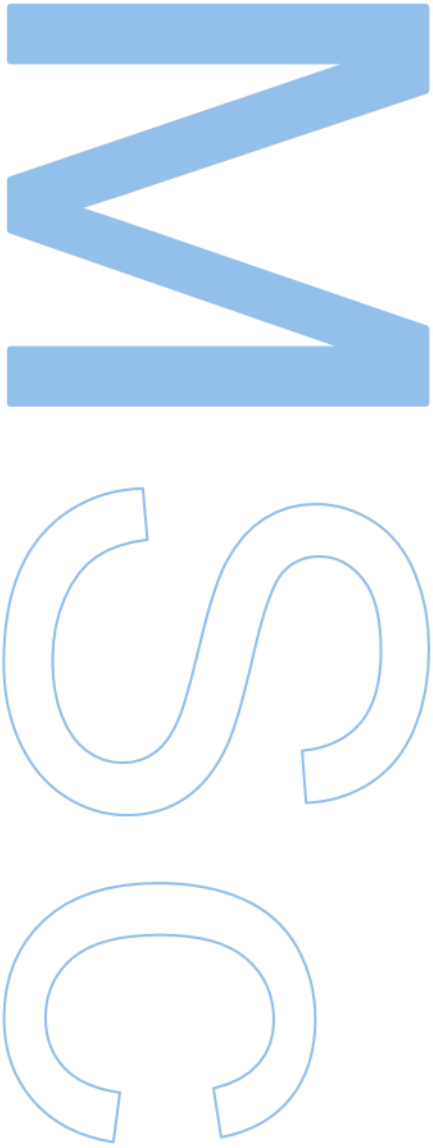
Competing risks modeling in survival analysis



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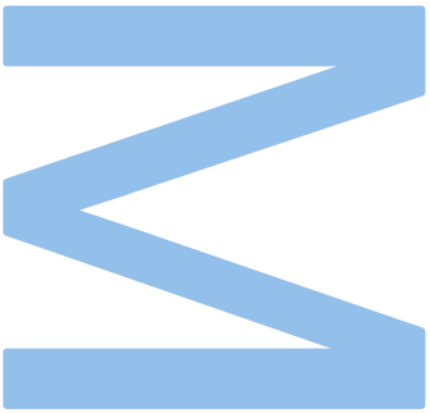

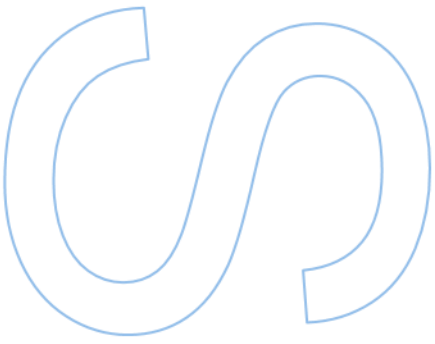

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29th of June, 2023

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Abstract

This study focuses on the different approaches for competing risks analysis in application to the data on peritoneal dialysis patients. The project provides an overview of the theoretical basics of the main methods used in this field. Additionally, it describes using simulated data an analytical strategy for two approaches: competing risks model in case of multiple mutually exclusive outcomes with no intermediate events and an illness-death model for situation with multiple outcomes including an intermediate event (peritonitis). A competing risks model was applied to real data on peritoneal dialysis patients, where three possible events are considered: death, transfer to haemodialysis, and renal transplantation. For this purpose, a basic descriptive analysis of the available data was performed. The cumulative incidence functions were estimated using non-parametric methods, both overall and by subgroups. Factors associated with the events of interest were explored using semi-parametric methods: the cause-specific proportional hazards model and the Fine and Gray subdistribution proportional hazards model.

Keywords: time-to-event analysis, survival function, hazard ratio, censoring, cumulative incidence function, competing risks, subgroup analysis, multi-state models, Cox regression, Fine and Gray model, cause-specific hazards, subdistribution hazards, peritoneal dialysis.

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List of Abbreviations

CCDF	Complementary cumulative distribution function
CDF	Cumulative distribution function
CI	Confidence interval
CIC	Cumulative incidence curve
CIF	Cumulative incidence function
CKD	Chronic kidney disease
CSH	Cause-specific hazards
ESKD	End-stage kidney disease
FCUP	Faculty of Sciences of the University of Porto
GBD	Global Burden of Disease
HD	Haemodialysis
HIV/AIDS	Human immunodeficiency virus / Acquired immunodeficiency syndrome
HR	Hazard ratio
IID	Independent and identically distributed
KM	Kaplan-Meier
MAX	Maximum
MIN	Minimum
MLE	Maximum likelihood estimator
PD	Peritoneal dialysis
PDF	Probability density function
PMF	Probability mass function
Q1	1st quartile
Q3	3rd quartile
ROC	Receiver operating characteristic
RT	Renal transplantation
SDH	Subdistribution hazards
SD	Standard deviation
SI	Syncytium inducing HIV phenotype
STAR	Structured additive regression

1. Introduction

Understanding the timing of events is crucial for decision-making in various fields. For example, in healthcare, one may want to estimate a patient's survival time after receiving a particular treatment or the probability of a patient developing a certain complication. In engineering, it may be necessary to estimate the time until a component fails or the probability of a system experiencing a severe event.

Survival analysis is a set of statistical procedures used to analyze data where the outcome variable of interest is the time until an event occurs. The situation when two or more events can potentially happen and compete with each other for the occurrence is referred to as competing events (or risks). Competing risks data can be encountered, for example, in clinical studies where patients are at risk for more than one mutually exclusive event or failure cause, or where the possible events are not mutually exclusive, but the interest lies in time to the first event[1]. The survival analysis in the presence of competing risks becomes more challenging[2], and it's important to be mindful of the potential implications of using standard survival methods in those situations. For example, the standard Cox regression, a commonly used method in survival analysis, could give unreliable estimates, as it ignores associations between the competing events. To address this issue, competing risks models have been proposed.

