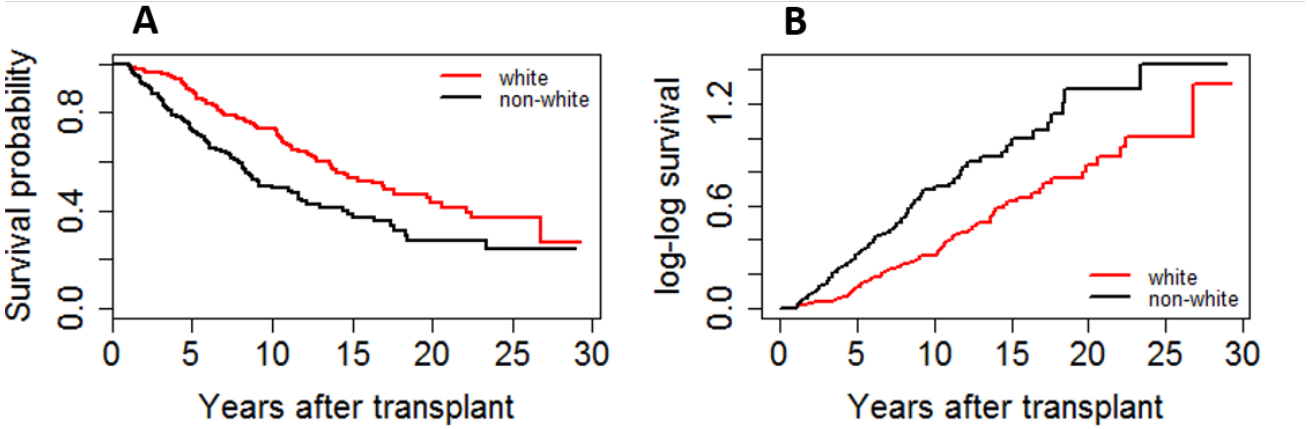


**Figure 5.19:** Graphs of KM estimates of adjusted (A) survival function and (B) cumulative hazard function from the stratified Cox regression model with no interaction for the LT graft survival analysis

**Table 5.25:** Results of the Cox regression model with main effect of ethnicity predictor and its interaction with time for LT graft survival analysis.

| Variable | Coefficient | HR | (95% CI) | SE | *p*-value |
|---|---|---|---|---|---|
| dnr_type | -0.651 | 0.52 | (0.30-0.89) | 0.274 | 0.018 |
| diabetes | 0.775 | 2.17 | (1.40-3.37) | 0.224 | 0.001 |
| ethnicity | 0.876 | 2.69 | (1.88-3.07) | 0.125 | <0.001 |
| recip_age | 0.138 | 1.15 | (1.08-1.21) | 0.030 | <0.001 |
| diabetes×recip_age | -0.088 | 0.92 | (0.87-0.97) | 0.027 | 0.001 |
| ethnicity×time | 0.076 | 1.08 | (1.01-1.14) | 0.030 | 0.011 |

Reference category: dnr_type (cadaveric), diabetes (no) and ethnicity (white).

**Table 5.26:** Result of the extended Cox regression model with Heaviside functions (HV1 and HV2) for assessing PH assumption for recipient ethnicity in the LT graft survival analysis.

| Variable | Coefficient | HR | 95% CI | SE | *p*-value |
|---|---|---|---|---|---|
| dnr_type | -0.650 | 0.52 | (0.31-0.89) | 0.273 | 0.017 |
| diabetes | 0.772 | 2.16 | (1.40-3.32) | 0.220 | <0.001 |
| recip_age | 0.139 | 1.15 | (1.08-1.22) | 0.031 | <0.001 |
| diabetes×recip_age | -0.089 | 0.91 | (0.86-0.96) | 0.027 | 0.001 |
| HV1 | 0.686 | 1.99 | (1.42-2.76) | 0.170 | <0.001 |
| HV2 | 0.300 | 1.35 | (0.97-1.88) | 0.281 | 0.286 |

Reference category: dnr_type (cadaveric), diabetes (no) and ethnicity (white).

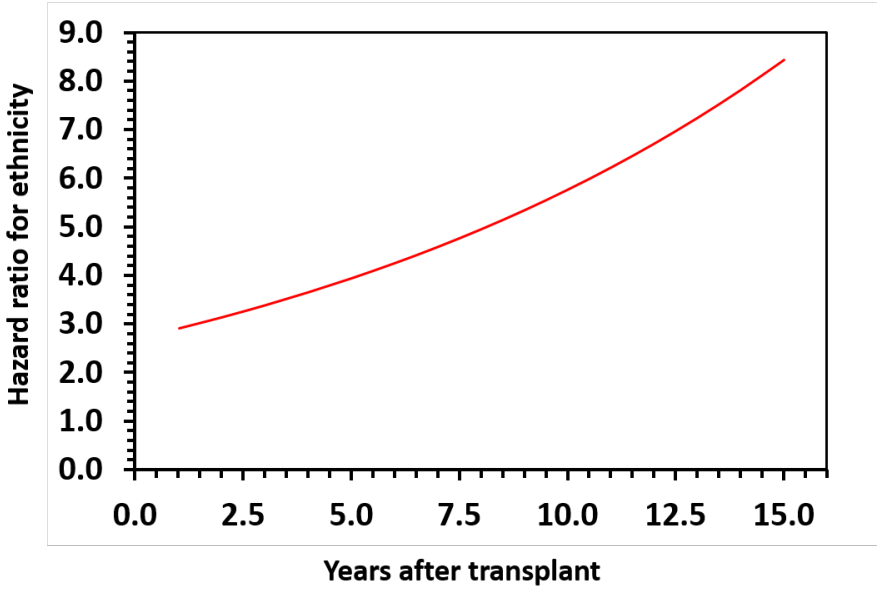


**Figure 5.20:** The plot of hazard ratio for recipient ethnicity versus time, illustrating the non-proportional effect of the covariate (ethnicity) in LT graft survival analysis

### 5.4.4 Accelerated failure time models for long-term graft survival

The selected predictors used to fit the final Cox regression model (Table 5.23, page 89) were also used to fit parametric models (Table 5.27, page 92). All the models identified these predictors as significant risk factors of LT graft survival. Table 5.28 presents the statistical criterion used to compare the fit of the fitted models. The lower the value of this criterion, the better the model fit. This table shows that the Cox PH model has the highest AIC value. The exponential model performed poorly compared to the other parametric models, reflecting what was observed in the previous analyses. The Log-normal, log-logistic and gamma models are comparable according to the AIC. In the Cox-Snells residual plots, it appears that the Weibull model provides a better fit compared to the other models (Figure 5.21, page 93). However, we conclude on model performance based on AIC values because of the limitation of the Cox-Snell residuals plot. Thus, the log-normal model fit (with the predictors) in the LT analysis is given by:

$$\begin{aligned} LogT = {} & 2.820 + 0.338 dnr\_type - 0.526 diabetes - 0.100 recip\_age - 0.427 ethnicity \\ & - 0.065 diabetes \times recip\_age + 1.035. \end{aligned}$$

The interaction effect of 'diabetes' with 'recipient age' (centered on the mean) is also significant in the log-normal model. According to this model, $\alpha_2 = -0.526$, $\alpha_3 = -0.100$ and $\alpha_5 = 0.065$. $\alpha_2$ indicates the difference in graft survival between a diabetic patient and a non-diabetic patient. The time ratio for 'recipient age' is 0.90 ($e^{-0.100}$), this indicates shorter survival time is more likely for elderly recipients. This average effect is referred to the category of non-diabetic patients (reference category). The average effect of age on diabetic patients is 0.97 ($e^{(-0.100+0.065)}$). The average effect of age on LT graft survival has a larger impact on non-diabetic recipients compared to diabetic recipients.

The index plot of the deviance residuals (used to assess the adequacy of the log-normal model) shows no peculiar pattern and outlying observations (Figure 5.22, page 94). While assessing the model adequacy, the dfbeta plot was further used to determine whether any observation had undue influence on the model regression estimates that could affect inferences made from the fitted models. Figure 5.23 (page 94) presents the dfbeta residual for each predictors in the log-normal model. This figure shows that the highest change in estimated coefficients is 0.08 (in absolute value), which is less than 1 for overly influential observations in a small dataset.

**Table 5.27:** Analysis of risk factors associated with the LT graft survival data based on the multivariable parametric accelerated failure time models ($N$=490).

| Model | Factor | Coeffient | TR | (95%CI) | SE | $p$-value |
|---|---|---|---|---|---|---|
| **Exponential** | Intercept | 3.314 | | | | |
| | dnr_type | 0.702 | 2.02 | (1.18-3.45) | 0.273 | 0.010 |
| | diabetes | -0.793 | 0.45 | (0.29-0.70) | 0.223 | <0.001 |
| | recip_age | -0.128 | 0.89 | (0.83-0.93) | 0.029 | <0.001 |
| | ethnicity | -0.410 | 0.66 | (0.50-0.88) | 0.146 | 0.005 |
| | diabetes×recip_age | 0.081 | 1.08 | (1.03-1.14) | 0.026 | 0.002 |
| | Scale | 1.000 | | | | |
| | Shape | 1.000 | | | | |
| **Weibull** | Intercept | 3.112 | | | | |
| | dnr_type | 0.531 | 1.70 | (1.14-2.55) | 0.206 | 0.010 |
| | diabetes | -0.622 | 0.54 | (0.38-0.75) | 0.170 | <0.001 |
| | recip_age | -0.106 | 0.90 | (0.86-0.94) | 0.022 | <0.001 |
| | ethnicity | -0.317 | 0.73 | (0.59-0.91) | 0.111 | 0.004 |
| | diabetes×recip_age | 0.068 | 1.07 | (1.03-1.11) | 0.020 | <0.001 |
| | Scale | 0.748 | | | | |
| | Shape | 1.337 | | | | |
| **Log-normal** | Intercept | 2.820 | | | | |
| | dnr_type | 0.338 | 1.40 | (0.97-2.02) | 0.186 | 0.070 |
| | diabetes | -0.526 | 0.59 | (0.40-0.87) | 0.199 | 0.008 |
| | recip_age | -0.100 | 0.90 | (0.86-0.95) | 0.024 | <0.001 |
| | ethnicity | -0.427 | 0.65 | (0.52-0.83) | 0.120 | <0.001 |
| | diabetes×recip_age | 0.065 | 1.07 | (1.02-1.12) | 0.023 | 0.005 |
| | Scale | 1.035 | | | | |
| **Log-logistic** | Intercept | 2.812 | | | | |
| | dnr_type | 0.456 | 1.58 | (1.06-2.34) | 0.202 | 0.024 |
| | diabetes | -0.566 | 0.57 | (0.40-0.82) | 0.185 | 0.002 |
| | recip_age | -0.101 | 0.90 | (0.86-0.95) | 0.024 | <0.001 |
| | ethnicity | -0.425 | 0.65 | (0.52-0.83) | 0.119 | <0.001 |
| | diabetes×recip_age | 0.063 | 1.07 | (1.02-1.11) | 0.021 | 0.003 |
| | Scale | 0.586 | | | | |
| **Gamma** | Intercept | 2.931 | | | | |
| | dnr_type | 0.424 | 1.53 | (1.03-2.26) | 0.200 | 0.034 |
| | diabetes | -0.566 | 0.57 | (0.40-0.82) | 0.185 | 0.002 |
| | recip_age | -0.103 | 0.90 | (0.86-0.95) | 0.024 | <0.001 |
| | ethnicity | -0.394 | 0.67 | (0.53-0.85) | 0.120 | 0.001 |
| | diabetes×recip_age | 0.066 | 1.07 | (1.02-1.12) | 0.022 | 0.003 |
| | Scale | 0.939 | | | | |
| | Shape | 0.356 | | | | |

Reference category: dnr_type (cadaveric), diabetes (no) and ethnicity (white).

This indicates that no single patient observation influenced the parameter estimates for these covariates in the model.

**Table 5.28:** AIC values signifying the performance of the respective models in fitting LT graft survival analysis.

| Model | Cox | Exponential | Weibull | Log-normal | Log-logistic | Gamma |
|---|---|---|---|---|---|---|
| AIC | 2147.735 | 1591.870 | 1569.856 | 1563.227 | 1564.411 | 1563.955 |

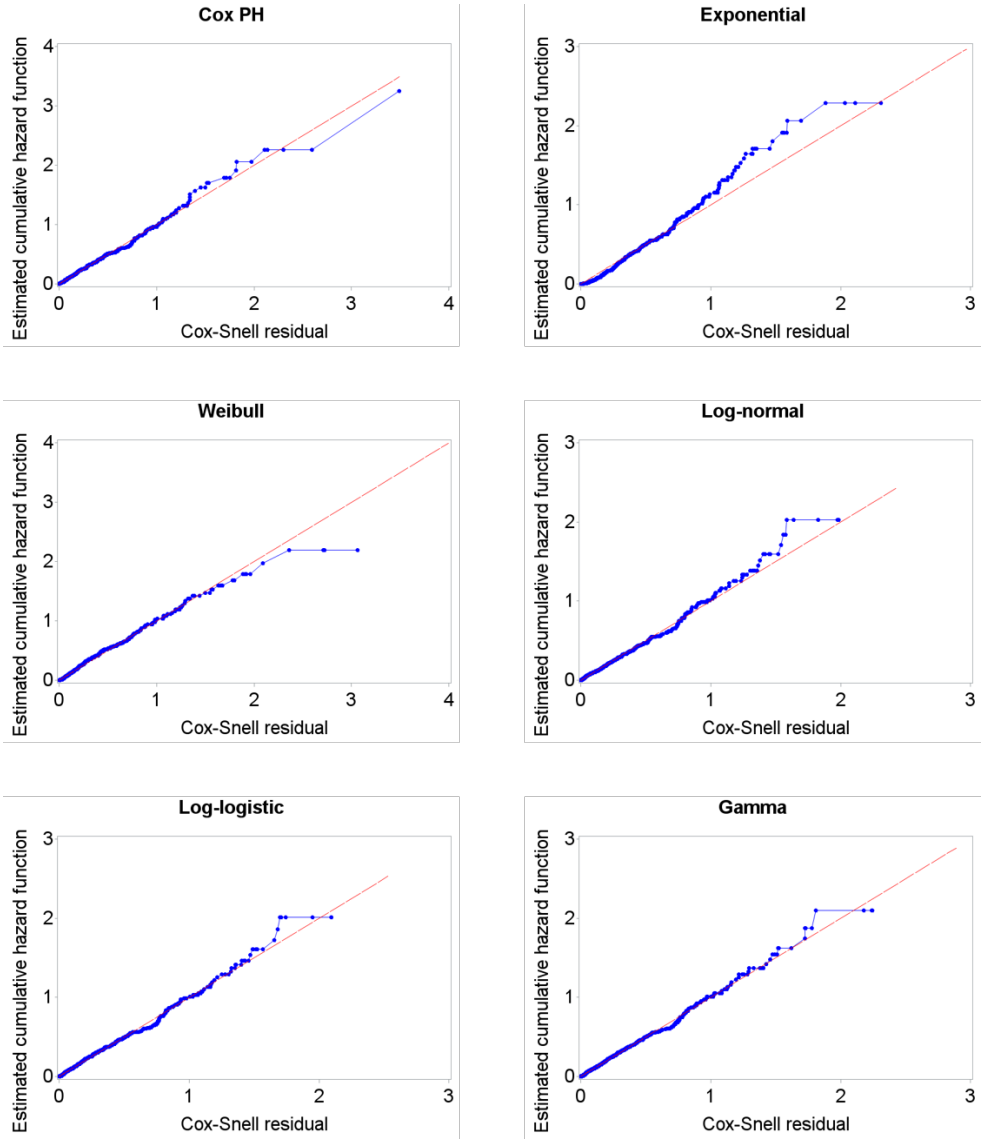


**Figure 5.21:** Cox-Snell residuals obtained from fitting the corresponding survival models to the LT graft survival data. The dashed lines represent the reference with a unit slope and zero intercept.

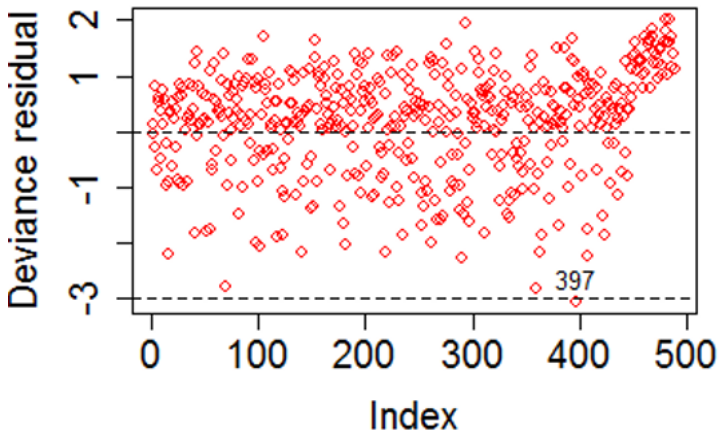


**Figure 5.22:** Assessment of goodness-of-fit using an index plot of the deviance residual for the log-normal model in the LT graft survival analysis.