Methodology for analyzing competing risks data has rapidly expanded over the last decades[3]. Several techniques have been proposed in the statistical and machine learning literature. State-of-the-art methods have extended classical approaches with more flexible assumptions that can improve predictive performance, allow high dimensional data and missing values, among others.

However, modern approaches have not been widely employed in applied settings. Clinical studies often ignore competing risks or the multistate process of clinical endpoint generation and there appears to be a limited awareness of the importance and pitfalls of competing risks in the clinical community[4].

This work focuses on the different approaches for competing risks analysis in the peritoneal dialysis context and is organized as follows. Chapter 2 introduces the basic ideas of the standard methods of survival analysis. The most commonly used non-parametric estimators and hypothesis tests are presented, as well as the semi-parametric Cox proportional hazard model. Furthermore, the approaches to the problem of competing risks are discussed, such as cumulative incidence functions, cause-specific

and subdistribution hazards models, and multi-state models. Chapter 2 also includes motivation for studying the competing risks in the peritoneal dialysis context.

Chapter 3 is dedicated to a detailed description of the analysis procedure using the methods presented in Chapter 2, with the example of simulated data. Data simulation and analytical algorithms, as well as programming tools used in this study, are also discussed.

Competing risks analysis applied to real peritoneal dialysis data is then presented in Chapter 4. It includes data description, exploratory data analysis and competing risks analysis using the non-parametric methods (overall and subgroup analysis by age, gender and diabetes) and semi-parametric cause-specific and subdistribution hazards models (univariable and multivariable). The results obtained are discussed allowing the comparison between the different approaches.

2. Background

This chapter gives a brief introduction to survival analysis: mathematical fundamentals, key notation and terminology, problems addressed by survival analysis, and the methodology for solving them. Special attention is paid to the competing risks problem and different approaches to analyzing and modeling the competing risks.

2.1. Basic concepts of survival analysis

Survival or time-to-event analysis is a set of statistical methodologies to investigate and model the time until an event of interest occurs. An event here refers to an outcome of interest that occurred within a specific time period. This outcome could be a disease, death, failure of a mechanical component, or any other event of interest that is being studied. The time until the occurrence of the event is also known as the survival time or time-to-event. Classical survival analysis typically focuses on a single event for each individual and characterizes the event's occurrence using survival curves and hazard rates and the effect of covariates by means of regression models. However, by connecting together several events that occur for an individual over time, event histories can be obtained[5].

Survival and event history analysis finds application as a tool in various settings. In manufacturing, it can be of interest to evaluate the reliability of components as well as mechanical, electrical, or electronic systems. In sociology, survival analysis has been used to estimate the probability of divorce and the duration of marriages based on various factors, such as age at marriage, education level, income, and race. Recent areas of interest include unemployment data, lengths of time on and off welfare, and some unusual applications such as interviewer bias in sociological surveys[6].

Applications of survival analysis methodology in clinical research appear to be ever-widening. It can help clinicians understand the effectiveness of a particular treatment, identify risk factors, and make decisions about patient care. Some areas of interest include clinical studies in chronic diseases (cancer, AIDS and others), epidemiology studies, genetic susceptibility to disease incidence, and complex time-dependent effects in clinical studies[6].

A typical feature of survival data is *censoring*. It occurs when the event of interest is not observed for some individuals before the study is terminated. These incomplete observations are termed *right-censored* (or simply *censored*) *survival times*. Figure 1 illustrates a hypothetical study where 10 patients are followed during a time period to see whether a particular event occurs (or until the end of the study). For patients ID numbers 1, 2, 4, 5, 6, and 9 the event was observed within the period of the study, and we have complete observation of their survival times. For patients 3, 7, 8, and 10, survival times are right-censored. In real-life clinical studies, right-censored observations may occur when a person does not experience the event of interest before the study ends, a person withdraws from the study because of some reason, for example, adverse drug reaction or death (if death is not the event of interest), or is lost to follow-up[5,7]. Further in the text, we will refer to right-censored data as censored.

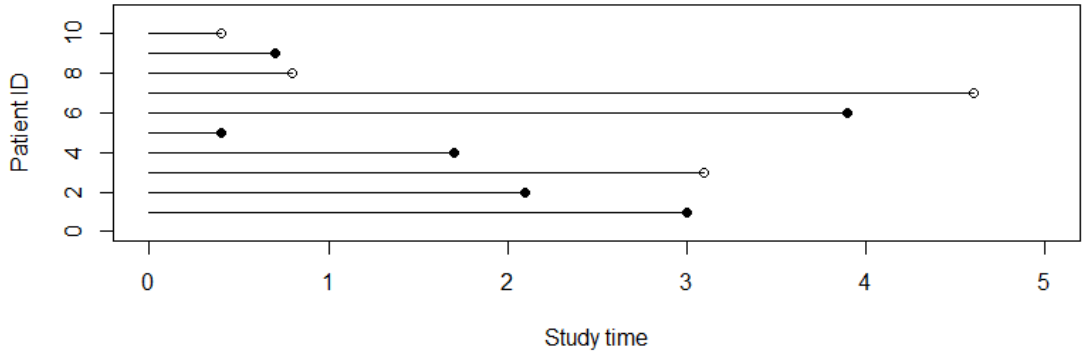

Figure 1 – Patient follow up in a hypothetical study. A filled circle indicates occurrence of the event, while an open circle indicates censoring.

The set of individuals who have not experienced the event of interest prior to a time t, is known as the *risk set* at time t. In the case shown in Figure 1, the risk set starts with 10 individuals and then gradually decreases to one and finally zero individuals.

Although most survival analysis data is right-censored, it can also be left-censored or interval-censored. If a person is *left-censored* at time t, we know they had an event between time 0 and t, but we do not know the time of event exactly. Also, the term delayed entry may be used for such data[5]. In other words, true survival time is less than or equal to the observed survival time. Similarly, if a subject's true (but unobserved) survival time is within a certain known specified time interval, such a person is *interval-censored*.

If event time of interest is censored by any mechanism related to the event, this phenomenon is referred to as *dependent* (*informative*) censoring[8]. The *independent* (*non-informative*) censoring assumption (that is, censoring mechanisms are unrelated to the event of interest) is crucial to the validity of most of the standard survival analysis methods and its violation can mislead the outcomes of analysis. The independent censoring assumption is often used for drawing correct inferences that compare the survival experience of two or more groups[7]. If censoring mechanisms involve dropout or withdrawal due to a worsening of the symptoms, censoring may introduce bias into the results of statistical analysis. This type of dropout is often called informative dropout and it is just one of many contributing causes of censoring[8].

The analysis of the time-to-event outcomes is based on the distribution function that describes the probability distribution of a random variable.

If a random variable X is discrete, the cumulative distribution function, CDF, denoted by $F_X(x)$, is a step function of x defined by

$$F_X(x) = P_X(X \leq x) = \sum_{x_i \leq x} f_X(x_i)\,,$$

where $f_X(x)$ is the probability mass function (PMF) of a discrete random variable X:

$$f_X(x) = P(X = x) \quad \text{for all } x.$$

For a continuous random variable X, $F_X(x)$ is a continuous function defined by

$$F_X(x) = P_X(X \leq x) = \int_a^b f_X(t)dt\,,$$

where $f_X(x)$ is the probability density function (PDF) of a continuous random variable X.

The complementary CDF, or CCDF, is the probability that random variable X takes a value greater than x. It is equivalent to $1 - F_X(x)$ and also known as the *survival function*[9]. In the survival analysis context, the survival function, $S(t)$, gives the probability that an individual survives longer than some specified time t:

$$S(t) = Prob(T > t).$$

Theoretically, $S(t)$ can be graphed as a smooth curve that will start from 1 at $t = 0$ and fall to zero if the study period increased without limit (Figure 2).

In practice, $\hat{S}(t)$ is usually a step function rather than a smooth curve. Additionally, since the study period is never infinite and there may be competing events, it is possible that not all individuals experience the event of interest[7].

The survival function is often defined in terms of the *hazard function* $h(t)$, which is the instantaneous failure rate. It is the probability that, given that a subject has survived up to time t, he or she fails in the next small interval of time Δt, divided by the length of that interval:

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

In contrast to a survival function, the $h(t)$ graph does not necessarily start at 1 and go down to zero but rather can start anywhere and go up and down in any direction over time (Figure 2). Moreover, the $h(t)$ is always non-negative and it has no upper bound[7].

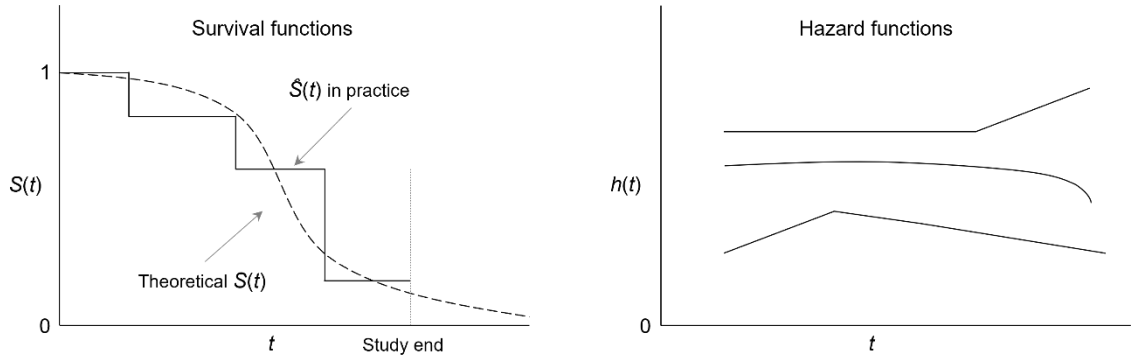

Figure 2 – Graphical representation of survival (on the left) and hazard (on the right) functions

If the form of $S(t)$ is known, one can derive the corresponding $h(t)$, and vice versa. The relationship between the two can be expressed by the formula:

$$h(t) = -\left[\frac{dS(t)/dt}{S(t)}\right].$$

The *cumulative hazard function* provides the total accumulated risk of experiencing the event of interest that has been gained by progressing to time t:

$$H(t) = \int_0^t h(x)dx\,.$$

While the instantaneous hazard function $h(t)$ can increase or decrease over time, the cumulative hazard function $H(t)$ can only increase or remain the same.

The survival function $S(t)$ can also be expressed using the cumulative hazard function as:

$$S(t) = exp\big(-H(t)\big).$$

This suggests that the estimation of $S(t)$ could also be based on $H(t)$[7].