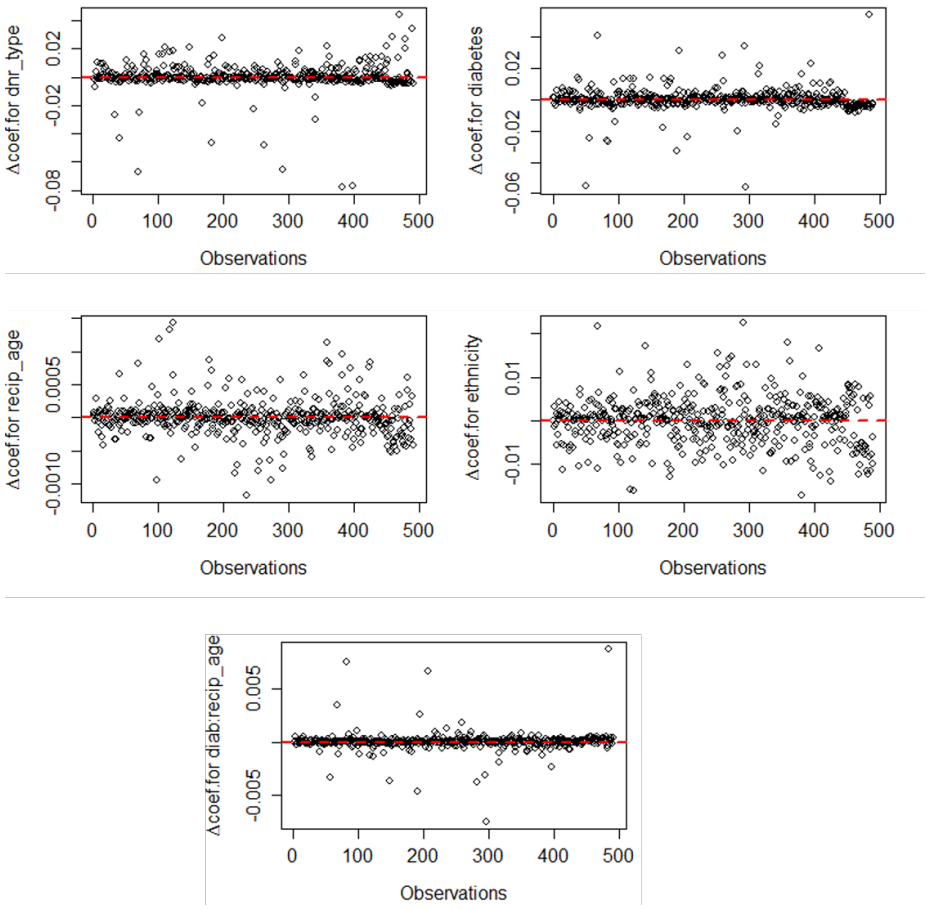


**Figure 5.23:** Graphs of the dfbeta statistic illustrating the diagnostics of the estimated regression coefficients for all the terms in the log-normal model for LT graft survival analysis.

### 5.4.5 Assessing goodness-of-fit of the log-normal model through simulation

The parameters estimated from the log-normal model using the real data (Table 5.27) were used for simulating a comparable cohort for LT analysis. The predictors with their respective effect size, distribution and proportion for the non-reference categories are detailed in Table 5.29. The event and censorship times are based on the log-normal distribution. The scale of the time to event, scale of the time to censorship, as well as their intercepts are indicated in the table footnote. Using a sample size of 490, we set a random seed of 250 and performed a simulation. The result of the log-normal model (based on the simulated data) suggests that all the predictors are significant risk factors of LT graft survival (Table 5.30, page 96). The log-normal fits from both the simulated and real data estimated comparable TR for diabetes, recipient age and diabetes-age interaction. The simulated fit suggests that LT graft survival for recipients of living kidneys is twice that of cadaveric kidney recipients, while the fit from the real data suggest the difference in graft survival between these groups is 40%. Also, the estimates from the real and simulated data show that non-white recipients had 35% and 41% shorter graft survival times compared to white patients, respectively. Hence, it can be concluded that the simulation-based data approximates the real data, indicating the log-normal model is reasonable for LT graft survival. Nevertheless, the Cox-Snell residual plot of the log-normal model based on the simulated data appears to provide a slightly better fit compared to log-normal model fit with the real data (Figure 5.24, page 96).

**Table 5.29:** Details of the predictors used for the simulation of a 490 cohort based on the log-normal model for the LT analyses.

| Factors | Coefficient | Distribution | Probability or mean(var) |
|---|---|---|---|
| dnr_type (living) | 0.338 | Bernoulli | 0.179591837 |
| diabetes (no) | -0.526 | Bernoulli | 0.079591837 |
| recipient_age | -0.100 | Normal | 0(119.932) |
| ethnicity (non-white) | -0.427 | Bernoulli | 0.377551020 |
| diabetes × recipient_age | 0.065 | Normal | -0.1820075(135.6675) |

seed=250, n=490, foltime=29, anc.ev=1.04, beta0.ev=2.8196, anc.cens= 0.853, beta0.cens=2.33159

**Table 5.30:** Goodness-of-fit assessment for LT graft survival analysis using the simulation-based method. The table shows comparisons between the estimated coefficients, time ratios with 95% confidence interval and $p$-values for the real (Real) and the log-normal-based simulated (Sim) data.

| Variable | Coefficient | | TR | | (95% CI) | | $p$-value | |
|---|---|---|---|---|---|---|---|---|
| | Real | Sim | Real | Sim | Real | Sim | Real | Sim |
| Intercept | 2.820 | 3.461 | | | | | | |
| dnr_type | 0.338 | 0.694 | 1.40 | 2.00 | (1.38-1.43) | (1.97-2.03) | 0.070 | <0.001 |
| diabetes | -0.526 | -0.530 | 0.59 | 0.59 | (0.58-0.60) | (0.57-0.60) | 0.008 | 0.043 |
| recip_age | -0.100 | -0.102 | 0.90 | 0.90 | (0.86-0.95) | (0.86-0.95) | <0.001 | <0.001 |
| ethnicity | -0.427 | -0.523 | 0.65 | 0.59 | (0.65-0.66) | (0.59-0.60) | <0.001 | <0.001 |
| diabetes×recip_age | 0.065 | 0.065 | 1.07 | 1.07 | (1.06-1.07) | (1.07-1.07) | 0.005 | <0.001 |

Reference category: dnr_type (cadaveric), diabetes (no) and ethnicity (white).

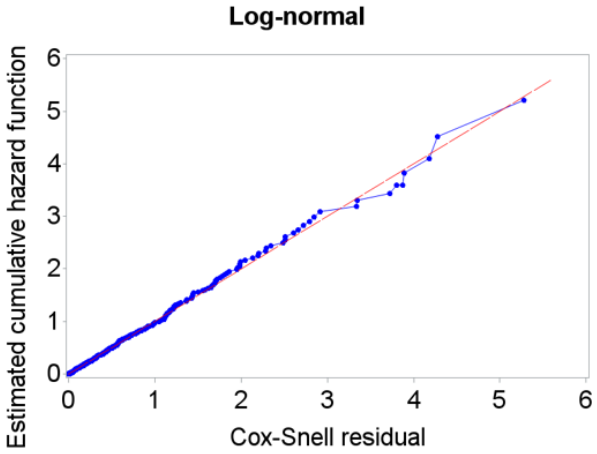


**Figure 5.24:** Cox-Snell residuals obtained from fitting a log-normal survival model to the simulated data in LT graft survival analysis. The dashed lines represent the reference with a unit slope and zero intercept.

# Chapter 6

# Discussion and Conclusion

## 6.1 Discussion

Kidney transplant remains the treatment of choice for a patient with ESKD because, a successful kidney transplant increases the patient's quality of life and life span. Several prognostic factors including recipient and donor related factors influence ST and LT graft survival (Paul, 1999; Irish et al., 2010). Proper modelling and identification of these factors is crucial to organ donors, recipients of new kidneys, organ transplant units and public health sectors, especially in most developing countries where resources for kidney re-transplants are limited. The Cox regression model is commonly used in analysing risk factors of both graft and patient survival post-kidney transplant because of its familiarity and convenience. However, parametric models provide a better description of kidney transplant data compared to the popular Cox regression model (Hashemian et al., 2013). To the best of our knowledge, this is the first study to analyse graft survival using a combination of semi-parametric and parametric models with data generated in South Africa.

We studied a subset of patients that received either living or cadaveric donor kidney in CMJAH during the cyclosporine immunosuppressive treatment era because of the following reasons: (1) innovation in surgical practices will not be captured if the entire cohort was analysed, (2) inconsistencies and changes in data capturing methods for some variables, which resulted in missing data and (3) many censored grafts due to the long follow-up of patients. The estimated graft survival rates for 1, 5, 10 and 15 years (82%, 67%, 51% and 37%, respectively) in this study favourably compare with local and international published studies (Wafa et al., 2011;

Ghoneim et al., 2013; Fabian et al., 2016). The hazard and the cumulative hazard plots enable visualisation of changes in the risk of graft failure throughout the follow-up period. Overall, this study reveals that the hazard of graft failure is most probable within the first year of a kidney transplant.

Fitting a large number of variables from a study could add noise to the estimated quantities, resulting in collinearity among the variables and increase the cost of modelling unnecessary predictors. With the help of variable selection in a model building procedure, a sub-group of these variables that describe the study data is selected. The purposeful selection method based on the Cox regression model was used in model building. This procedure for selecting, deleting, fitting and re-fitting a model helps to examine retention of each covariate in the model. Although this method seems complex especially when there are many predictors in the data, it results in a richer model (with significant factors and important confounders) compared to other selection methods when prediction and identification of risk factors is of interest (Hosmer Jr and Lemeshow, 1999; Bursac et al., 2008). Previous studies showed that factors selected in this study using the purposeful variable selection strategy influence survival of graft post-kidney transplant (McGee et al., 2010; Fabian et al., 2016). Out of 19 predictors included in the analyses, 'recipient age', 'donor type', 'ethnicity', 'diabetes', DGF, 'no_complication', 'nephrectomy' and 'ureteric' are the significant predictors of graft survival.

'Ethnicity' and 'diabetes' are the common variables selected in the three analyses (overall, ST and LT). 'No_complication', 'nephrectomy' and 'ureteric' were only selected in the ST analysis. All the variables selected in the LT data analysis are subset of variables selected in the overall data analysis. DGF was not selected in the LT analysis but rather in ST and overall data analyses. This is expected because earlier studies observed that DGF influences ST survival of the graft (McLaren et al., 1999; Quiroga et al., 2006). Factors including 'donor age', 'donor-recipient gender', 'acute rejection' and 'hypertension', previously shown to be important risk factors of graft survival (Tan et al., 2012; González-Molina et al., 2014; Koo et al., 2015), are neither significant nor confounders in this study. The difference between the findings of the present study and these studies (Tan et al., 2012; González-Molina et al., 2014; Koo et al., 2015) could be due to differences in sample size (number of graft failures observed), year of transplant, duration of follow-up and method of data analysis. It is noteworthy that our findings agree with studies that have shown that the aforementioned variables do not significantly affect graft survival (McGee et al., 2010; Shahbazi et al., 2015).

The final predictors selected in the overall data analysis are 'recipient age', 'donor type',

'recipient ethnicity', DGF and 'diabetes'. The linearity assumption is satisfied for 'recipient age' and none of the two-way interaction between these predictors was significant at the 5% level. Moreover, the PH assumption was not tenable for all these predictors, except donor type. As expected, the effects of study variables are prone to non-proportionality when the study period is long. Therefore, a follow-up period can be shortened if non-proportionality is established in a study (Moreau et al., 1985; Bellera et al., 2010). Furthermore, the focus of several kidney transplant studies is on factors that impact on ST and LT graft survival. The exploratory data analysis for the overall graft survival (Figure 5.1) supports the need to sub-divide the analysis into ST and LT analyses. Hence, the motivation to study the effect of these factors associated with survival of the grafted kidney regarding ST and LT follow-up periods with the overall follow-up period.

The three variables common to both the overall and ST graft analyses (DGF, 'diabetes' and 'ethnicity') violated the PH assumption in the overall graft survival analysis. However, only DGF violated the PH assumption in the ST graft survival. These variables exhibited varying behaviours across the two analyses (overall and ST graft survival); therefore, highlighting the need to partition the follow-up time when there is evidence of non-proportionality. In the PH assumption assessment for the LT graft survival analysis, 'diabetes' and 'recipient age' (which violated the PH assumption in the overall analysis) satisfied the PH assumption. Perhaps, this shows the influence of these predictors on graft survival (except 'donor type') differs across ST and LT analyses. Violating the PH assumption by a variable signifies a non-constant effect of that variable on the outcome of interest. That is to say that the resulting parameter estimates could be biased or inaccurate because the true estimate of the HR can be under or over-estimated when non-proportionality is present (Bellera et al., 2010). This observation (in this study) supports the relevance of PH assumption test, because the true HR of each study variable violating the PH assumption needs to be estimated at various time points throughout the follow-up period.

Having established the non-proportional effect of DGF and 'ethnicity' in the ST and LT analyses, stratified models were fitted to control the non-proportional effect of these variables. Also, a product term of 'DGF' or 'ethnicity' with some function of time was incorporated in the Cox PH model to account for time-dependency effect of these predictors on graft survival. Accounting for non-proportionality in this study, using the extension of the Cox PH model resulted in a more complete interpretation of the study findings. The extended Cox PH model was not considered in the overall analysis because the idea is to reduce the non-proportionality effect of the predictors on graft survival. Moreover, stratification method could lead to loss

of analytical power, which could be severe when multiple predictors are stratified. Stratifying the variable or including its interaction with time in a Cox regression model provides a more appropriate interpretation of its parameter estimates. This is supported by previous studies (Borucka, 2014; Abdelaal and Zakria, 2015), which reported that a stratification model and time-by-covariate interaction model outperformed the standard Cox regression model.

The estimation based on AFT models can be questionable if the underlying observed survival time distribution fails to follow the assumed distribution. Selecting parametric survival models based on prior knowledge of the outcome variable may not be sufficient in determining the underlying distribution of graft failure, post-kidney transplant. The hazard function profiles in the exploratory analyses provided invaluable information, which assisted in selecting appropriate AFT models for this study. Selecting the appropriate AFT model on the basis of the hazard shape function has been reported (Khanal et al., 2014). The hazard function plot in the overall analysis does not show well-defined characteristics; however, it displays a monotone decreasing function that suggests the Weibull model may provide a better fit. In the ST analysis, a decreasing hazard is observed, which is closer to a log-logistic distribution (when $k \leq 1$), log-normal (when $\sigma > 1$) and Weibull distributions (when $\gamma < 1$). The LT analysis illustrates that the baseline hazard functions are much closer to the shape of a log-normal and log-logistic distribution (uni-modal shape). Hence, we considered the Weibull, log-normal, log-logistics AFT models. The exponential model was also included because it is one of the standard parametric distributions used in survival analysis and is a special case of the Weibull model. The generalised gamma model was considered in this study because the exponential, Weibull and log-normal models are its special cases. Thus, the generalised gamma distribution was used to discriminate between the exponential, Weibull and log-normal models if the generalised gamma distribution provided a better fit.

One major impediment in survival analysis is the amount of censoring in a data. Nardi and Schemper (2003) suggested the percentage of censoring in a study should not be over 40-50% to discriminate among parametric models or to attain a proper fit of parametric models. Although, the percentage of right-censoring in this study is 57%, the parametric models show an appropriate fit. Other studies (Hashemian et al., 2013; Pourhoseingholi et al., 2011) with higher percentage (80% and 60%) of censoring reported appropriate fits of their parametric models. To compare the fitted models (goodness-of-fit), graphical and numerical procedures based on the Cox-Snell residuals, AIC and simulation-based study were used. Assessing and comparing model goodness-of-fit is a good practice prior to interpretation of the estimated parameters. The Cox-Snell residuals was applied in previous studies (Zare et al., 2013; Vahedi et al., 2016) to

evaluate model fits. The plot of Cox-Snell residuals used in this study enabled the visualisation of each model's performance. Therefore, the Cox regression model performed better than some parametric models in the analyses on the basis of the performance of the Cox-Snell residuals plot. The Cox-Snell residuals plot could result in a straight line even when the model fit is not appropriate. Hence, the Cox-Snell residuals plot may not be effective in detecting deviation from expected model-fit, except if the model fit is overtly inadequate (Collett, 2003). Collett (2003) suggested the use of other residuals methods such as the deviance and martingale residuals methods. Perhaps, this could be the reason the Cox PH model performance (on the basis of the Cox-Snell residuals and AIC) differs in certain conditions. Thus, it was important to use additional criteria to judge model performance.

This study further shows the need to assess the goodness-of-fit of a fitted model through a simulation-based method. Previous studies have shown the need for model evaluation through simulation methods (Allcroft and Glasbey, 2003; Burton et al., 2006). The simulation studies were based on the Weibull and log-normal distributions because these models provide appropriate fits in this study. To generate a simulated data comparable to the real data, we optimised the seed value. The seed chosen for each simulation study resulted in the most comparable data (to the real data). Parameter values were re-estimated and the Cox-Snell residuals were plotted based on the simulated data to observe if the simulated data is comparable the real data. Simulation-based approach used in this study shows that the fit of the models in the analyses are reasonable. Bar charts constructed for each of the categorical variables from the simulated data show that the simulated group proportion are comparable to the real data group proportions (Figure C.2, page 131). Distribution of 'recipient age' is approximately normal from the real data; however, this variable was simulated based upon a normal distribution. Therefore, this resulted in large variance in the simulated 'recipient age'. The estimated parameters for this variable using the real data are comparable with the parameters estimated using the simulated data. This validates the performance of the 'survsim' package in simulating a comparable survival population.