Next, we will define the likelihood function (or simply likelihood) which is a central concept for the parameter estimation in modern statistics. Let $X_1, \ldots, X_n$ be IID with PDF (or PMF) $f(x|\theta)$. The likelihood function is just the joint density of the data and defined by

$$L_n(\theta) = \prod_{i=1}^{n} f(x_i|\theta).$$

The basic idea of maximum likelihood estimation is to find the value of θ that maximizes the likelihood function, so that, under the assumed statistical model, the observed data is the most probable. Such a value of θ that maximizes $L_n(\theta)$ is called maximum likelihood estimator, MLE, and denoted by $\hat{\theta}_n$. The MLE possesses several key properties that make it an appealing choice of estimator: under general conditions, in large samples, it is consistent, equivariant, efficient and asymptotically normally distributed[9].

This product formula of the likelihood function can be difficult to work with, so we can apply a logarithmic transformation to convert it into a sum, known as the log-likelihood function:

$$l_n(\theta) = log\, L_n(\theta).$$

Since the log transformation is monotonic, the value of θ that maximizes the log-likelihood also maximizes the original likelihood function[10].

The likelihood principle specifies how the likelihood function should be used for a data reduction as follows: if $\boldsymbol{x}$ and $\boldsymbol{y}$ are two sample points such that $L(\theta|\boldsymbol{x})$ is proportional to $L(\theta|\boldsymbol{y})$, that is, there exists a constant $C(\boldsymbol{x}, \boldsymbol{y})$ such that

$$L(\theta|\boldsymbol{x}) = C(\boldsymbol{x}, \boldsymbol{y})L(\theta|\boldsymbol{y}) \text{ for all } \theta,$$

then the conclusions drawn from $\boldsymbol{x}$ and $\boldsymbol{y}$ should be identical[11].

The constant $C(\boldsymbol{x}, \boldsymbol{y})$ may be different for different $(\boldsymbol{x}, \boldsymbol{y})$ pairs but $C(\boldsymbol{x}, \boldsymbol{y})$ does not depend on θ.

The likelihood ratio test can be used for testing hypothesis for a scalar or a vector-valued parameter. Consider testing:

$$H_0 : \theta \in \Theta_0 \quad versus \quad H_1 : \theta \notin \Theta_0 .$$

The likelihood ratio statistic is[9]

$$\lambda = 2\, log \frac{sup_{\theta \in \Theta} L(\theta)}{sup_{\theta \in \Theta_0} L(\theta)} = 2\, log \left(\frac{L(\hat{\theta})}{L(\hat{\theta}_0)} \right) ,$$

where $\hat{\theta}$ is the MLE and $\hat{\theta}_0$ is restricted to lie in Θ_0.

2.2. Methods of survival analysis

Since survival data is often incomplete due to censoring, regular statistical methods are not suitable for them. However, such data can be analyzed with the use of methods based on two fundamental concepts in survival analysis: the survival function and the hazard rate defined above. For this purpose, *non-parametric*, *parametric*, and *semi-parametric* methods can be applied.

Non-parametric methods make no assumptions about the underlying distribution of survival times. The *Kaplan-Meier* (KM) estimator[12] is a popular and widely used non-parametric method that allows to estimate the survival function from censored data when there are no covariates. This analysis relies on three assumptions. The first assumption is that at any time patients who are censored have the same survival prospects as those who continue to be followed. Secondly, the survival probabilities are assumed to be the same for subjects recruited early and late in the study. Lastly, we assume that the event occurs at the time specified[13]. The KM estimator (also known as the product limit estimator) is the product, taken over the ordered set of distinct event times, of the complement of the number of events divided by the number at risk. Formally,

$$\hat{S}(t) = \prod_{k \in t_k \leq t} (1 - d_k / n_k) ,$$

where d_k is the number of events and n_k is the number at risk, both at time t_k, the k^{th} distinct event time[14]. This becomes a step-down function, with each step at each time an event of interest happens. The height of a step at a given time is the proportion of individuals at risk just before the given time, who experience the event at that time[15].

The *Aalen-Johansen* estimator[16] is a matrix version of the Kaplan-Meier estimator. It can be used to estimate the transition probability matrix in case of multiple events of interest in a multi-state model approach which will be discussed further.

The most common estimator of the cumulative hazard function for the no-covariate case is the Nelson-Aalen estimator[17]:

$$\widehat{H}(t) = \sum_{t_k \leq t} d_k/n_k \, .$$

It is an increasing right-continuous step function with increments d_k/n_k at the observed failure times[18].

The Nelson-Aalen is also used as an alternative estimator for the survival function based on the relationship $S(t) = exp\big(-H(t)\big)$. Numerous asymptotic results have been reported for KM and Nelson-Aalen estimators in the literature. In particular, it has already been proved that they are asymptotically equivalent[19]. But the Nelson-Aalen estimator can be applied in a number of situations where the KM estimator does not make sense, moreover, the KM estimator can be derived as a function of the Nelson-Aalen estimator[5].

In survival analysis, investigators often want to test the hypothesis that the hazard rates, or equivalently the survival functions, are the same in two or more populations. A number of tests have been proposed for time-to-event data with censored observations that allow to compare estimates based on different values of a covariate, for example, treatment versus placebo groups, men versus women, or smokers versus non-smokers.

The *log-rank test*, which is also known as the Mantel-Haenszel test, is the most commonly used test for comparing survival curves. It is used to test the null hypothesis that there is no difference between the populations in the probability of an event at any time point (all survival curves are the same). Rejecting the null hypothesis means that at least one survival curve differs significantly from the others at some point in time[20].

The log-rank test is based on looking at the population at each event time and computing the expected number of events in proportion to the number of individuals at risk in each group k:

$$E_k(t) = N(t)\frac{R_k(t)}{R(t)},$$

where $E_k(t)$ is the expected number of events in group k at time t; $N(t)$ is the total number of events in all groups at time t; $R_k(t)$ is the number of individuals at risk in group k at time t, and $R(t)$ is the total number of individuals at risk in the study at time t.