The present study reveals that the Weibull model is more appropriate in describing the graft survival distribution for the overall graft survival, which agrees with the hazard function curve (Figure 5.1C). In addition, the log-normal AFT model is more appropriate in describing the ST and LT graft survival distributions. This is also observed in the hazard function curve. It is convenient to expect that graft survival post-kidney transplant should follow a certain distribution; however, the findings of this study further affirms the need to examine the graft survival of a long follow-up study at different time points. Unfortunately, we could not

exhaustively compare the appropriate models in this study with earlier studies, because not much work has been done on kidney transplants using parametric models. However, Hashemian et al. (2013) analysed data collected over 5-years following kidney transplant and showed that the log-normal model provided the most appropriate fit for predicting the graft survival post-kidney transplant, while the exponential model was the worst model. In a review by Gore and Gore (1983), the authors reported that satisfying the assumption for an exponential distribution is rare in modelling graft survival. Similarly, the shapes of the baseline hazard in this study do not show that hazard of graft survival are constant following kidney transplant. This study also agrees with Hashemian et al. (2013), which showed poor model fit in modelling graft survival with the Cox regression model.

Most kidney transplant studies using the Cox regression model presented their findings in HR. It would have been convenient to relate the findings of this study with previous works using HR. However, we based the discussion and comparison on the parametric models reasonable in the three analyses (ST, LT and overall) because the Cox regression model did not provide the most appropriate fit of our data (in comparison with the AFT models). This study suggests 'recipient ethnicity' and 'diabetes' are important predictors of graft survival post-kidney transplant. The progression of graft failure accelerates depending on the ethnicity of the recipient, and the graft survival difference between white and non-white patients diminishes as time progresses. Based on the suitable models in ST and LT analyses, non-white patients had about 66% shorter graft survival times as compared to white recipients in the ST analysis, while in the LT analysis the survival difference reduced to 35%. Several studies reported that recipient ethnicity (or race) influenced graft survival (Schulman et al., 1992; Malek et al., 2011; Fabian et al., 2016). These studies (except Fabian et al. (2016)) also reported that non-white recipients have lower graft survival post-kidney transplant compared to white recipients.

The ethnicity variable in this study was originally captured in four categories 'white', 'black', 'Asian' and 'mixed'. However, there are insufficient frequencies for the 'Asian' and 'mixed' categories because these racial groups are the minorities in South Africa. These racial groups were not eliminated from the study; rather they were pooled with the 'black' category to form a single category ('non-white') to have fewer categories and sufficient frequencies for the ethnicity variable. The grouping of the ethnicity variable into 'white' and 'non-white' in this study is because about 9% of South African population is white; however, almost 60% of the patients in this study is white. This is related to what was reported by Moosa and Kidd (2006) and White et al. (2008) regarding the easy accessibility of kidney transplant by whites compared to other racial groups both in South Africa and the USA. Statistically, the KM estimates for the

ethnicity variable was plotted (Figure C.1), and the significance of this plot was assessed using the Cox PH model (Table C.1). 'Black' category was used as the reference category because it has neither the smallest nor the largest sample size. We observed that there is no graft survival difference between black patients and other racial groups except white. In addition, we observed that the assumption of PH was violated for this variable (Figure C.1B, Table C.2). Hence, we assessed and compared the graft survival of whites and non-whites in this study. However, we suggest further study could analyse the individual racial graft survival rate to shed more light on their distinct impact on graft survival, because collapsing of categories could result in loss of information. In Johannesburg region, Fabian et al. (2016) analysed a single centre kidney transplant data, but the mixed ethnicity patients were not included in the study because of fewer frequency and lower graft survival. The findings by Fabian et al. (2016) show Asian recipients, compared to white and black recipients, had higher graft survival. Although in the same region, the present study shows that Asian, compared to white recipients, experienced lower graft survival. The reason for the disparity between this study and that of Fabian et al. (2016), may be because Fabian et al. (2016), analysed kidney transplant data collected in new generation era (2004-2013), which may have a different demographic character compared to the CYA data used in this study.

The effect of diabetes on ST graft survival may not be correctly interpreted, because the estimates result in large standard errors with broader confidence intervals for all the models in ST analysis. This could not be due to multicollinearity amongst the predictors, because VIF was used to assess multicollinearity in the analyses. The highest VIF calculated is 1.196 in all the analyses, which shows that the predictors are either moderately correlated or not correlated. Hence, we suspect this could be a result of fewer incidences of diabetic patients with graft failure in ST analysis. Therefore, our interpretation of the effect of diabetes on graft survival is based on the LT and overall analyses because 'diabetes' is a common prognostic factor selected across the three analyses. The current study suggests that non-diabetic recipients experienced a better graft survival compared to diabetics. There is correlation between the findings of this study and that of previous work regarding the influence of diabetes at transplant on graft survival (Hariharan et al., 2002; Morales et al., 2012). Yet, Kim and Cheigh (2001) found no significant difference between non-diabetic and diabetic recipients regarding graft survival. Kim and Cheigh (2001) analysed 10 years data following kidney transplant and the statistical method used was KM with log-rank test, which does not adjust for other variables that could impact on graft survival. This present study also used univariable analysis and found 'diabetes' to influence graft survival in ST and LT analyses. Nonetheless, we found non-significant association between

diabetes and graft survival in the overall data analysis, which becomes significant when adjusted for other covariates. Maybe Kim and Cheigh (2001) would have found a significant relationship in their study if they had considered a multivariable model.

Previous studies by Morris et al. (1999) and Moosa (2003), highlighted the influence of recipient age in grafted kidney survival. This study supports the findings of these previous studies that the age of a kidney recipient at the time of transplant influences LT graft survival. We observed that the older the kidney recipient, the higher the chances of graft failure. Besides providing insights into the influence of recipient age and diabetes as individual predictors of graft survival, the outcome of the LT analysis identifies the interaction between recipient age and diabetes as a risk factor associated with graft failure rate. Perhaps, the reason 'age-diabetes interaction' was not significant ($p$=0.064, at the 5% level) in the overall analysis is because 'recipient age' have no significant impact on ST graft survival. Recipient age as a continuous variable was centered on the mean for ease of interpretation of the interaction effect. Centring this variable only causes a minor change in the estimated coefficient, but does not change the prediction. The interaction effect presented in this study reveals that the average influence of patients' age on survival of the graft is larger for non-diabetic patients compared to diabetic patients. Using a multivariable model, Morales et al. (2012) showed that diabetes interact with recipients'age (<40 years) in predicting graft survival.

In agreement with both local and international studies (Nemati et al., 2014; Fabian et al., 2016), this study affirms that 'donor type' significantly influence LT graft survival. We observed that graft survival is prolonged (doubled) among recipients of live kidneys in comparison with recipients of cadaveric kidneys. 'Donor-type' and 'recipient age' are not predictors of ST graft survival in this study. This shows that survival of the graft within the first year of kidney transplant is independent of the patient's age or whether the patient received a live or cadaveric kidney. In agreement with this finding, McGee et al. (2010) showed that 'recipient age' and 'donor type' do not significantly predict graft survival. Interestingly, the follow-up time analysed in the study (McGee et al., 2010) is too short to observe the non-effect of 'donor type' and 'recipient age' on graft survival.

The ST and overall survival analyses showed that DGF is associated with graft survival post-kidney transplant. Specifically, this study shows that DGF does not significantly influence LT graft survival, but rather influences graft survival within the first year of transplant. From a clinical perspective, this observation is reasonable and was reported in a study by McLaren et al. (1999). Another factor found to be associated with graft survival within the first 12

months of transplant is 'no surgical complication'. Based on the log-normal model, we found that patients that had surgical complications immediately after transplant experienced 70% shorter graft survival compared with patients that had no surgical complications. These two predictors ('DGF' and 'surgical complication') measured immediately after transplant seems to be correlated to detect the effectiveness of a kidney transplant. Perhaps, that is why they are both risk factors for ST graft survival.

## 6.2 Conclusion

Assessing and accounting for assumptions of the Cox model prior to its parameter interpretation should be an essential practice in analysing survival data on the basis of the Cox PH model. This study further emphasises the need to evaluate the interaction between covariates in predicting the outcome of interest because it assists with the appropriate interpretation of a covariate effect when a significant interaction is detected in a Cox PH model. This work has shown that the modified Cox regression model can provide a more detailed result interpretation when a time-varying covariate effect is detected in a Cox PH model. Although comparing the stratified with the non-stratified model is not straight forward due to different procedures in their constructions. However, each of these models has its unique advantages and disadvantages. Even though estimating HR using the Cox regression model is a frequent practice in medical research such as kidney transplant studies, interpretation of this quantity is more challenging especially to clinicians (Patel et al., 2006). The effects of predictors are modelled directly on survival time in AFT models. Therefore, clinicians can acquaint themselves with a predictor effect acting to either accelerate or decelerate graft survival time post-kidney transplant. Our study suggests that AFT models provide an appropriate summary of this study data when compared to the standard Cox PH model. Therefore, AFT models should be used as alternatives to the standard Cox PH model in modelling graft survival, after kidney transplant.

Overall, this study has shown the significance of simultaneously studying both ST and LT graft survival following kidney transplant because some of prognostic factors critical for ST and LT survival differ. The findings of this study affirm that surviving the first 12 months (ST) post-kidney transplant could be essential for LT survival. Therefore, controlling for DGF and 'surgical complications' is vital for the patient's graft to progress into the longer phase of survival. Although the type (living or cadaveric) of kidney donated may not be controlled for, receiving kidney from a living donor should be encouraged. Patients with diabetes and older

patients should not top the list of patients awaiting donor kidney.

We have used a rational approach in analysing this secondary data by using and comparing semi-parametric and parametric survival models. Inaccurate and inconsistent data recording are limitations in any secondary dataset because the analyst had no control over the data collection. However, these problems were checked in this study during the process of data cleaning. In addition, incomplete observation of some predictors is frequently encountered in a secondary data. The quality of statistical inferences made from a study is directly associated with the amount of missingness in the data. However, there is no conventional cut-off (from literature) for acceptable proportion of missingness in a data to enable validity in statistical inferences (Dong and Peng, 2013). Imputing the 17.7% cases dropped from the dataset would have added more information in this study. Even though these cases are missing completely at random (Table C.3, page 132), no attempt was made to imput these missing observations because imputation is beyond the scope of this study. Nonetheless, we believe the outcomes of this study is without bias because the deleted cases are missing completely at random. Moreover, Tabachnick and Fidell (2012) postulated that the mechanisms and patterns of missingness in a data have much larger influence on the results of a research than does the percentage of missingness in the data.

As previously mentioned, specifying the underlying survival time distribution is a drawback in using an AFT model. Future study using this data could apply the non-parametric AFT models to aid comparison with the standard AFT models. In addition, survival models such as the Aalen Additive model may provide an insight into the time-varying effect of DGF and 'ethnicity' on graft survival time.

Even though the follow-up period in this study was advantageously long, this study is limited to findings from a single centre with a small cohort of transplant patients ($N$=751). Therefore, this single centre data may not be representative of the entire South Africa. Similar graft survival studies from other parts of the country are needed to substantiate the findings of this study. Hence, knowledge of graft survival after kidney transplant in South Africa will be extended. This study also focused on one transplant era (the CYA era). Perhaps, analysing graft survival of patients that received kidney transplant during pre-CYA and new-generation eras may provide a better insight into prognostic factors of graft survival post-kidney transplant across these transplant eras. In addition, another notable limitation in this study is the absence of some covariates in the data. Potential covariates such as the period between EKSD diagnosis and transplant (waiting time), cold ischemic time and serum creatinine are significant covariates

that could have added value to this study. Studies have shown that lengthier waiting periods negatively impact on graft survival after kidney transplant (Meier-Kriesche et al., 2000; Gill et al., 2005). Also cold ischemic time (Kayler et al., 2011) and serum creatinine measured periodically after transplant have been studied as potential prognostic factor that influence graft survival (Hariharan et al., 2002).

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# Appendix A

# Short-term graft survival analysis

**Table A.1:** Univariable analysis of the relationship between the study variables and ST graft survival. $p$-values for the categorical variables and the continuous variables were calculated based on log-rank test and the Cox regression model results, respectively.

| **Variable** | ***p*-value** |
|---|---|
| dnr_type | 0.076 |
| renal_disease | 0.018 |
| hypertension | <0.001 |
| urological | 0.356 |
| inherited | 0.175 |
| nephrectomy | 0.048 |
| wound_sepsis | 0.510 |
| wound_haematoma | 0.204 |
| ureteric | 0.412 |
| no_complication | 0.014 |
| delayed_gf | <0.001 |
| diabetes | 0.007 |
| AR_clinical | 0.863 |
| AR_histological | 0.017 |
| new_gender | 0.604 |
| new_bloodgroup | 0.613 |
| ethnicity | <0.001 |
| dnr_age | 0.431 |
| recip_age | 0.102 |

**Table A.2:** Multivariable Cox regression model containing significant covariates at 25% level in the univariable analysis (Table A.1) for ST survival. The variable in bold font is deleted in the succeeding model.

| Model | Variable | $p$-value | % change | 2LL | 2LL diff | $p$-value |
|---|---|---|---|---|---|---|
| 1 | dnr_type | 0.669 | | 1455.056 | | |
| | renal_disease | 0.578 | | | | |
| | hypertension | 0.874 | | | | |
| | inherited | 0.503 | | | | |
| | nephrectomy | 0.035 | | | | |
| | **wound_haematoma** | 0.909 | | | | |
| | no_complication | 0.014 | | | | |
| | delayed_gf | 0.009 | | | | |
| | diabetes | 0.058 | | | | |
| | AR_histological | 0.046 | | | | |
| | ethnicity | 0.038 | | | | |
| | recip_age | 0.139 | | | | |
| 2 | dnr_type | 0.667 | 0.8 | 1455.069 | 0.013 | 0.909 |
| | renal_disease | 0.581 | 0.7 | | | |
| | **hypertension** | 0.867 | 5.4 | | | |
| | inherited | 0.505 | 0.3 | | | |
| | nephrectomy | 0.033 | 0.5 | | | |
| | no_complication | 0.007 | 1.7 | | | |
| | delayed_gf | 0.009 | 0.1 | | | |
| | diabetes | 0.058 | 0.2 | | | |
| | AR_histological | 0.047 | 0.1 | | | |
| | ethnicity | 0.039 | 0.2 | | | |
| | recip_age | 0.140 | 0.3 | | | |
| 3 | dnr_type | 0.664 | 0.8 | 1455.098 | 0.028 | 0.866 |
| | **renal_disease** | 0.457 | 15.5 | | | |
| | inherited | 0.453 | 7.4 | | | |
| | nephrectomy | 0.032 | 0.6 | | | |
| | no_complication | 0.007 | 0.7 | | | |
| | delayed_gf | 0.009 | 0.3 | | | |
| | diabetes | 0.058 | 0.1 | | | |
| | AR_histological | 0.047 | 0.0 | | | |
| | ethnicity | 0.016 | 3.7 | | | |
| | recip_age | 0.132 | 1.3 | | | |
| 4 | **dnr_type** | 0.625 | | 1455.657 | | |
| | inherited | 0.575 | | | | |
| | nephrectomy | 0.032 | | | | |
| | no_complication | 0.006 | | | | |
| | delayed_gf | 0.010 | | | | |
| | diabetes | 0.049 | | | | |
| | AR_histological | 0.049 | | | | |
| | ethnicity | 0.003 | | | | |
| | recip_age | 0.110 | | | | |
| 5 | **inherited** | 0.565 | 2.7 | 1455.904 | 0.248 | 0.619 |
| | nephrectomy | 0.033 | 0.6 | | | |
| | no_complication | 0.006 | 0.2 | | | |
| | delayed_gf | 0.008 | 2.6 | | | |
| | diabetes | 0.049 | 0.2 | | | |
| | AR_histological | 0.047 | 0.8 | | | |
| | ethnicity | 0.002 | 2.3 | | | |
| | recip_age | 0.078 | 7.4 | | | |
| 6 | nephrectomy | 0.031 | 0.9 | 1456.256 | 0.352 | 0.553 |
| | no_complication | 0.006 | 0.5 | | | |
| | delayed_gf | 0.007 | 1.6 | | | |
| | diabetes | 0.051 | 0.8 | | | |
| | AR_histological | 0.046 | 0.7 | | | |
| | ethnicity | 0.001 | 4.7 | | | |
| | recip_age | 0.085 | 2.8 | | | |

**Table A.3:** Result of adding covariates not significant at the univariable ST graft survival analysis (Table A.1) to the multivariable Model 6. The $p$-value with * is for the likelihood ratio test, %$\Delta$ if the highest change in estimated the coefficients of other variables in the model.

| **Model** | | ***p*-value** | **-2LL** | **-2LL$\Delta$** | ***p*-value*** | **%$\Delta$** |
|---|---|---|---|---|---|---|
| Model 6 | | | 1456.256 | | | |
| Model 6 + urological | | 0.700 | 1456.100 | 0.156 | 0.984 | 1.9 |
| Model 6 + wound_sepsis | | 0.298 | 1455.135 | 1.121 | 0.772 | 13.2 |
| Model 6 + ureteric | | 0.056 | 1451.650 | 4.606 | 0.203 | 12.2 |
| Model 6 + uretric + AR_clinical | | 0.693 | 1451.494 | 0.155 | 0.984 | 0.8 |
| Model 6 + uretric + new_gender | | | 1449.916 | 1.734 | 0.629 | 3.8 |
| | ff | 0.280 | | | | |
| | mf | 0.545 | | | | |
| | mm | 0.220 | | | | |
| Model 6 + uretric + new_bloodgroup | | 0.811 | 1451.594 | 0.056 | 0.997 | 0.7 |
| Model 6 + uretric + dnr_age | | 0.394 | 1450.916 | 0.733 | 0.865 | 2.6 |
| (Model 6 + ureteric) - recip age | | 0.128 | 1453.972 | 2.323 | 0.508 | 7.8 |
| ((Model 6 + ureteric) - recip age) - AR_hist | | 0.054 | 1457.388 | 3.416 | 0.332 | 13.3 |

*ff* (female to female), *mf* (male to female) and *mm*(male to male).

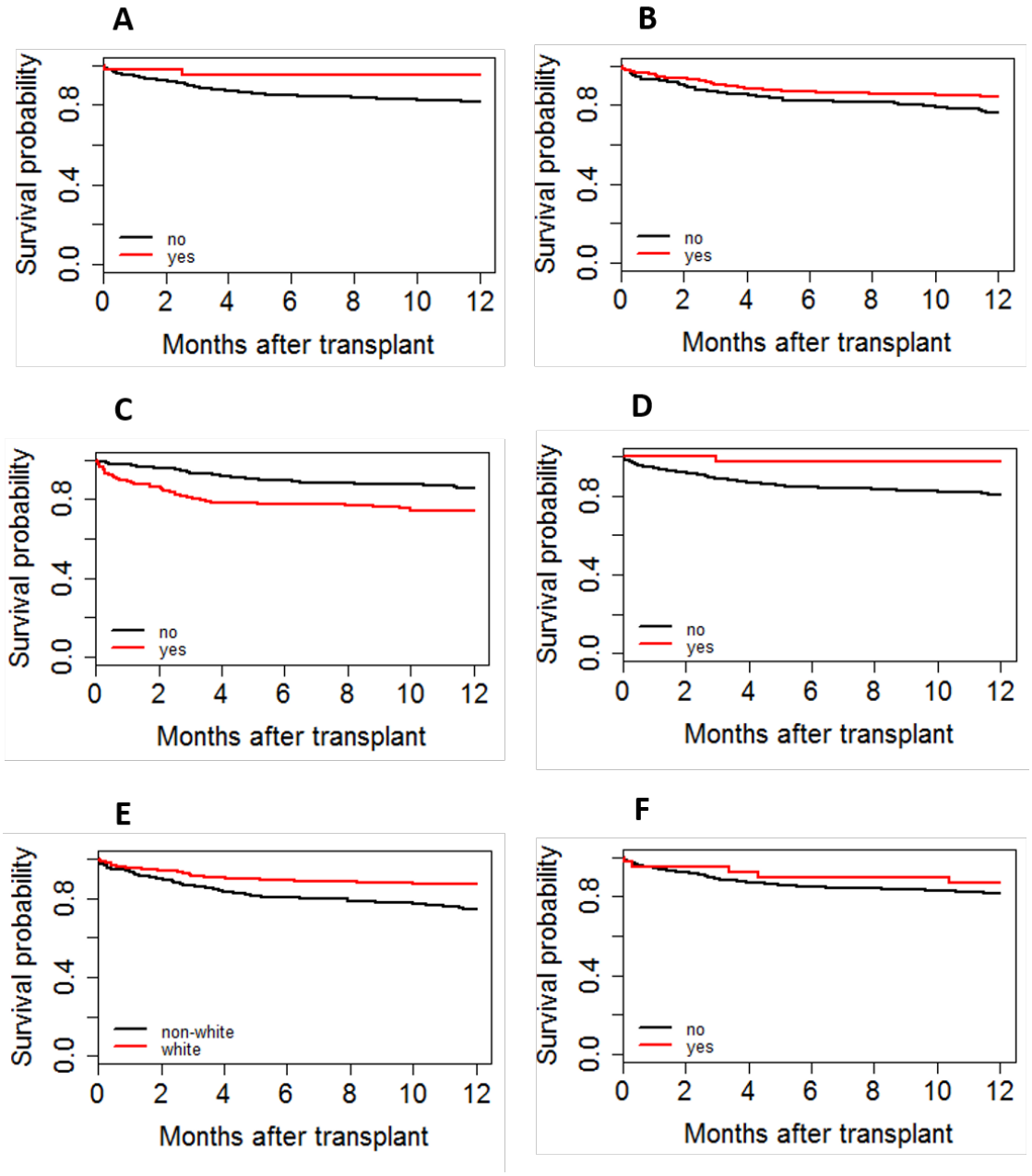


**Figure A.1:** Graphs of KM estimates of survival function for (A) nephrectomy, (B) no_complication, (C) delayed_gf, (D) diabetes, (E) ethnicity and (F) ureteric for ST graft survival analysis ($N$=751).

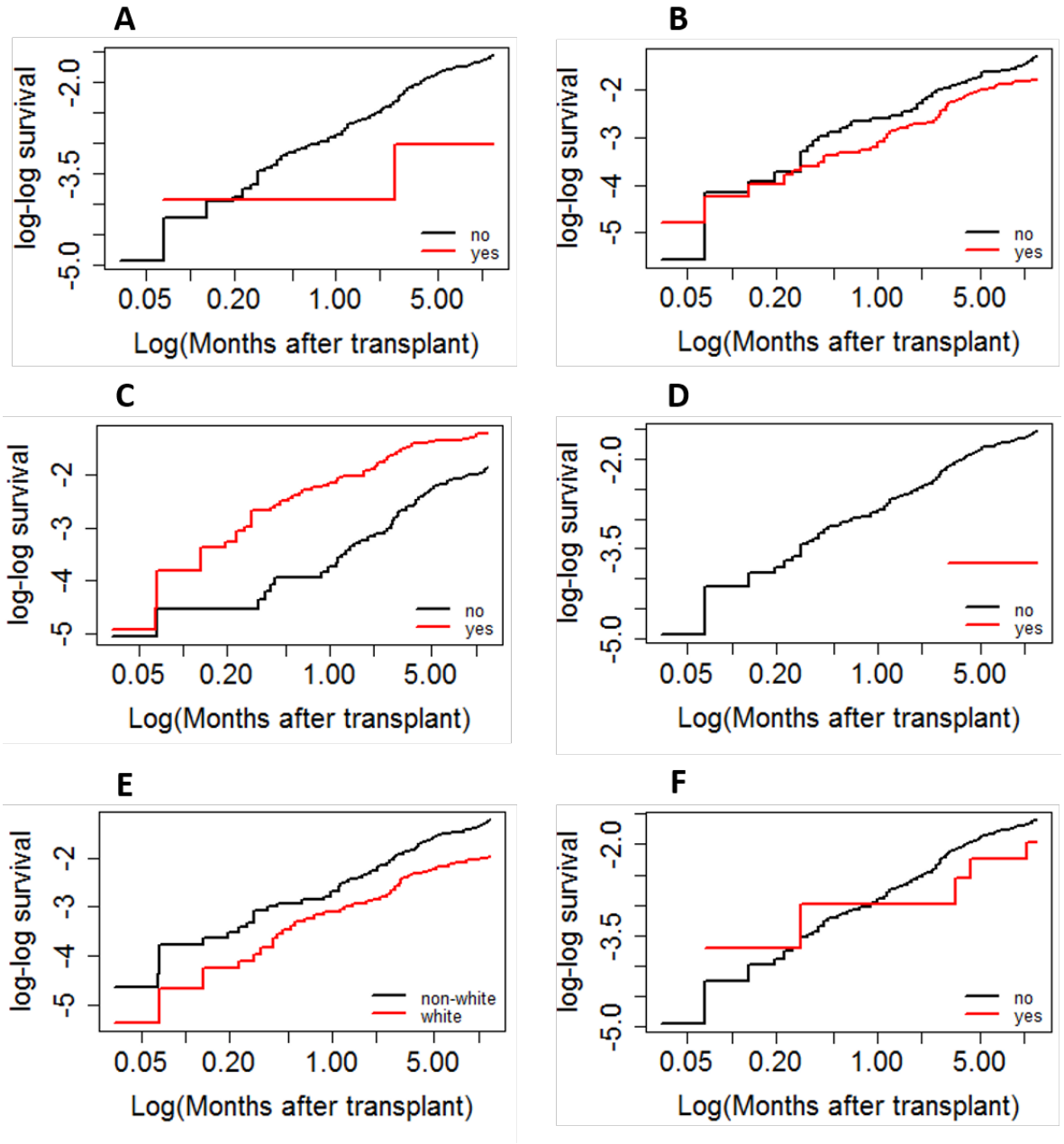


**Figure A.2:** Graphs of log cumulative hazards for (A) nephrectomy, (B) no_complication, (C) delayed_gf, (D) diabetes, (E) ethnicity and (F) ureteric for ST graft survival analysis ($N$=751).

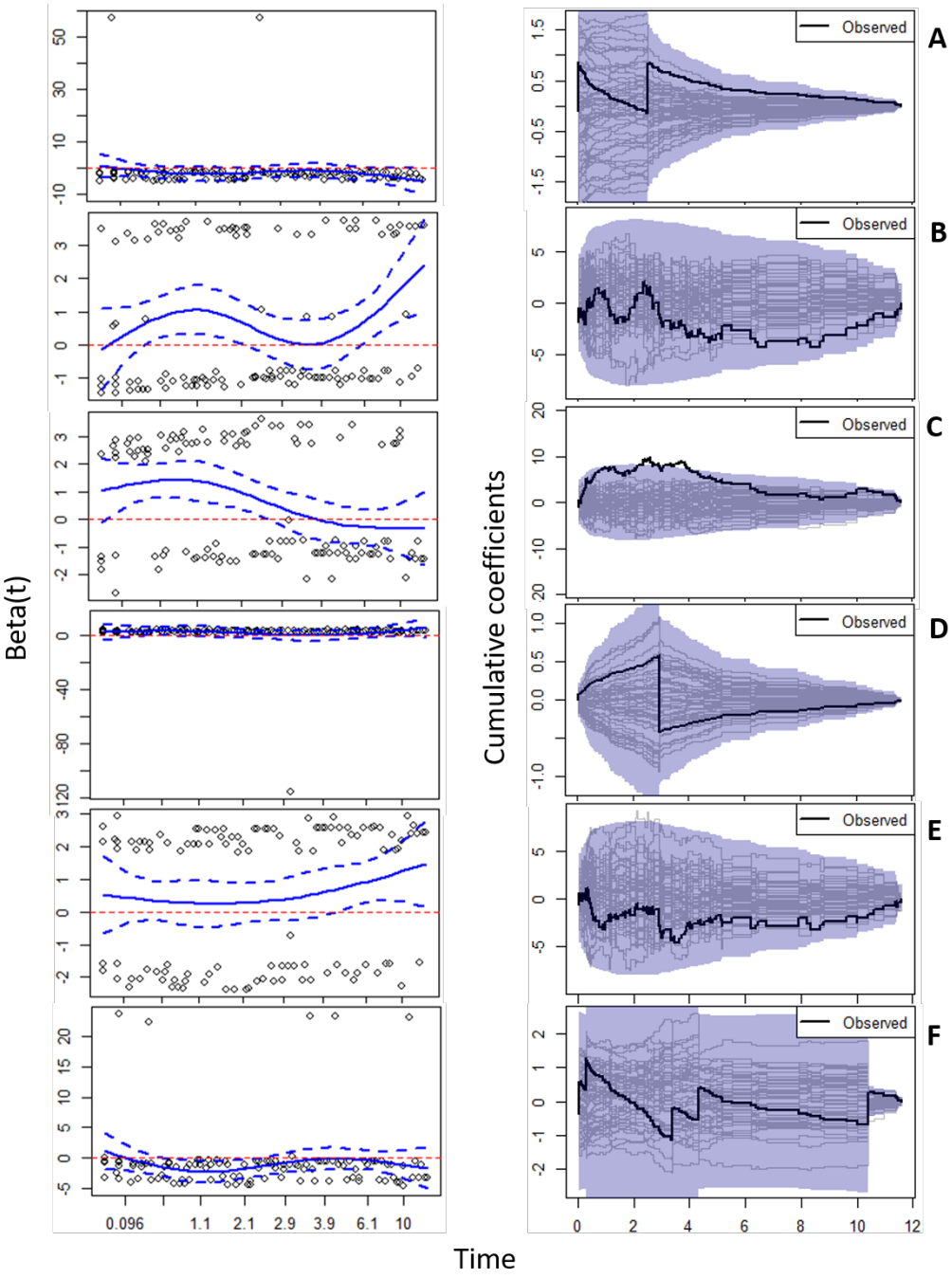


**Figure A.3:** Assessment of PH assumption for ST graft survival analysis. Left-panel: graphs of the scaled Schoenfeld residuals versus transformed time for each covariate in the Cox regression model. The solid and the broken lines represent the smoothing spline fit and the ±2 standard error for the fit. Right-panel: graphs of observed test process with 50 simulated process for each covariate in the Cox PH model. The solid black profile signifies the observed pattern. (A) nephrectomy, (B) no_complication, (C) delayed_gf, (D) diabetes (E) ethnicity and (F) ureteric.

**Table A.4:** Non-proportionality test in the stratified Cox regression with no-interaction model for ST graft survival. $p$-value* is for the cumulative residuals tests.

| **Variable** | **rho** | **chisq** | ***p*-value** | ***p*-value*** |
|---|---|---|---|---|
| no_complication | 0.094 | 1.055 | 0.304 | 0.740 |
| diabetes | 0.021 | 0.050 | 0.822 | 0.240 |
| ethnicity | 0.127 | 2.014 | 0.156 | 0.760 |
| ureteric | -0.004 | 0.002 | 0.961 | 0.600 |
| GLOBAL | NA | 3.241 | 0.518 | |

**Table A.5:** Result of variance inflation factor for assessment of multi-collinearity among the predictors based on the Cox PH model used for model building and the log-normal model as the most appropriate model in the ST analysis.

| | **nephrectomy** | **no_complication** | **delayed_gf** | **diabetes** | **ethnicity** | **ureteric** |
|---|---|---|---|---|---|---|
| **VIF (Cox)** | 1.024 | 1.093 | 1.023 | 1.004 | 1.019 | 1.071 |
| **VIF (log-normal)** | 1.092 | 1.196 | 1.028 | 1.032 | 1.048 | 1.114 |

# Appendix B

# Long-term graft survival analysis

**Table B.1:** Univariable analysis of the relationship between the study variables and LT graft survival. $p$-values for the categorical variables and the continuous variables were calculated based on log-rank test and the Cox regression model results, respectively.

| **Variable** | ***p*-value** |
|---|---|
| dnr_type | <0.001 |
| renal_disease | 0.589 |
| hypertension | 0.230 |
| urological | 0.164 |
| inherited | 0.202 |
| nephrectomy | 0.858 |
| wound_sepsis | 0.158 |
| wound_haematoma | 0.757 |
| ureteric | 0.589 |
| no_complication | 0.641 |
| delayed_gf | 0.576 |
| diabetes | 0.002 |
| AR_clinical | 0.667 |
| AR_histological | 0.455 |
| new_gender | 0.762 |
| new_bloodgroup | 0.365 |
| ethnicity | 0.064 |
| dnr_age | 0.416 |
| recip_age | <0.001 |

**Table B.2:** Multivariable Cox regression model containing significant covariates at 25% level in the univariable analysis (Table B.1) for LT survival. The variable in bold font is deleted in the succeeding model

| Model | Variable | *p*-value | % change | -2LL | -2LL Δ | *p*-value |
|---|---|---|---|---|---|---|
| 1 | dnr_type | 0.014 | 0.0 | 2143.734 | | |
| | hypertension | 0.404 | 0.0 | | | |
| | urological | 0.512 | 0.0 | | | |
| | inherited | 0.045 | 0.0 | | | |
| | **wound_sepsis** | 0.667 | 0.0 | | | |
| | diabetes | <0.001 | 0.0 | | | |
| | ethnicity | 0.015 | 0.0 | | | |
| | recip_age | <0.001 | 0.0 | | | |
| 2 | dnr_type | 0.015 | 1.4 | 2143.916 | 0.182 | 0.670 |
| | hypertension | 0.414 | 2.3 | | | |
| | **urological** | 0.516 | 0.9 | | | |
| | inherited | 0.042 | 1.4 | | | |
| | diabetes | <0.001 | 1.5 | | | |
| | ethnicity | 0.014 | 1.1 | | | |
| | recip_age | <0.001 | 0.7 | | | |
| 3 | dnr_type | 0.015 | 0.6 | 2144.360 | 0.444 | 0.505 |
| | **hypertension** | 0.423 | 2.1 | | | |
| | inherited | 0.049 | 3.5 | | | |
| | diabetes | <0.001 | 2.7 | | | |
| | ethnicity | 0.010 | 3.7 | | | |
| | recip_age | <0.001 | 0.3 | | | |
| 4 | dnr_type | 0.016 | 1.2 | 2145.004 | 0.644 | 0.422 |
| | inherited | 0.064 | 7.8 | | | |
| | diabetes | <0.001 | 2.3 | | | |
| | ethnicity | 0.012 | 11.0 | | | |
| | recip_age | <0.001 | 1.8 | | | |

**Table B.3:** Result of adding covariates (except for [a]) not significant at the univariable LT graft survival analysis (Table B.1) to the multivariable Model 4. $p$-value* is for the likelihood ratio test, %Δ if the highest change in estimated the coefficients of other variables in the model.

| **Variable** | ***p*-value** | **-2LL** | **-2LL Δ** | ***p*-value*** | **%Δ** |
|---|---|---|---|---|---|
| Model 4 | | 2145.004 | | | |
| Model 4 + nephrectomy | 0.791 | 2144.935 | 0.069 | 0.793 | 0.6 |
| Model 4 + wound_haematoma | 0.560 | 2144.647 | 0.357 | 0.550 | 1.2 |
| Model 4 + ureteric | 0.821 | 2144.954 | 0.050 | 0.823 | 0.6 |
| Model 4 + no_complication | 0.985 | 2145.004 | 0.000 | 0.985 | 0.1 |
| Model 4 + delayed_gf | 0.752 | 2144.905 | 0.099 | 0.753 | 2.2 |
| Model 4 + AR_clinical | 0.687 | 2144.841 | 0.163 | 0.686 | 1.5 |
| Model 4 + AR_histological | 0.619 | 2144.748 | 0.255 | 0.613 | 1.8 |
| Model 4 + new_gender | | 2142.216 | 2.788 | 0.095 | 5.8 |
| ff | 0.425 | | | | |
| mf | 0.900 | | | | |
| mm | 0.688 | | | | |
| Model 4 + new_bloodgroup | 0.923 | 2144.995 | 0.009 | 0.923 | 0.5 |
| Model 4 + dnr_age | 0.952 | 2145.000 | 0.004 | 0.952 | 0.6 |
| Model 4 + renal_disease | 0.860 | 2144.973 | 0.031 | 0.860 | 0.3 |
| Model 4 - inherited[a] | 0.064 | 2148.821 | 3.818 | 0.051 | 10.7 |

*ff* (female to female), *mf* (male to female) and *mm* (male to male).