Then, the test statistic is calculated. This statistic has a chi-square distribution with $k-1$ degrees of freedom. When two groups are being compared, the log-rank test statistic is given by the formula[20]:

$$\text{Log-rank} = \frac{(O_1 - E_1)^2}{Var(O_1 - E_1)},$$

where E_1 is the total number of events expected in group 1; O_1 is the total number of events observed in group 1. The variance is calculated as:

$$\text{Var}(O_1 - E_1) = \sum_t \frac{R_1(t)R_2(t)N(t)[R(t) - N(t)]}{R(t)^2[R(t) - 1]}.$$

When there are more than two groups, the test statistic is more complicated mathematically, involving both variances and covariances of summed observed minus expected scores for each group. A convenient mathematical formula can be given in matrix terms[7].

The log-rank test assesses statistical significance but does not estimate an effect size. Moreover, it is most likely to detect a difference between groups when the risk of an event is consistently greater for one group than another[21]. Also, there are some situations where the validity of the log-rank test is questionable, for example, in the case of Kaplan-Meier survival curves that cross, indicating non-proportional hazards. The alternative approaches are the weighted log-rank tests (Wilcoxon, Tarone-Ware, Peto and Fleming-Harrington) which are variations of the log-rank test[22].

The log-rank statistic gives all observations the same weight, regardless of the time at which an event occurs. The weighted tests are based on statistics that give weight to the observations according to the importance one wants to give to the beginning or end of the survival time.

The *Wilcoxon* test weights the observed minus expected score at time t_j by the number at risk $R(t_j)$ over all groups at time t_j. Thus, the Wilcoxon test places more emphasis on the information at the beginning of the survival curve where the number at risk is large

allowing early failures to receive more weight than later failures. This type of weighting may be used to assess whether the effect of a treatment on survival is stronger in the earlier phases of administration and tends to be less effective over time[7].

The *Tarone-Ware* test statistic also applies more weight to the early failure times by weighting the observed minus expected score at time t_j by the square root of the number at risk, $\sqrt{R(t_j)}$. The *Peto* test weights the failure time t_j by the survival estimate $\tilde{S}(t_j)$ calculated over all groups combined. This survival estimate is similar but not exactly equal to the Kaplan-Meier survival estimate[7]. The *Flemington-Harrington* test uses the Kaplan-Meier survival estimate $\hat{S}(t)$ over all groups to calculate its weights for the failure time t_j, $\hat{S}(t_{(j-1)})^p[1-\hat{S}(t_{(j-1)})]^q$.

In contrast to non-parametric methods, parametric methods assume a specific distribution for the outcome (survival time) and estimate the parameters of the chosen distribution to predict survival probabilities. Common distributions utilized for survival data include Weibull, exponential (a special case of Weibull), log-logistic, log-normal, and generalized gamma. The advantage of parametric models is that they are often easier to work with because they are defined by a small and fixed number of unknown parameters. This allows us to use for parameter estimation and inference methods based on the likelihood principle[10].

Many parametric models are acceleration failure time (AFT) models which assume that the effect of covariates is multiplicative with respect to survival time. In contrast, the proportional hazards model discussed further assumes that the effect of covariates is multiplicative with respect to the hazard[7].

Parametric methods are adequate in several biomedical studies when the data can be assumed to follow some distribution, but the most important role in biomedical applications is played by non-parametric and semi-parametric methods, as they offer flexibility in accommodating various forms of hazard functions[10].

The *Cox proportional hazards model* is a popular semi-parametric model used for time-to-event data in the presence of one or more predictors. It is not a fully parametric model. Rather it is a semi-parametric model because even if the regression parameters are known, the distribution of the outcome remains unknown, and it does not rely on distributional assumptions for the outcome. The Cox model is usually written in terms of the hazard model formula giving an expression for the hazard at time *t* for a patient with a vector of explanatory variables[7]:

$$h(t,x) = h_0(t)e^{\sum_{i=1}^{p}\beta_i x_i}.$$

The Cox model is often called Cox "proportional hazards" model since it assumes the proportional hazards between two groups and that the proportionality constant is independent of time. This is also known as the proportional hazards (PH) assumption.

According to the formula above, the hazard at time t is the product of the baseline hazard function, $h_0(t)$ and the exponential term e to the linear sum of $\beta_i x_i$, where the sum is over the p explanatory variables. The baseline hazard, $h_0(t)$, is an unspecified function, that makes the Cox model a semi-parametric model. The exponential term involves x's but not t (x's are time-independent). If there is an interest in time-dependent variables, the Cox model form may still be used, but it no longer satisfies the PH assumption and is called the extended Cox model.

In the expression for the Cox PH model above, e^{β_i} gives an estimated *hazard ratio* (HR) for the effect of each variable adjusted for the other variables in a model. A HR is the result of comparing the hazard rates between two groups (e.g., in clinical trials, treated versus the control group[23]). A HR of 1 means equal hazard rates in the two groups. HR less than 1 means a lower hazard rate in persons with a risk factor compared to the persons from reference group. A HR greater than 1 means that the hazard rate is higher in one group compared to the other.

For the inference on regression coefficients, to test the null hypothesis $\beta = \beta_0$, the following tests can be applied[5,17]:

- The likelihood ratio test statistic:

$$\chi^2_{LR} = 2\{log\, L(\hat{\beta}) - log\, L(\beta_0)\}$$

- The score test statistic:

$$\chi^2_{SC} = U(\beta_0)^T \mathcal{J}(\beta_0)^{-1} U(\beta_0),$$

where $\mathcal{J}(\beta_0)$ is the expected information matrix and $U(\beta_0) = \frac{\partial}{\partial\beta} log\, L(\beta)$ is written for the vector of score functions.