**Table B.4:** Non-proportionality test in the stratified Cox regression with no-interaction model for LT graft survival. $p$-value* is for the cumulative residuals tests.

| **Variable** | **rho** | **chisq** | ***p*-value** | ***p*-value*** |
|---|---|---|---|---|
| dnr_type | -0.048 | 0.456 | 0.499 | 0.615 |
| diabetes | 0.075 | 1.155 | 0.283 | 0.076 |
| recip_age | 0.027 | 0.161 | 0.688 | 0.385 |
| diabetes:recip_age | 0.005 | 0.005 | 0.943 | 0.576 |
| **GLOBAL** | NA | 1.711 | 0.789 | |

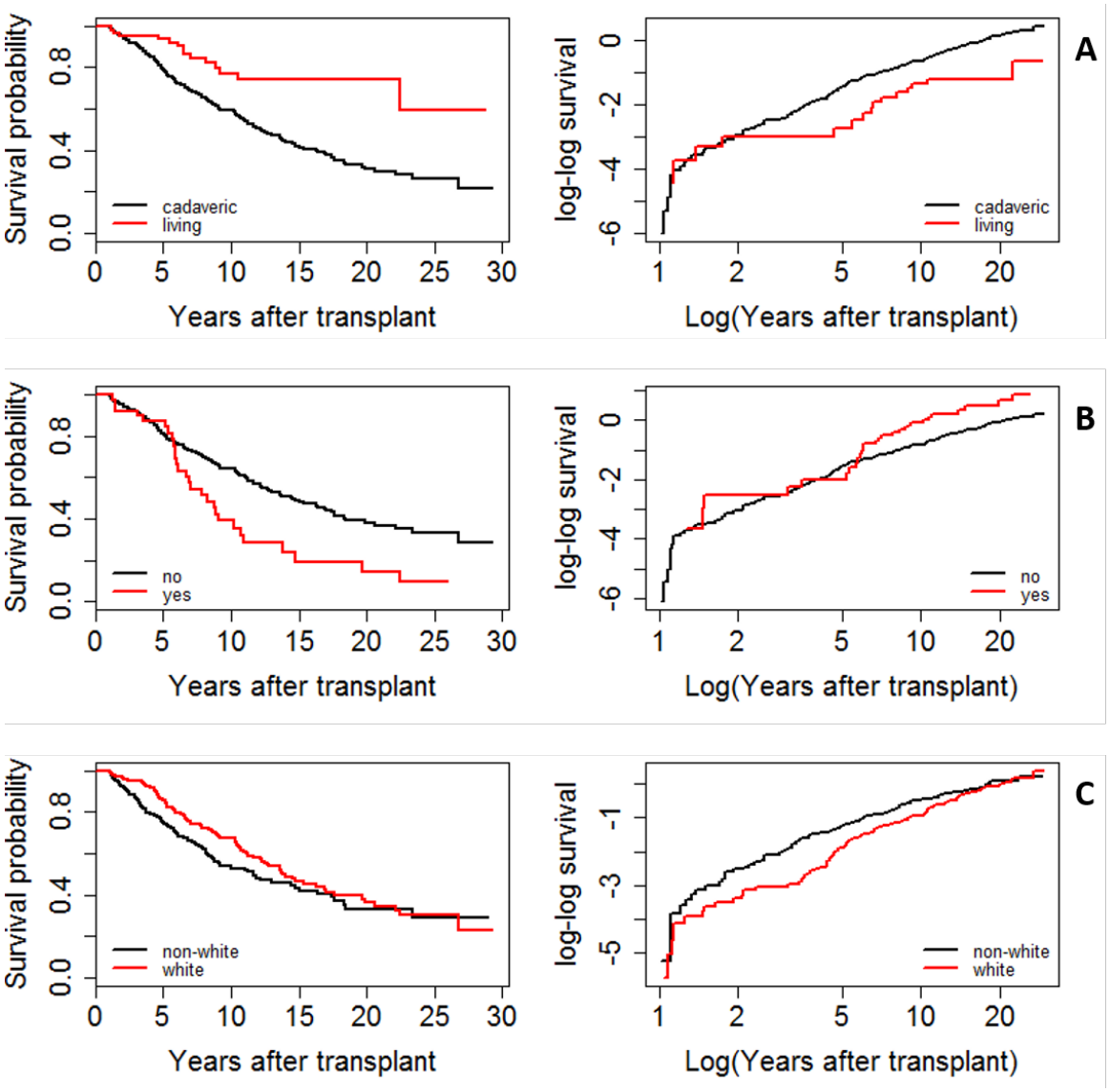


**Figure B.1:** Graphs of KM estimates of survival function (left panels) and log cumulative hazards (right panels) for (A) dnr_type, (B) diabetes and (C) ethnicity for LT graft survival analysis ($N$=490).

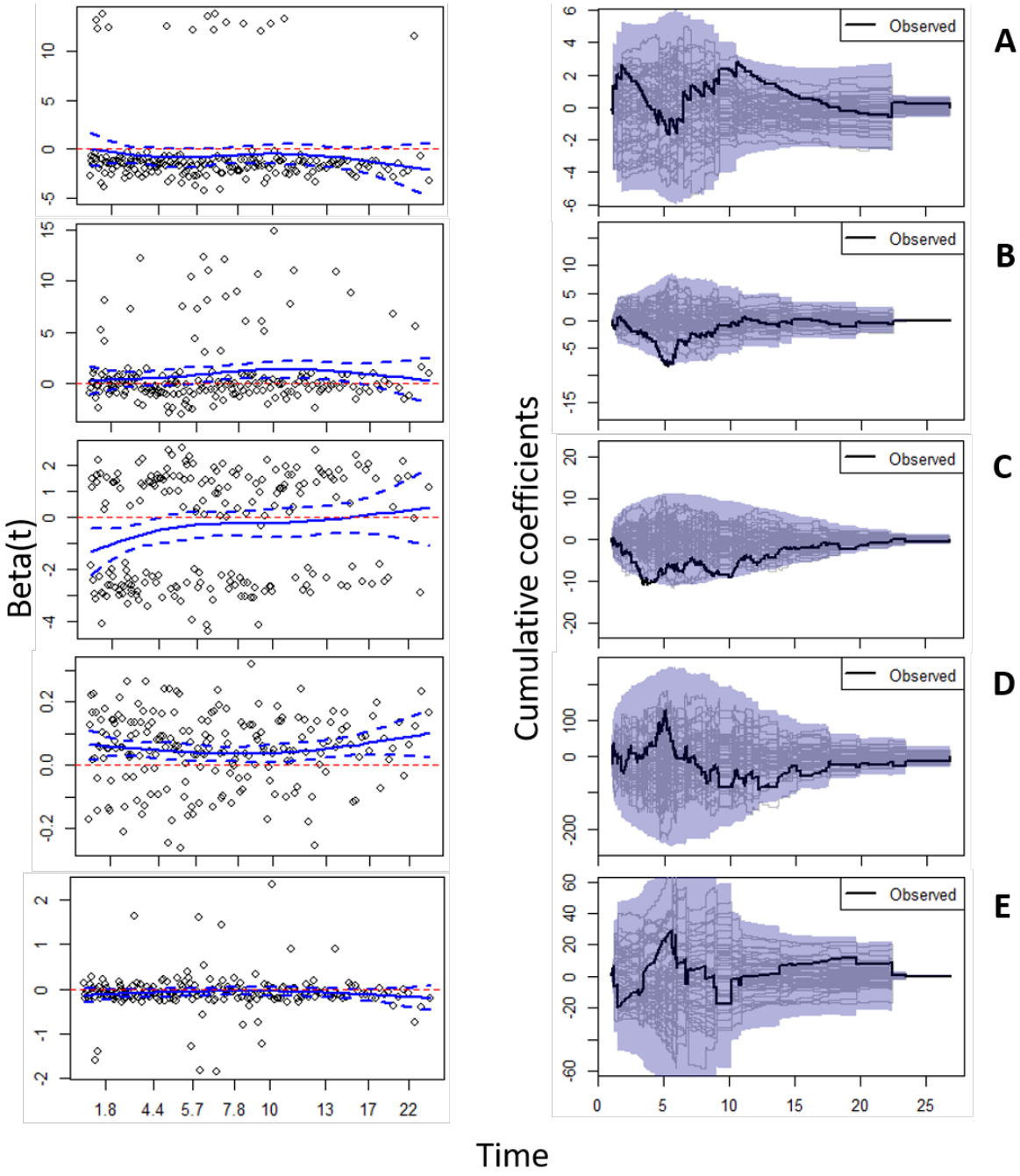


**Figure B.2:** Assessing of PH assumption for LT graft survival analysis. Left-panel: graphs of the scaled Schoenfeld residuals versus transformed time for each covariate in the Cox regression model. The solid and the broken lines represent the smoothing spline fit and the $\pm 2$ standard error for the fit. Right-panel: graphs of observed test process with 50 simulated process for each covariate in the Cox PH model. The solid black profile signifies the observed pattern. (A) dnr_type, (B) diabetes, (C) ethnicity, (D) recip_age and (E) diabetes:recip_age.

**Table B.5:** Result of variance inflation factor for assessment of multi-collinearity among the predictors based on the Cox PH model used for model building and the log-normal model as the most appropriate model in the LT analysis.

| | **dnr_type** | **diabetes** | **recip_age** | **ethnicity** | **diabetes × recip_age** |
|---|---|---|---|---|---|
| **VIF (Cox)** | 1.037 | 1.208 | 1.224 | 1.078 | 1.226 |
| **VIF (log-normal)** | 1.074 | 1.138 | 1.201 | 1.068 | 1.156 |

# Appendix C

# Overall graft survival analysis

**Table C.1:** Univariable analysis of the relationship between ethnicity and overall graft survival.

| Variable | Coefficient | HR | 95% CI | SE | *p*-value |
|---|---|---|---|---|---|
| ethnicity(white) | -0.456 | 0.634 | (0.50-0.81) | 0.124 | <0.000 |
| ethnicity(mixed) | -0.342 | 0.710 | (0.46-1.09) | 0.219 | 0.119 |
| ethnicity(asian) | 0.369 | 1.447 | (0.91-2.29) | 0.234 | 0.115 |

**Table C.2:** Non-proportionality test for ethnicity variable.

| Variable | rho | chisq | *p*-value |
|---|---|---|---|
| ethnicity(white) | 0.200 | 12.750 | <0.000 |
| ethnicity(mixed) | 0.103 | 3.340 | 0.068 |
| ethnicity(asian) | 0.104 | 3.550 | 0.059 |
| GLOBAL | | 13.730 | 0.003 |

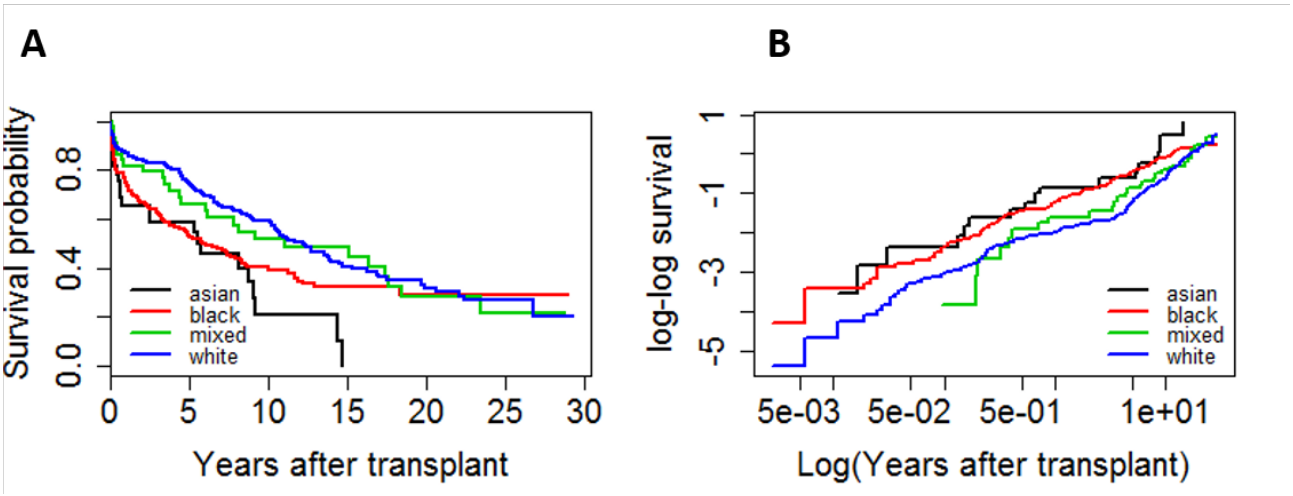


**Figure C.1:** Graphs of KM estimates of survival function (A) and log cumulative hazards (B) for ethnicity variable.

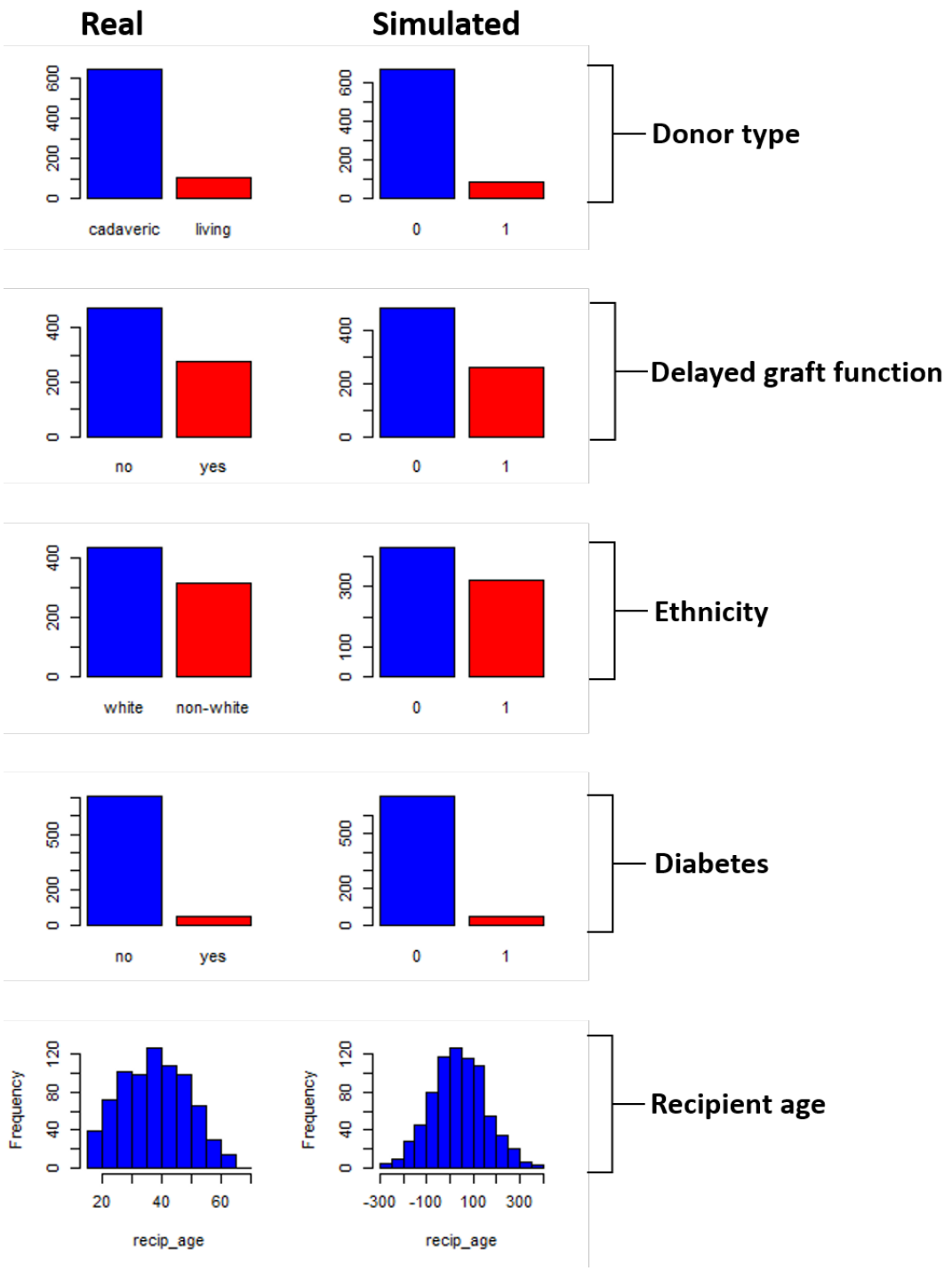


**Figure C.2:** Representative bar charts and histograms illustrating how comparable the covariates in the real and the simulated data are with respect to their proportions or distribution (for recipient age) for the overall analyses. The bar colours in the real and the simulated data corresponds with each other.

**Table C.3:** Summary of Little's missing completely at random test for all the study variables.

| **Variable** | ***p*-value** |
|---|---|
| dnr_age | 0.938 |
| ethnicity | 0.147 |
| recip_age | NM |
| donor_type | 0.934 |
| renal_disease | NM |
| hypertension | NM |
| urological | NM |
| inherited | NM |
| surgical complications | 0.069 |
| delayed_gf | 0.153 |
| diabetes | 0.086 |
| AR_clinincal | NM |
| AR-histological | NM |
| new_gender | 0.885 |
| new_bloodgroup | 0.490 |

NM (no missing observation); variables under surgical complications are nephrectomy, wound_sepsis, wound_haematoma, ureteric and no_complication

**Table C.4:** Result of variance inflation factor for assessment of multi-collinearity among the predictors based on the Cox PH model used for model building and the Weibull model as the most appropriate model in the overall analysis.

| | **recip_age** | **dnr_type** | **ethnicity** | **delayed_gf** | **diabetes** |
|---|---|---|---|---|---|
| **VIF (Cox)** | 1.071 | 1.059 | 1.065 | 1.035 | 1.050 |
| **VIF (Weibull)** | 1.111 | 1.074 | 1.090 | 1.039 | 1.058 |

# Appendix D

# Supplementary analysis

**Table D.1:** Variable selection using AIC, BIC and the LASSO methods for imputed data (*N=915*) and complete case data (*N=751*). ✓for selected and ✗for not selected.

| **Variable** | **AIC** | | **BIC** | | **LASSO** | |
|---|---|---|---|---|---|---|
| | *N=915* | *N=751* | *N=915* | *N=751* | *N=915* | *N=751* |
| AR_histological | ✗ | ✗ | ✗ | ✗ | ✓ | ✓ |
| delayed_gf | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| diabetes | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ |
| donor_type | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ |
| ethnicity | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| gender | ✗ | ✗ | ✗ | ✗ | ✓ | ✓ |
| inherited | ✗ | ✓ | ✗ | ✗ | ✓ | ✓ |
| nephrectomy | ✗ | ✗ | ✗ | ✗ | ✗ | ✓ |
| no_complication | ✓ | ✗ | ✗ | ✗ | ✓ | ✓ |
| Recip_Age | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| ureteric | ✗ | ✗ | ✗ | ✗ | ✓ | ✓ |
| urological | ✗ | ✗ | ✗ | ✗ | ✓ | ✓ |

**Table D.2:** Add caption

| **Data** | **Variables** | **AIC** | | | **BIC** | | | **LASSO** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Coef | SE | $p$-value | Coef | SE | $p$-value | Coef | SE | $p$-value |
| | delayed_gf | 0.352 | 0.110 | 0.001 | 0.392 | 0.108 | <0.001 | 0.343 | 0.113 | 0.002 |
| | diabetes | 0.457 | 0.180 | 0.011 | | | | 0.403 | 0.185 | 0.030 |
| | donor_type | -0.415 | 0.185 | 0.025 | | | | -0.443 | 0.188 | 0.019 |
| N=915 | ethnicity | 0.404 | 0.105 | <0.001 | 0.377 | 0.103 | <0.001 | 0.371 | 0.108 | 0.001 |
| | no_complication | | | | | | | -0.240 | 0.115 | 0.038 |
| | Recip_Age | 0.030 | 0.005 | <0.001 | 0.032 | 0.005 | <0.001 | 0.031 | 0.005 | <0.001 |
| | delayed_gf | 0.291 | 0.121 | 0.016 | 0.340 | 0.119 | 0.004 | 0.285 | 0.124 | 0.022 |
| | diabetes_tx | 0.403 | 0.200 | 0.044 | | | | | | |
| N=751 | donor_type | -0.460 | 0.207 | 0.026 | | | | -0.477 | 0.210 | 0.023 |
| | ethnicity | 0.445 | 0.117 | <0.001 | 0.463 | 0.113 | <0.001 | 0.423 | 0.119 | <0.001 |
| | Recip_Age | 0.033 | 0.006 | <0.001 | 0.034 | 0.005 | <0.001 | 0.033 | 0.006 | <0.001 |

# Appendix E

# Extract of the study data

**Table E.1:** A four-line extract from the study data depicting the study variables.

| ID# | dnr_age | Patstatus | Patsurvtime | Recip_Age_cont | donor_type | renal_disease | hypertension | urological |
|---|---|---|---|---|---|---|---|---|
| 1 | 16 | 1 | 9.076712 | 41 | cadaveric | yes | no | no |
| 2 | 23 | 1 | 8.516611 | 48 | cadaveric | no | no | no |
| 3 | 24 | 1 | 0.949315 | 43 | cadaveric | no | yes | no |
| 4 | NA | 0 | 6.242907 | 43 | cadaveric | yes | no | no |

| ID# | inherited | nephrectomy | wound_sepsis | wound_haematoma | ureteric | no_complication | delayed_gf | diabetes_tx |
|---|---|---|---|---|---|---|---|---|
| 1 | no | no | no | no | no | yes | no | no |
| 2 | no | yes | yes | no | no | no | no | no |
| 3 | no | no | no | yes | no | no | no | no |
| 4 | no | no | no | no | no | yes | no | no |

| ID# | Transplant_era | AR_clinical | AR_histological | Grftsurvtime | Graftstatus | new_gender | new_bloodgroup | ethnicity |
|---|---|---|---|---|---|---|---|---|
| 1 | CYA | yes | no | 9.076712 | 1 | male-female | 1 | non-white |
| 2 | CYA | no | no | 8.516611 | 1 | male-male | 1 | non-white |
| 3 | CYA | yes | yes | 0.949315 | 1 | female-male | 1 | non-white |
| 4 | CYA | yes | no | 6.242907 | 0 | male-male | 1 | non-white |