- The Wald test statistic:

$$\chi^2_W = (\hat{\beta} - \beta_0)^T \mathcal{J}(\hat{\beta})(\hat{\beta} - \beta_0).$$

These three test statistics are asymptotically equivalent, and they are all approximately chi-squared distributed under the null hypothesis. Although these tests are usually quite similar; if they disagree, conclusions should be based on the likelihood ratio test[24].

These tests can be generalized to test a composite null hypothesis that *r* of the *p* regression coefficients are equal to zero. In particular, if β^* is the maximum partial likelihood estimator under the null hypothesis, then the likelihood ratio statistic takes the form $\chi^2_{LR} = 2\{log\, L(\hat{\beta}) - log\, L(\beta^*)\}$ and is approximately chi-squared distributed with *r* degrees of freedom when the null hypothesis holds true[5].

The semiparametric nature of relative risk regression models in survival analysis makes it impossible to use ordinary likelihood methods to estimate the regression coefficients. Instead one has to resort to a partial likelihood (or Cox likelihood)[5]. Partial likelihood considers probabilities only for individuals who fail and not for individuals who are censored[7] and can be applied to Cox proportional hazards model.

2.3. Competing risks

When more than one event is investigated, such as death from various causes, the statistical problem can be considered as a competing risks situation (Figure 3). In this case, an individual or entity faces multiple possible outcomes that cannot all occur simultaneously. A competing risk refers to an event that precludes the observation of an event of interest or alters the probability of its occurrence[25].

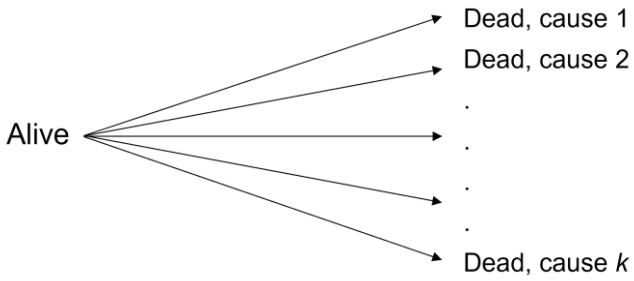

Figure 3 – A competing risks situation with k causes of failure.

In the analysis of time-to-event data, the occurrence of competing risks is common. For example, in transplant research, competing risks arise when a patient has a risk of dying from causes unrelated to the transplant, such as infection or cardiovascular disease[26]. In life insurance, competing risks arise when a policyholder has a risk of developing different critical illnesses such as cancer, heart attack, and stroke[27].

Competing risks impose additional challenges to survival analysis and may lead to biased results if not properly accounted for. Competing risks are assumed to be independent, but we can never explicitly prove that competing risks are or are not independent for a given dataset[7].

In the presence of competing risks, two different hazard functions have been defined: the cause-specific hazard function and the subdistribution hazard function[28].

The *cause-specific hazard function* generalizes the classical concept of the hazard function to the competing-risks setting[29]. The competing risks data is represented by the random variable T, time of failure, the cause of failure D, along with possible covariate vector z. Inference therefore is to be based on the joint distribution of T and D, possibly given z. The cause-specific hazard function is a fundamental concept in competing risks models as it determines the hazard of failing from a given cause in the presence of the competing events[2]:

$$h_k^{cs}(t) = \lim_{\Delta t \to 0} \frac{Prob(t \leq T < t + \Delta t, D = k | T \geq t)}{\Delta t}.$$

The cause-specific hazard function for a given event type k is the instantaneous rate of occurrence of the given type of event in subjects who are currently event-free[28].

The *subdistribution hazard function*, introduced by Fine and Gray, for a given type of event is defined as the instantaneous rate of occurrence of the given type of event in subjects who have not yet experienced an event of that type[28]:

$$h_k^{sd}(t) = \lim_{\Delta t \to 0} \frac{Prob\big(t \leq T < t + \Delta t, D = k | T \geq t \cup (T < t \cap D \neq k)\big)}{\Delta t}.$$

It means that for the subdistribution hazard function, the rate of the event is considered in those subjects who are either currently event-free or who have previously experienced a competing event[28].

The Kaplan–Meier method is one of the most frequently used as well as the most controversial technique in the context of competing risks. The KM survival curve may not be very informative because it is based on an independence assumption about

competing risks that cannot be verified[7]. This has led to alternative methods for handling competing risk data. One such alternative is the *cumulative incidence curve* (CIC).

In the simplest case, if there is only one event of interest, the CIC is $(1 - KM)$ estimate. When there are competing risks, however, the CIC is derived from a cause-specific hazard function, provides estimates of the ”marginal probability” of an event in the presence of competing events, and does not require the assumption that competing risks are independent[7]. The cumulative incidence (or subdistribution) function of cause k, $I_k(t)$, is defined by the probability $Prob(T \leq t, D = k)$ of failing from cause k before time t. It can be expressed in terms of the cause-specific hazards as[2]

$$I_k(t) = \int_0^t h_k(s)S(s)\, ds\,.$$

Nevertheless, the CIC does require that the overall hazard equals to the sum of the individual hazards for all the risks. This assumption will be satisfied, however, whenever competing risks are mutually exclusive and events are nonrecurrent, i.e., only one event can occur at any one time and only once over time[7].