# Appendix F

# Representative SAS and R codes

```
#SAS-code for data cleaning#
data redcap.CMJAH;  * Create a new dataset;
set redcap.cmjahclean; * Read in original data;
where hosp=1; * select only cases where hospital=1;
rec_age_no_dob2=rec_age_no_dob*1; * converting age recodes variable
from text to numeric*;
Agecal=int((date_tx-rec_dob)/365.25);* Calculating age from date transplant and
date of birth*;
if Agecal=. then Agecal = rec_age_no_dob2;
if  Agecal <18 and Agecal~=. then delete; * delete cases that are paediatrics*;
IF  redcap_event_name='transplant_1_arm_1'  THEN EVENT = 'First transplant';
*recoding redcap event*;
IF redcap_event_name~='transplant_1_arm_1' THEN EVENT = 'Retransplants';
if Event='First transplant' then Event2=0;
if Event='Retransplants' then Event2=1;
Patstatus=.; ***Create event status  varibles ***;
Graftstatus=.;
if date_death~=. then Patstatus='1';
if date_death=. and last_seen~=. then Patstatus ='0';
if graft_loss~=. or date_death~=. then Graftstatus="1";
if graft_loss=. and date_death=. and last_seen~=. then Graftstatus="0";
Survdod=yrdif(date_tx,date_death,'Actual');* create survival time variable*;
```

```
Survdls=yrdif(date_tx,last_seen,'Actual');
SurvGrft=yrdif(date_tx,graft_loss,'Actual');
if Agecal=. then delete;
Patsurvtime=.;
Grftsurvtime=.;
if Survdod~=. then Patsurvtime=Survdod;
if Survdod=. and Survdls~=. then Patsurvtime=Survdls;
if Survdod=. and Survdls=. then Patsurvtime=.;
if SurvGrft~=. then Grftsurvtime=SurvGrft;
if SurvGrft=. and Survdls=. and Survdod~=. then Grftsurvtime=Patsurvtime;
if SurvGrft=.  and Survdod=. and Survdls~=. then Grftsurvtime=Survdls;
if SurvGrft=. and Survdls=. and Survdod=. then Grftsurvtime=.;
if Survdod~=. and SurvGrft=. and Survdls~=. then Grftsurvtime=Patsurvtime;
if date_tx =. then delete;
Followup=yrdif(date_tx,'31Dec2014'd,'Actual'); *calculate follow up time
to know cases less than one year follow-up times*;
Patstatus2=Patstatus;
Patstatus3=Patstatus;
Graftstatus2=Graftstatus;
Graftstatus3=Graftstatus;
Patsurvtime2=Patsurvtime;
Patsurvtime3=Patsurvtime;
Grftsurvtime2=Grftsurvtime;
Grftsurvtime3=Grftsurvtime;
if Patsurvtime >1  then do; Patsurvtime2= '1';  Patstatus2='0'; end;
if Patsurvtime<=1 then do; Patsurvtime3='1';Patstatus3="0";  end;
if Grftsurvtime>1 then do Grftsurvtime2='1'; Graftstatus2="0"; end;
if Grftsurvtime<=1 then do; Grftsurvtime3='1';Graftstatus3="0";  end;
* recoding variables from continous to categorical*
*the proc format statement can be used)*;
Recip_Age_cont=Agecal;
if Agecal>=18 and Agecal<=29 then Recipient_age='18-29';
if Agecal>=30 and Agecal<=39 then Recipient_age='30-39';
if Agecal>=40 and Agecal<=49 then Recipient_age='40-49';
if Agecal>=50 then Recipient_age='50+';
```

```
if dnr_age>=41 and dnr_age<=50 then Donor_Age='41-50';
if dnr_age>=1 and dnr_age<=10 then Donor_Age='1-10';
if dnr_age>=11 and dnr_age<=20 then Donor_Age='11-20';
if dnr_age>=21 and dnr_age<=30 then Donor_Age='21-30';
if dnr_age>=31 and dnr_age<=40 then Donor_Age='31-40';
if dnr_age>50 then Donor_Age='>50';

biopsydate1= date_acbx1-date_tx;* calculating year difference between
*transplant date and acute rejection date*;
biopsydate2=date_acbx2-date_tx;
biopsydate3=date_acbx3-date_tx;
biopsydate4=date_acbx4-date_tx;
acuterej_clin=0;  acuterej_hist=0;
if biopsydate1 >= 0 and biopsydate1 <=60 then do;
if acrej_dx1___1=1 then acuterej_clin=1;
if acrej_dx1___2=1 then acuterej_hist=1;
end;
if biopsydate2 >= 0 and biopsydate2 <=60 then do;
if acrej_dx2___1=1 then acuterej_clin=1;
if acrej_dx2___2=1 then acuterej_hist=1;
end;
if biopsydate3 >= 0 and biopsydate3 <=60 then do;
if acrej_dx3___1=1 then acuterej_clin=1;
if acrej_dx3___2=1 then acuterej_hist=1;
end;
if biopsydate4 >= 0 and biopsydate4 <=60 then do;
if acrej_dx4___1=1 then acuterej_clin=1;
if acrej_dx4___2=1 then acuterej_hist=1;
end;
Transp_era=.;
if date_tx<='31Dec1983'd then Transp_era='0';
if date_tx>'31Dec1983'd and date_tx<='31Dec2000'd then Transp_era='1';
if date_tx>'31Dec2000'd the Transp_era='2';
run;
```

```
proc print data=redcap.cmjah;
where Event="Retransplants";
var Event;
run;
*PRINT SECTION*;
proc print data=redcap.CMJAH; *print where age at transp is missing*;
where age_at_tx=.;
var job_id rec_last_name rec_first_name rec_hosp_no age_at_tx rec_dob
date_tx redcap_event_name;
TITLE 'MISSING AGE AT TRANSPLANT';
run;
proc print data=redcap.CMJAH; *print where calculated age is missing*;
where Agecal=.;
var job_id rec_last_name rec_first_name rec_hosp_no age_at_tx rec_dob
Agecal redcap_event_name;
TITLE 'MISSING  calculated AGE';
run;
proc print data=redcap.CMJAH; *print where age records are not equal*
*to age calculated *;
where (age_at_tx ~= Agecal and Agecal~=. and age_at_tx~=.)
OR (rec_age_no_dob2 ~= Agecal and Agecal~=. and  rec_age_no_dob2~=.)
or (rec_age_no_dob2 ~= age_at_tx and  age_at_tx~=.
and  rec_age_no_dob2~=.) ;
var job_id rec_last_name rec_first_name rec_hosp_no age_at_tx rec_dob
date_tx rec_age_no_dob Agecal ;
TITLE 'UNEQUAL INPUT OF AGE';
run;
proc print data=redcap.CMJAH;
*print where follow up is less than one year *;
where Followup <1 and Followup~=.;
title Less than one year followup;
run;
proc print data=redcap.CMJAH;
* print where date of death and last seen are missing*;
where date_death=. and last_seen=.;
```

```
title 'MISSING DATE OF DEATH AND LAST SEEN';
var job_id rec_last_name rec_first_name rec_hosp_no date_death
last_seen graft_loss
Patsurvtime date_tx redcap_event_name ;
run;
proc print data=redcap.CMJAH;
* print where date of death is less than last seen*;
where date_death < last_seen and date_death~=.;
title 'DEATH BEFORE LAST SEEN';
var job_id rec_last_name rec_first_name rec_hosp_no date_death
last_seen Patsurvtime
date_tx redcap_event_name ;
run;
proc print data=redcap.CMJAH;
*print where date of death is less than transp date*;
where date_death < date_tx and date_death~=.;
title 'DEATH BEFORE TRANSPLANT';
var job_id rec_last_name rec_first_name rec_hosp_no date_death
date_tx last_seen
Patsurvtime redcap_event_name;
run;
proc print data=redcap.CMJAH;
*print where date of last seen is less than transp date*
*DID NOT INCLUDE IN THE PROC PRINT FOR CORRECTION*;
where last_seen < date_tx and last_seen~=.;
title 'LAST SEEN BEFORE TRANSPLANT';
var job_id rec_last_name rec_first_name rec_hosp_no date_death
date_tx last_seen Grftsurvtime Patsurvtime redcap_event_name;
run;
proc print data=redcap.CMJAH;
* print where date of graft loss and last seen are missing*;
where (last_seen=. and graft_loss =.) or (last_seen=. and date_death =.) or
(last_seen=. and graft_loss =. and date_death=.);
title 'MISSING DATE OF GRAFT LOSS AND LAST SEEN';
var job_id rec_last_name rec_first_name rec_hosp_no date_death
```

```
date_tx last_seen
graft_loss Grftsurvtime Patsurvtime redcap_event_name;
run;
proc print data=redcap.CMJAH;
*print where date of graft loss is less than last seen*;
where last_seen < graft_loss and last_seen~=.;
title 'LAST SEEN BEFORE GRAFT LOSS';
var job_id rec_last_name rec_first_name rec_hosp_no date_death
last_seen graft_loss
Grftsurvtime date_tx redcap_event_name;
run;
proc print data=redcap.CMJAH;
*print where date of graft loss is less than transp date*;
where graft_loss < date_tx and graft_loss~=.;
title 'GRAFT LOSS BEFORE TRANSPLANT';
var job_id rec_last_name rec_first_name rec_hosp_no
date_death last_seen
date_tx graft_loss Grftsurvtime redcap_event_name;
run;
proc print data=redcap.CMJAH;
*print where date of graft loss is less than transp date*;
where  date_death < graft_loss and date_death~=.;
title 'DEATH BEFORE GRAFT LOSS';
var job_id rec_last_name rec_first_name rec_hosp_no date_death
last_seen date_tx graft_loss Grftsurvtime redcap_event_name;
run;
proc print data=redcap.cmjah;
var job_id rec_last_name rec_first_name rec_hosp_no date_death
date_tx graft_loss last_seen Patsurvtime Grftsurvtime redcap_event_name;
run;
proc print data=redcap.cmjah;
where Grftsurvtime<0;
var Grftsurvtime;
run;
```

```
#DATA RECODING#
#importing main data from a csv file format#
MSc_redcap <- read.csv("C:/Users/Ike/Desktop/MSc_Data/MSc_data3.csv")
is.na(MSc_redcap) <-MSc_redcap== "." ## setting empty cells to missing
names(MSc_redcap)
#Data subsetting#
pre_CYA <- subset (MSc_redcap, Transplant_era=="pre_CYA")
CYA <- subset (MSc_redcap, Transplant_era=="CYA")
New_gen <- subset (MSc_redcap, Transplant_era=="New_gen")
sum(is.na(pre_CYA))/prod(dim(pre_CYA))
mean(is.na(pre_CYA))
sum(is.na(CYA))/prod(dim(CYA))
mean(is.na(CYA))
sum(is.na(New_gen))/prod(dim(New_gen))
mean(is.na(New_gen))
summary(CYA[!complete.cases(CYA),])
newdata <- na.omit(CYA)
complete.cases(pre_CYA)
#pre-CYA data analysis#
# varaiable selection #
names(CY1)
CY=CYA [complete.cases(CYA$AR_clinical,CYA$AR_histological,
CYA$delayed_gf,CYA$diabetes_tx,
CYA$dnr_age,CYA$dnr_bld_grp,CYA$dnr_gender,CYA$donor_type,
CYA$hypertension,CYA$inherited,CYA$nephrectomy,CYA$no_complication,
CYA$ rec_bld_grp,CYA$rec_ethnicity,CYA$rec_sex,CYA$Recip_Age_cont,
CYA$renal_disease,CYA$ureteric,CYA$urological,CYA$wound_haematoma,
CYA$wound_sepsis),]
pre=pre_CYA [complete.cases(pre_CYA$AR_clinical,pre_CYA$AR_histological,
pre_CYA$delayed_gf,
pre_CYA$diabetes_tx,pre_CYA$dnr_age,pre_CYA$dnr_bld_grp,
pre_CYA$dnr_gender,pre_CYA$donor_type,pre_CYA$hypertension,
pre_CYA$inherited,pre_CYA$nephrectomy,pre_CYA$no_complication,
pre_CYA$ rec_bld_grp,pre_CYA$rec_ethnicity,pre_CYA$rec_sex,
pre_CYA$Recip_Age_cont,pre_CYA$renal_disease,pre_CYA$ureteric,
```

```
pre_CYA$urological,pre_CYA$wound_haematoma,pre_CYA$wound_sepsis),]
new=New_gen [complete.cases(New_gen$AR_clinical,New_gen$AR_histological,
New_gen$delayed_gf,New_gen$diabetes_tx,New_gen$dnr_age,
New_gen$dnr_bld_grp,New_gen$dnr_gender,New_gen$donor_type,
New_gen$hypertension,New_gen$inherited,New_gen$nephrectomy,
New_gen$no_complication,New_gen$ rec_bld_grp,New_gen$rec_ethnicity,
New_gen$rec_sex,New_gen$Recip_Age_cont,New_gen$renal_disease,
New_gen$ureteric,New_gen$urological,New_gen$wound_haematoma,
New_gen$wound_sepsis),]
#importing main data from a csv file format#
CYA <- read.csv("C:/Users/Ike/Desktop/MSc_data/CYA.csv", header =TRUE)
names(CYA)
MSc_CYA<-CYA
names(MSc_CYA)
#merging recipient gender and donor gender#
MSc_CYA$new_gender = ifelse(MSc_CYA$rec_sex=="male" & MSc_CYA$dnr_gender=="male",
"male-male",
ifelse(MSc_CYA$rec_sex=="female" & MSc_CYA$dnr_gender=="female", "female-female",
ifelse(MSc_CYA$rec_sex=="female" & MSc_CYA$dnr_gender=="male", "female-male",
"male-female")))
MSc_CYA[,c("rec_sex","dnr_gender","new_gender")]
#printing the new gender variable along with originalvariable#
#blood group#
MSc_CYA$new_bloodgroup = ifelse(MSc_CYA$rec_bld_grp=="O" &
MSc_CYA$dnr_bld_grp=="O", "1",
ifelse(MSc_CYA$rec_bld_grp=="A" & MSc_CYA$dnr_bld_grp=="A", "1",
ifelse(MSc_CYA$rec_bld_grp=="B" & MSc_CYA$dnr_bld_grp=="B", "1",
ifelse(MSc_CYA$rec_bld_grp=="AB" & MSc_CYA$dnr_bld_grp=="AB", "1",
ifelse(MSc_CYA$rec_bld_grp=="O" & MSc_CYA$dnr_bld_grp=="A", "O","O")
))))
MSc_CYA[,c("rec_bld_grp","dnr_bld_grp","new_bloodgroup")]
#printing the new blood group variable along with originalvariable#
MSc_CYA <- MSc_CYA[c(-2,-4,-6,-7)]#remove the variables after recording#
names(MSc_CYA)
#ethnicity#
```

```
MSc_CYA$ethnicity<-ifelse(MSc_CYA$rec_ethnicity=="white","white",
ifelse(MSc_CYA$rec_ethnicity=="black","non-white",
ifelse(MSc_CYA$rec_ethnicity=="asian","non-white",
ifelse(MSc_CYA$rec_ethnicity=="mixed","non-white",F))))
table(MSc_CYA$ethnicity)
MSc_CYA$ethnicity<-factor(MSc_CYA$ethnicity)
MSc_CYA$ethnicity <- relevel(MSc_CYA$ethnicity, ref="white")
#changing reference group to black, still two categotries are not signif#
names(MSc_CYA)
MSc_CYA <- MSc_CYA[c(-3)]#Remove rec_ethnicity after recording#
names()
#Number of complete cases#
MSc_comp=MSc_CYA [complete.cases
(MSc_CYA$ job_id, MSc_CYA$ dnr_age, MSc_CYA$ donor_type,
MSc_CYA$ renal_disease, MSc_CYA$ hypertension, MSc_CYA$ urological,
MSc_CYA$ inherited, MSc_CYA$ nephrectomy, MSc_CYA$ wound_sepsis,
MSc_CYA$ wound_haematoma, MSc_CYA$ ureteric, MSc_CYA$ no_complication,
MSc_CYA$ delayed_gf, MSc_CYA$ diabetes_tx, MSc_CYA$ AR_clinical,
MSc_CYA$ AR_histological, MSc_CYA$ Grftsurvtime, MSc_CYA$ Graftstatus,
MSc_CYA$ new_gender, MSc_CYA$ new_bloodgroup, MSc_CYA$ ethnicity),]
#exporting data from r to csv#
write.csv(MSc_comp, file='MSc_comp.csv')
#importing main data from a csv file format#
MSc_comp <- read.csv("C:/Users/Ike/Desktop/MSc_data/MSc_comp.csv", header =TRUE)
names(MSc_comp)
#Exploratory data analysis#
#Similar format of codes was used for Short_term and long term analysis#
#hazard and km plotc
trans_haz <- pehaz(MSc_comp$Grftsurvtime, MSc_comp$Graftstatus,width=2,
max.time=29.3)
haz_smooth <-muhaz(MSc_comp$Grftsurvtime, MSc_comp$Graftstatus, bw.smooth = 30,
b.cor = "left", max.time =29.25)
trans_km <-survfit(Surv(MSc_comp$Grftsurvtime, MSc_comp$Graftstatus)~1)
par(mfrow=c(2,2))
hist<-hist(MSc_comp$Grftsurvtime, xlab = "Years after transplant",
```

```
main = NULL, col=blues9, ylim=c(0,350),cex.axis =1.5,cex.lab=1.5)
lines(density(hist), col="blue", lwd=2)
plot(trans_km,xlab="Years after transplant", ylab= "Survival prbability",
mark.time = T, col="blue", conf.int = F,cex.axis =1.5,cex.lab=1.5)
plot(trans_haz, ylim=c(0,0.1),col="blue", lwd=2,
ylab = "Estimated hazard function",
xlab="Years after transplant",cex.axis =1.5,cex.lab=1.5)
lines(haz_smooth, lwd=2, col="red")
plot(trans_km, fun="cumhaz",ylab="Estimated cumulative hazard",
xlab="Years after transplant", conf.int = F, col="blue",lwd=2,cex.axis=1.5,
cex.lab=1.5)
summary(MSc_comp$Grftsurvtime)
#Model Building based on the Cox PH model#
#response variable#
MSc_compsurv<-with(MSc_comp, Surv(Grftsurvtime,Graftstatus))
#purposeful variable selection#
#Stage 1#
purv1A<-coxph(MSc_compsurv~dnr_age, data=MSc_comp)# for continuous variables#
summary(purv1A)
#for categorical variables#
survdiff(Surv(Grftsurvtime,Graftstatus) ~ dnr_type,data=MSc_comp)
#Stage 2#
purv2<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+hypertension+delayed_gf+
no_complication+renal_disease+inherited+urological+wound_sepsis,data=MSc_comp)
summary(purv2)
#drop wound sepsis#
purv3<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+hypertension+delayed_gf+
no_complication+renal_disease+inherited+urological,data=MSc_comp)
summary(purv3)
VIF(purv3)
#likelihood ratio test#
X.lr3=-2*purv3$loglik[2]-(-2*purv2$loglik[2]) # test statistics
X.lr3
1-pchisq(X.lr3,1) # p-value
delta.coff<-abs((coef(purv3)-coef(purv2)[-10])/coef(purv2)[-10])
```

```
round(delta.coff,5)
#hypertension and renal_d were drop because hypertension influenced renal_d#
purv4<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf+
no_complication+renal_disease+inherited+urological,data=MSc_comp)
summary(purv4)
# likelihood ratio test#
X.lr4=-2*purv4$loglik[2]-(-2*purv3$loglik[2]) # test statistics
X.lr4
1-pchisq(X.lr4,1) # p-value
delta.coff<-abs((coef(purv4)-coef(purv3)[-4])/coef(purv3)[-4])
round(delta.coff,5)
purv5<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+no_complication+inherited+urological,data=MSc_comp)
summary(purv5)
#drop urological#
purv6<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+no_complication+inherited,data=MSc_comp)
summary(purv6)
# likelihood ratio test#
X.lr5=-2*purv6$loglik[2]-(-2*purv5$loglik[2]) # test statistics
X.lr5
1-pchisq(X.lr5,1) # p-value
delta.coff<-abs((coef(purv6)-coef(purv5)[-7])/coef(purv5)[-7])
round(delta.coff,5)
#no complication#
purv7<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+inherited,data=MSc_comp)
summary(purv7)
#likelihood ratio test#
X.lr6=-2*purv7$loglik[2]-(-2*purv6$loglik[2]) # test statistics
X.lr6
1-pchisq(X.lr6,1) # p-value
delta.coff<-abs((coef(purv7)-coef(purv6)[-5])/coef(purv6)[-5])
round(delta.coff,5)
#Stage 3#
```

```
#add var not significant at univariate analysis#
#AR_clinical, AR_histological,new_gender, new_bloodgroup#
purv8<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+inherited+diabetes,data=MSc_comp)
summary(purv8)
#likelihood ratio test#
X.lr6=-2*purv7$loglik[2]-(-2*purv8$loglik[2]) # test statistics
X.lr6
1-pchisq(X.lr6,1) # p-value
delta.coff<-abs((coef(purv7)-coef(purv8)[-7])/coef(purv8)[-7])
round(delta.coff,5)
purv9<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+inherited+diabetes+new_gender,data=MSc_comp)
summary(purv9)
#likelihood ratio test#
X.lr6=-2*purv8$loglik[2]-(-2*purv9$loglik[2]) # test statistics
X.lr6
1-pchisq(X.lr6,1) # p-value
delta.coff<-abs((coef(purv8)-coef(purv9)[-7])/coef(purv9)[-7])
round(delta.coff,5)
purv10<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+inherited+diabetes,data=MSc_comp)
summary(purv10)
purv11<-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+diabetes,data=MSc_comp)
summary(purv11)
#likelihood ratio test#
X.lr7=-2*purv11$loglik[2]-(-2*purv10$loglik[2]) # test statistics
X.lr7
1-pchisq(X.lr7,1) # p-value
delta.coff<-abs((coef(purv11)-coef(purv10)[-5])/coef(purv10)[-5])
round(delta.coff,5)
#assessment of the functional form#
MSc_comp$ethnicity <- relevel(MSc_comp$ethnicity, ref="white")
#changing reference group to black, two categotries are not signif#
```

```
fn_form <-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+diabetes,data=MSc_comp)
smooth_SEcurve<-function(yy,xx){
list_x<-min(xx) + ((0:100)/100)*(max(xx)-min(xx))
yy_xx<-predict(loess(yy~xx),se=T,newdata=data.frame(xx=list_x))
lines(yy_xx$fit ~list_x, lwd=2,col="blue")
lines(yy_xx$fit - qt(0.975,yy_xx$df)*yy_xx$se.fit~list_x, lty=2)
lines(yy_xx$fit + qt(0.975,yy_xx$df)*yy_xx$se.fit~list_x, lty=2)
}
#martingale residual from a null model#assessment of linearity#
mart <-coxph(Surv(MSc_comp$Grftsurvtime, MSc_comp$Graftstatus)~1)
martR <-residuals(mart, type="martingale")
par(mfrow=c(2,2))
plot(martR~MSc_comp$recip_age,xlab="recip_age",
ylab = "Martingale residual",
col="red",cex.axis =1.5,cex.lab=1.5)
smooth_SEcurve(martR,MSc_comp$recip_age)
#pspline#
ps_cox <-coxph(MSc_compsurv~pspline(recip_age,df=4)+dnr_type
+ethnicity+delayed_gf+diabetes, data=MSc_comp)
ps_cox
termplot(ps_cox,se=T, terms = 1,ylabs = "Log hazard",
col.term = "blue",col.se = "blue",cex.axis =1.5,cex.lab=1.5,
lwd.term = 2,lwd.se = 2)

**Cummulative martingale **; done with SAS
ODS RTF FILE='C:\Users\Ike\Desktop\fun.rtf'style=statistical;
ODS LISTING CLOSE;
ODS GRAPHICS on;
PROC PHREG DATA=mydata4;
class donortype ethnicity dgf diab;
MODEL Grftsurvtime*Graftstatus(0) = recip_age donortype ethnicity
dgf diab;
ASSESS VAR=(recip_age) / RESAMPLE;
axis1 value=(h=5 font=arial);
```

```
axis2  value=(h=3 font=arial);
RUN;
ODS GRAPHICS oFF;ODS RTF CLOSE;ODS LISTING;QUIT;

#interaction among predictors#

intrc <-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+diabetes+recip_age:diabetes,data=MSc_comp)
summary(intrc)

#interaction among predictors#

no_intrc <-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity
+delayed_gf+diabetes,data=MSc_comp)
summary(intrc)
X.lr12=-2*no_intrc$loglik[2]-(-2*intrc$loglik[2]) #test statistics#
X.lr12
1-pchisq(X.lr12,1) #p-value#
#PH assumption#

KM1= survfit(Surv(Grftsurvtime, Graftstatus)~ dnr_type,
subset = {dnr_type=="cadaveric"},data=MSc_comp)
KM1b= survfit(Surv(Grftsurvtime, Graftstatus)~ dnr_type,
subset = {dnr_type=="living"},data=MSc_comp)
survtimec<-KM1$time
survsurvc<-KM1$surv
logtimec<-log(survtimec)
clogclogc<-log(-log(survsurvc))
survtimel<-KM1b$time
survsurvl<-KM1b$surv
logtimel<-log(survtimel)
clogclogl<-log(-log(survsurvl))
plot(clogclogc~logtimec,type="s",col="red",
xlab="Log (years after transplant)",
ylab="log-log survival",lwd=2.0,cex.axis =1.5,cex.lab=1.5)
```

```
lines(clogclogl~logtimel,type="s",col="black",
xlab="Log (years after transplant)",
ylab="log-log survival",lwd=2.0,cex.axis =1.5,cex.lab=1.5)
legend("topleft",c("cadaveric","living"),
col=c("red","black"),lty=1,bty='n')
KM2= survfit(Surv(Grftsurvtime, Graftstatus)~ ethnicity,
subset={ethnicity=="white"},data=MSc_comp)
KM2b= survfit(Surv(Grftsurvtime, Graftstatus)~ ethnicity,
subset={ethnicity=="non-white"},data=MSc_comp)
survtimew<-KM2$time
survsurvw<-KM2$surv
logtimew<-log(survtimew)
clogclogw<-log(-log(survsurvw))
survtimen<-KM2b$time
survsurvn<-KM2b$surv
logtimen<-log(survtimen)
clogclogn<-log(-log(survsurvn))
plot(clogclogw~logtimew,type="s",col="red",
xlab="Log (years after transplant)",
ylab="log-log survival",lwd=2.0,cex.axis =1.5,cex.lab=1.5)
lines(clogclogn~logtimen,type="s",col="black",
xlab="Log (years after transplant)",
ylab="log-log survival",lwd=2.0,cex.axis =1.5,cex.lab=1.5)
legend("topleft",c("white", "non-white"),col=c("red","black"),
lty=1,bty='n' )
KM3= survfit(Surv(Grftsurvtime, Graftstatus)~ delayed_gf,
subset = {delayed_gf =="no"},data=MSc_comp)
KM3b= survfit(Surv(Grftsurvtime, Graftstatus)~ delayed_gf,
subset = { delayed_gf =="yes"},data=MSc_comp)
survtimen<-KM3$time
survsurvn<-KM3$surv
logtimen<-log(survtimen)
clogclogn<-log(-log(survsurvn))
survtimey<-KM3b$time
survsurvy<-KM3b$surv
```

```
logtimey<-log(survtimey)
clogclogy<-log(-log(survsurvy))
plot(clogclogn~logtimen,type="s",col="red",
xlab="Log (years after transplant)",
ylab="log-log survival",lwd=2.0,cex.axis =1.5,cex.lab=1.5)
lines(clogclogy~logtimey,type="s",col="black",
xlab="Log (years after transplant)",
ylab="log-log survival",lwd=2.0,cex.axis =1.5,cex.lab=1.5)
legend("topleft",c("no", "yes"),col=c("red","black"),
lty=1,bty='n' )
KM4= survfit(Surv(Grftsurvtime, Graftstatus)~ diabetes,
subset={diabetes=="no"},data=MSc_comp)
KM4b= survfit(Surv(Grftsurvtime, Graftstatus)~ diabetes,
subset={diabetes=="yes"},data=MSc_comp)
survtimen<-KM4$time
survsurvn<-KM4$surv
logtimen<-log(survtimen)
clogclogn<-log(-log(survsurvn))
survtimey<-KM4b$time
survsurvy<-KM4b$surv
logtimey<-log(survtimey)
clogclogy<-log(-log(survsurvy))
plot(clogclogn~logtimen,type="s",col="red",
xlab="Log (years after transplant)",
ylab="log-log survival",lwd=2.0,cex.axis =1.5,cex.lab=1.5)
lines(clogclogy~logtimey,type="s",col="black",
xlab="Log (years after transplant)",
ylab="log-log survival",lwd=2.0,cex.axis =1.5,cex.lab=1.5)
legend("topleft",c("no", "yes"),col=c("red","black"),lty=1,bty='n')
#Survival plots#
KM1= survfit(Surv(Grftsurvtime, Graftstatus)~ dnr_type, data=MSc_comp)
plot(KM1,lwd =2, xlab="Years after transplant",ylab= "Survival probability",
col=1:2, conf.int = F,cex.axis =1.5,cex.lab=1.5)
legend("bottomleft",c("cadaveric","living"),col=1:2,lty=1,bty='n')
KM2 = survfit(MSc_compsurv~ ethnicity, data=MSc_comp)
```

```
plot(KM2,lwd =2,  xlab="Years after transplant",ylab= "Survival probability",
col=1:4, conf.int = F,cex.axis=1.5,cex.lab=1.5)
legend("bottomleft",c("white", "non-white"),col=1:2,lty=1,bty='n' )
KM3 = survfit(MSc_compsurv~ delayed_gf, data=MSc_comp)
plot(KM3,lwd =2,  xlab="Years after transplant",ylab= "Survival probability",
col=1:2, conf.int = F,cex.axis=1.5,cex.lab=1.5)
legend("bottomleft",c("no","yes"),col=1:2,lty=1,bty='n')
KM4= survfit(MSc_compsurv~ diabetes, data=MSc_comp)
plot(KM4,lwd =2,  xlab="Years after transplant",ylab= "Survival probability",
col=1:2, conf.int = F,cex.axis=1.5,cex.lab=1.5)
legend("bottomleft",c("no","yes"),col=1:2,lty=1,bty='n')
#Proportional hazards tests by P. Grambsch and T. Therneau (1994)#
ph_assump <-coxph(MSc_compsurv~recip_age+dnr_type+ethnicity+delayed_gf
+diabetes,data=MSc_comp)
cox.zph(ph_assump)
#recipient ethnicity does not satisfy PH assumption; thus removed#
ph_assump2 <-coxph(Surv(Grftsurvtime, Graftstatus) ~  dnr_type , data=MSc_comp)
cox.zph(ph_assump2)
AIC(ph_assump)
vif(ph_assump)#multicollinearity test#
summary(ph_assump)
names(ph_assump$coefficients)
#plots of the selected variables (schoenfeld residual)#
par(mfrow=c(2,2))
plot( cox.zph(ph_assump),ann=T, var=1, col="blue",lwd=2)
abline(h=0, lty=2,, col="red")
plot( cox.zph(ph_assump), ann=T, var=2, col="blue",lwd=2 )
abline(h=0, lty=2, col="red")
plot( cox.zph(ph_assump), ann=T, var=3 , col="blue",lwd=2)
abline(h=0, lty=2, col="red")
plot( cox.zph(ph_assump), ann=T, var=4, col="blue",lwd=2)
abline(h=0, lty=2, col="red")
plot( cox.zph(ph_assump), ann=T, var=5, col="blue",lwd=2)
abline(h=0, lty=2, col="red")
plot( cox.zph(ph_assump), ann=T, var=6,col="blue", lwd=2)
```

```
abline(h=0, lty=2, col="red")

*****parametric analysis-SAS********
****Similar code format was used for long_term and short_term analysis*******
proc import datafile="C:\Users\Ike\Desktop\MSc_comp.CSV"
out=mydata1 dbms=CSV replace;
getnames=yes;
run;
data mydata3;
set mydata1;
if dnr_type ="cadaveric" then donortype="2";
if dnr_type ="living" then donortype="1";
if diabetes ="no" then diab="2";
if diabetes ="yes" then diab="1";
if delayed_gf ="no" then dgf="2";
if delayed_gf ="yes" then dgf="1";
run;
data mydata4;
set mydata3;
keep Grftsurvtime Graftstatus  donortype diab  dgf recip_age ethnicity ;
run;

/*-----EXPONENTIAL--------*/
proc lifereg data=mydata4;
class donortype ethnicity dgf diab;
model Grftsurvtime*Graftstatus(0)=recip_age donortype ethnicity dgf diab
/distribution=exponential;
output out=exp cdf=f;
run;
data exp1;
set exp;
cox = -log( 1-f );
run;
proc lifetest data=exp1 outsurv=surv_exp noprint;
time cox *Graftstatus(0);
```

```
run;
data surv_exp1;
set surv_exp;
ls = -log(survival);
run;
goptions reset=all;
title h=3 "Exponential";
axis1 order=(0 to 4.0 by 1) minor=none label=(h=3 'Cox-Snell residual')
value=(h=3 font=arial);
axis2 order=(0 to 4.0 by 1) minor=none label=(h=3 a=90
'Estimated cumulative hazard function') value=(h=3 font=arial);
symbol1 i=l1p  c= blue v=dot h=1.0;
symbol2 i = join c = red l = 5;
proc gplot data=surv_exp1;
plot (ls cox)*cox / overlay haxis=axis1 vaxis= axis2;
run;
quit;
ods pdf close;
/*choose the appropraite distribution for other parametric models*/

/*-------Cox PH-------*/
proc phreg data=mydata4 ;
class donortype ethnicity dgf diab;
model Grftsurvtime*Graftstatus(0) = recip_age donortype ethnicity dgf diab;
output out = cox LOGSURV = h /method = ch;/
*-logsurv is the cox-snell residual*/
run;
data cox1;
set cox;
h = -h;
cons=1;
run;
proc phreg data = cox1 ;
model  h*Graftstatus(0) = cons;
output out = cox2 logsurv = ls /method = ch;
```

```
run;
data cox3;
set cox2;
haz = - ls;
run;
proc sort data = cox3;
by h;
run;
goptions reset=all;
title h=3 "Cox PH" ;
axis1 order=(0 to 4 by 1) minor=none label=(h=3 'Cox-Snell residual')
value=(h=3 font=arial);
axis2 order=(0 to 4 by 1) minor=none label=(h=3  a=90
'Estimated cumulative hazard function') value=(h=3 font=arial);
symbol1 i=l1p  c= blue v=dot h=1;
symbol2 i = join c = red l = 5;
proc gplot data = cox3;
plot haz*h =1 h*h =2 /overlay haxis=axis1 vaxis= axis2;
label haz = "Estimated Cumulative Hazard Rates";
label h = "Residual";
run;
quit;
ods html;ods graphics on;

#R-code example for weibull parametric analysis#
Weibull_full1 <- flexsurvreg(MSc_compsurv~recip_age+dnr_type+ethnicity
+delayed_gf+diabetes,data=MSc_comp, dist="weibull")
Weibull_full1
Weibull_full2 <- survreg(MSc_compsurv~recip_age+dnr_type+ethnicity
+delayed_gf+diabetes,data=MSc_comp, dist="weibull")
summary(Weibull_full2)
AIC(Weibull_full2)
VIF{weibull_full2}

#DEVIANCE#
```

```
par(mfrow=c(2,2))
dev_wei<-residuals(Weibull_full2,type="deviance")
plot(dev_wei,col="red",ylab="Deviance residual",cex.lab=1.5,
cex.axis =1.5,lty=1)
abline( h=0,lty=2)
abline( h=-3,lty=2)
identify(dev_wei)
#DFBETA#
wei_dfbeta <- residuals(Weibull_full2, type="dfbeta")
n.obs<-length(MSc_comp$Grftsurvtime)
index.obs<- 1:n.obs
par(mfrow=c(2,2))
plot(wei_dfbeta[,2]~index.obs,type="p", ylab=expression
(paste("",Delta,"coef.for recip_age")),
xlab="Observations",cex.lab=1.2, cex.axis =1.2)
abline(h=0, lty=2,lwd=2, col="red")
#identify(wei_dfbeta[,2]~index.obs, col="red")
plot(wei_dfbeta[,3]~index.obs,type="p", ylab=expression
(paste("",Delta,"coef.for dnr_type")),
xlab="Observations",cex.lab=1.2, cex.axis =1.2)
abline(h=0, lty=2,lwd=2, col="red")
#identify(wei_dfbeta[,3]~index.obs, col="red")
plot(wei_dfbeta[,4]~index.obs,type="p", ylab=expression
(paste("",Delta,"coef.for ethnicity")),
xlab="Observations",cex.lab=1.2, cex.axis =1.2)
abline(h=0, lty=2,lwd=2, col="red")
#identify(wei_dfbeta[,4]~index.obs, col="red")
plot(wei_dfbeta[,5]~index.obs,type="p", ylab=expression
(paste("",Delta,"coef.for delayed_gf")),
xlab="Observations",cex.lab=1.2, cex.axis =1.2)
abline(h=0, lty=2, lwd=2,col="red")
#identify(wei_dfbeta[,5]~index.obs, col="red")
plot(wei_dfbeta[,6]~index.obs,type="p", ylab=expression
(paste("",Delta,"coef.for diabetes")),
xlab="Observations",cex.lab=1.2, cex.axis =1.2)
```

```
abline(h=0, lty=2,lwd=2, col="red")
#identify(logn_dfbeta[,5]~index.obs, col="red")

# Survsim simulation using Weibull distribution#
#similar code format was used for log-normal distribution...#
in short and long term data simulation#
Weibull_full2 <- flexsurvreg(MSc_compsurv~recip_age+dnr_type+ethnicity
+delayed_gf+diabetes,data=MSc_comp, dist="weibull")
Weibull_full2
Weibull_full <- survreg(Surv(Grftsurvtime,1-Graftstatus)~recip_age
+dnr_type+ethnicity+delayed_gf+diabetes,data=MSc_comp, dist="weibull")
#Intercept)=5.3167#
#recip_age=-0.0508#
#dnr_typeliving=0.7891#
#ethnicitynon=-0.7965#
#delayed_gfyes=-0.525784#
#diabetesyes=-0.6617#
#foltime=29.25#
#estimating probabilities#
mean(MSc_comp$recip_age)
var(MSc_comp$recip_age)
table(MSc_comp$dnr_type)
table(MSc_comp$ethnicity)
table(MSc_comp$delayed_gf)
table(MSc_comp$diabetes)
set.seed(180)
overall_sim <- simple.surv.sim(n=751, foltime=29.250000,
dist.ev=c('weibull'),anc.ev=c(1.66),beta0.ev=c(5.3167),
dist.cens="weibull",anc.cens= 1.63,beta0.cens=1.7210,
z=NULL, beta=list(c(-0.0508), c(0.7891), c(-0.7965),
c(-0.525784),c(-0.6617)), x=list(c("normal", 38.13582,119.1682),
c("bern", 0.1438082557),c("bern", 0.4194407457),
c("bern", 0.3688415446),c("bern", 0.06391478029)))
lnormsim
overall_sim <- rename(overall_sim, replace = c("x" = "recip_age",
```

```
"x.1" = "dnr_type","x.2" = "ethnicity", "x.3" = "delayed_gf",
"x.4" = "diabetes","status"="Graftstatus", "stop"="Grftsurvtime"))
modelsim2 <-flexsurvreg(Surv(Grftsurvtime, Graftstatus) ~recip_age
+dnr_type+ethnicity+delayed_gf+diabetes, data=overall_sim,dist="weibull")
modelsim2
cbind(coef(Weibull_full2),coef(modelsim2))
write.csv(overall_sim, file = 'overall_sim.csv')

#Extension of Cox model for short term analysis#
#stratified modelfor short term #
strts<-coxph(Surv(Grftsurvtime, Graftstatus)~nephrectomy+no_complication+diabetes
+ethnicity+ureteric+strata(delayed_gf),data=short_term)
summary(strts)
cmrst <- cumres(strt,R=50)
cox.zph(strt)
AIC(strt)
BIC(strt)
strtkm=Surv(short_term$Grftsurvtime,short_term$Graftstatus==1)
kmfit=survfit(strtkm~1)
kmfit
kmfit2=survfit(strtkm~short_term$delayed_gf)
plot(kmfit2,col = c("black","red"))
legend("bottomright",c("no","yes"),lty=c("solid","solid"),
col=c("black","red"))
plot(kmfit2, fun = "cloglog",col = c("black","red"))
legend("bottomright",c("no","yes"),lty=c("solid","solid"),
col=c("black","red"))
summary(kmfit2, times=c(1,5,10,15,20,25,30))
# plotting adjusted survival#
CrossTable(short_term$delayed_gf,short_term$Graftstatus)
table(short_term$delayed_gf)
stratnews <- data.frame(nephrectomy=c("yes","no"),
no_complication=c("yes","no"),
ethnicity=c("white","non-white"),
delayed_gf=c("yes","no"),diabetes=c("no","yes"),
```

```
ureteric=c("no","yes"))
par(mfrow=c(2,2))
plot(survfit(strts,newdata=stratnews),conf.int =F,
lty=c("solid","solid"),
col = c("red","black"),xlab="Years after transplant",
ylab= "Survival prbability",lwd=2,cex.lab=1.5, cex.axis =1.5)
legend("bottomright",c("no","yes"),lty=c("solid","solid"),
col=c("black","red"))
plot(survfit(strts,newdata = stratnews),col = c("red","black"),
fun="cumhaz",lwd=2,cex.lab=1.5, cex.axis =1.5,
xlab="Years after transplant", ylab="log(-log(Survival))")
legend("bottomright",c("no","yes"),lty=c("solid","solid"),
col=c("black","red"))

/**SAS code for covariates by interactions with time**/
PROC PHREG DATA=short1;
class nephrec nocomp diab ethnic ure dgf;
MODEL Grftsurvtime*Graftstatus(0)= nephrec nocomp diab
ethnic ure dgf nephrect nocompt diabt
ethnict uret dgft;
nephrect=nephrec*Grftsurvtime;
nocompt =nocomp*Grftsurvtime;diabt=diab*Grftsurvtime;
ethnict=ethnic*Grftsurvtime;
uret=ure*Grftsurvtime; dgft=dgf*Grftsurvtime;
test_proportionality: test nocompt, diabt, ethnict, uret, dgft;
RUN;

/*** interactions model****/
PROC PHREG DATA=short1;
class nocomp diab ethnic ure dgf;
MODEL Grftsurvtime*Graftstatus(0) =nephrec nocomp diab ethnic
ure dgf dgft ;
dgft=dgf*Grftsurvtime;
test_proportionality: test  dgft;
output out = cox LOGSURV = h /method = ch;RUN;
```

```
/***Stratified cox***saving estimates of survival
and cumulative hazard functions in BASE dataset***/;
proc phreg data = short1;
baseline out = base survival = surv cumhaz = cumhaz;
strata  dgf;
class nephrec nocomp diab ethnic ure;
MODEL Grftsurvtime*Graftstatus(0) = nephrec nocomp diab
ethnic ure;
output out = cox LOGSURV = h /method = ch;
/*-logsurv is the cox-snell residual*/
run;
/******Heaviside function*******/
GOPTION RESET=ALL;
PROC PHREG DATA=short1;
dgfn=dgf*1;
class nephrec nocomp diab ethnic ure dgf;
MODEL Grftsurvtime*Graftstatus(0) = nephrec nocomp diab
ethnic dgf ure hv2;
if Grftsurvtime >= 6.6 then hv2 = dgfn; else hv2 = 0;
if Grftsurvtime < 6.6 then hv1 = dgfn; else hv1 = 0;
RUN;
```