Modeling covariate effects for competing risks data poses special challenges since it can be difficult to accurately define the hazard function on which the covariates should operate. Similar to how it's done in standard survival analysis, the effect of one or two binary covariates is most easily investigated by estimating CICs using non-parametric methods and testing whether the curves differ or not. Gray[30] developed a log-rank type test to compare cumulative incidence probabilities in several groups. Gray’s test is perhaps the most frequently used. It does not require the independence assumption, however, it does not adjust for covariates[7]. Also, other two tests have been proposed that directly compare the cumulative incidence functions in two groups (e.g., treatment versus placebo). The first, based on a suggestion of Lin[31], employs a Kolmogorov–Smirnov type statistic which compares the maximum distance between the two-sample cumulative incidence functions. The second, based on a suggestion of Pepe[32], compares (weighted) integrated difference between the two cumulative incidence curves[33].

If there is an interest in the effect of a covariate on an event of interest in the presence of competing events, two approaches based on proportional hazards are typically in use. The first approach imposes the PH assumption on the *cause-specific hazards* (CSH), while the second one is the proportional *subdistribution hazards* (SDH) model developed by Fine and Gray[34].

If either the covariate is continuous or if there is an interest in examining the simultaneous effect of multiple covariates on cause-specific failure, the most logical choice would be to use a competing risks analog of a Cox PH model. Since the cause-specific hazards are identifiable, it is possible to perform regression on the cause-specific hazards. In PH regression on the cause-specific hazards, the cause-specific hazard of cause k for a subject with covariate vector z is modeled as:

$$h_k(t|z) = h_{k,0}(t)exp(\beta_k z),$$

where $h_{k,0}(t)$ is the baseline cause-specific hazard of cause k, and the vector β_k represents the covariate effects on cause k. These covariate effects are proportional for the cause-specific hazards. The analysis is completely standard, but the interpretation requires caution. At each time some individual fails from cause k, the covariate values of this individual are compared with the covariates of all other individuals still event-free and in follow-up. Persons who fail from another cause are censored at their transition time[2].

If the number of competing events becomes large or when one of the events is rare, assuming the equality of effects or proportionality of baseline hazards can be necessary to prevent overfitting. In such cases, the reduced rank proportional hazards model for competing risks presented in Fiocco et al.[35] could be useful.

While the Cox model is extensively utilized in survival analysis, there are other models that can be employed for this purpose as well. In order to avoid the highly nonlinear effects of covariates on the CIFs when modeling is done on the cause-specific hazards, Fine and Gray introduced a way to regress directly on CIFs. They defined a subdistribution hazard as:

$$\bar{h}_k(t) = -\frac{d\, log\big(1 - I_k(t)\big)}{dt}.$$

When there is no censoring, individuals remain in the risk set forever. If they are given a censoring time that is greater than all event times, the analysis becomes completely standard. In the case of censoring, they remain in the risk set until their potential censoring time, which is unobservable if they experience another event before it. With administrative censoring, the potential censoring time remains known. If individuals may also be lost to follow-up, a censoring distribution is estimated from the data. Fine and Gray imposed a PH assumption on the subdistribution hazards[2]:

$$\bar{h}_k(t|z) = \bar{h}_{k,0}(t)exp\big(\beta_k^T z\big).$$

The Fine and Gray model may seem puzzling mainly because this approach considers individuals still at risk for an event type 1 after they experienced the competing event type 2, what is usually perceived as unnatural. However, the Fine and Gray method yields reliable inference[34].

2.4. Multi-state models

The multi-state framework models events as transitions between states and includes competing risks as a special case[36]. The survival data situation with competing risks may be described by the Markov process with one starting state and multiple exclusive absorbing states. Typically, the history of disease evolvement may also include intermediate events that can neither be classified as initial states nor as final states. This type of model is called a multi-state model. Figure 4 illustrates some of examples of multi-state models[37].

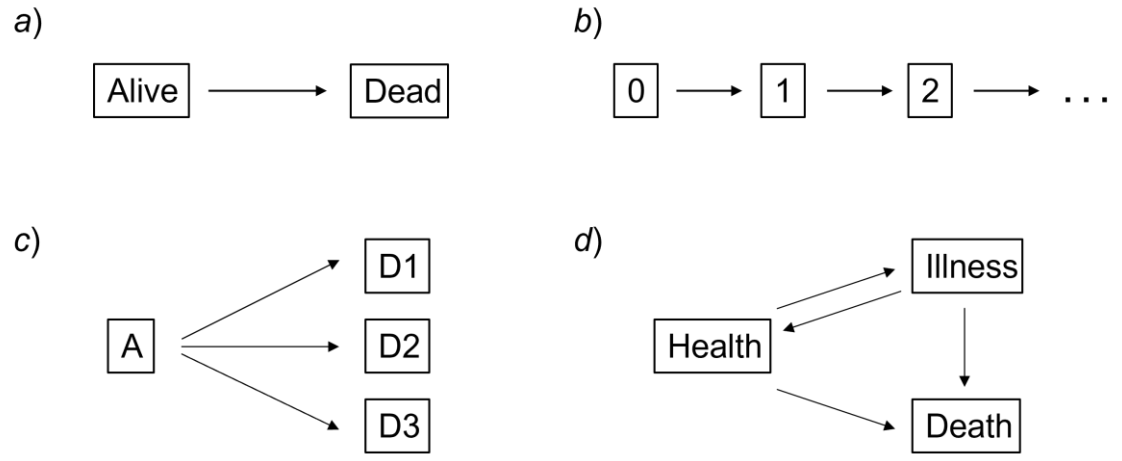

Figure 4 – Examples of multi-state models[37]: a) - simple survival, b) - sequential events, c) - competing risks situation, and d) - illness-death model.

Figure 4a shows a simple multi-state model with two states (alive and dead) with one possible transition between them. Diagram in Figure 4b represents sequential events (for instance, repeated infections). Figure 4c shows a classic competing risk situation, where all individuals start on the left and each individual can make a single transition to one of three terminal states. Lastly, diagram in Figure 4d shows a common multi-state situation known as the illness-death model[37] with recovery. In this class of models, individuals start out as healthy. They may become ill and afterwards they may die. They

may also recover from their illness and become healthy again (bi-directional illness-death model). Individuals may also die without first becoming ill. A typical situation that can be described with the illness-death model is when individuals infected with HIV may develop AIDS but may also experience a switch to syncytium inducing (SI) HIV phenotype. If the SI switch occurs first, it may change the risk to progress to AIDS[2].

Often, there are multiple options for the state-transition diagrams, and sometimes it is revealing to look at a specific problem from multiple views[37].

Multi-state models approach allows one to estimate the probability of being in a state (or a cluster of states) across time, the probabilities of transitioning between states, the mean length of stay in a state, and the probability of ever visiting a state, as well as the hazard rates/ratios for each transition[38].

In practice, it is often assumed that the multi-state model is a Markov model. For a multi-state model, this means that, given the current state and the event history of a patient, the next state to be visited and the time at which this will occur will only depend on the present state and not on the sequence of events that preceded it. Thus, competing risks models are always Markovian since there is no event history[2].

Considering uni-directional multi-state models without recurrent events, we represent a transition from state i to state j by "$i \rightarrow j$". We denote the hazard rate (transition intensity) of the $i \rightarrow j$ transition by:

$$h_{ij}(t) = \lim_{\Delta t \downarrow 0} \frac{Prob(t \leq T < t + \Delta t | T \geq t)}{\Delta t} ,$$

where T denotes the time of reaching state j from state i.

Then, the cumulative hazard for transition $i \rightarrow j$ is defined by:

$$H_{ij}(t) = \int_0^t h_{ij}(s) ds .$$

There are two approaches to define the time scale to which t refers, "clock forward" and "clock reset". According to "clock forward" approach, time t refers to the time since the subject entered the initial state. The clock keeps moving forward for the patient, also when intermediate events occur. In the "clock reset" approach, time t in $h_{ij}(t)$ refers to the time since entry in state i. The clock is reset to 0 each time the patient enters a new state. The primary factor in choosing between two approaches is the clinical context.

2.5. Motivation

In the 21st century, chronic kidney disease (CKD) has become one of the major causes of death. The number of people affected by CKD has also been increasing, partly due to risk factors like obesity and diabetes, affecting an estimated 843.6 million individuals worldwide in 2017. Despite a decline in mortality for end-stage kidney disease (ESKD) patients, the Global Burden of Disease (GBD) studies have shown that CKD has emerged as a leading cause of worldwide mortality. Therefore, it is crucial to identify, monitor, and treat CKD, and to implement systematic preventive and therapeutic measures worldwide[39].

Peritoneal dialysis (PD) is one of the main renal replacement therapies along with renal transplantation and haemodialysis. The progression of ESKD patients included in a PD program is monitored with regular control visits for recording the clinical parameters and time until the occurrence of relevant events. The main reasons for patients dropping out of a PD program are the competing events of death, transfer to haemodialysis, and renal transplantation. Therefore, to assess PD programs, indicators such as patient survival (with death as the endpoint of interest) and technique survival (with transfer to haemodialysis as the endpoint of interest) have been defined. In the PD program, a patient can experience one or more peritonitis episodes. Thus, peritonitis can be considered as a non-absorbing event before the observation of an absorbing event (death, transfer to haemodialysis, or renal transplantation)[40].

An evaluation of a PD program can provide valuable information on its performance and identify areas that need improvement. This information can help healthcare providers to optimize patient care, increase patient survival, and improve quality of life. From a statistical point of view, an approach that takes competing risks into account is the most suitable one. Competing risks models have been widely used in medical and epidemiological studies[41]. In oncology and cardiovascular medicine, the analytical problem of competing risks has been acknowledged for many years, whereas in nephrology, it has been addressed relatively recently[42]. Nevertheless, the competing risks are common in various areas of nephrology and studying it is particularly important. In PD context, a PD-related peritonitis episode can be considered as an event of interest, while death, renal transplantation and transfer to haemodialysis will be competing events because subjects who experience one of these events are no longer at risk of developing PD-related peritonitis[42]. In such studies, competing risks analysis can be also used to

evaluate patient and technique survival, peritonitis-free survival and hospitalization-free survival[43].

In this work, we perform competing risks analysis in application to real data on PD patients. For this purpose, a basic descriptive analysis of the studied dataset is performed. The CIFs are estimated nonparametrically. The factors associated with events of interest are defined using two semi-parametric methods: CSH and SDH regression models. A multi-state model with a transient state is applied to simulated data with intermediate event (peritonitis).

3. Competing risks modeling in a peritoneal dialysis context

3.1. Software used

There are various software options available for performing competing risks analysis (R Software, Stata, SAS, SPSS). The choice of software depends on the user's preference, familiarity, and the specific requirements of the analysis.

In this project, we used the R language and environment[44] to perform data analysis and modeling. R is a freely available widely used open-source statistical software that offers a variety of packages for different types of analyzes. We used the “survival” package, which provides a wide range of functions for time-to-event analysis, including the estimation of survival curves, hazard rates, and regression models. Additionally, we used the “cmprsk” package[45], which implements the Fine and Gray model for competing risks analysis, and the “mstate” package, which allows for the analysis of multi-state models.

Function *cuminc*() from “cmprsk” package allows us to estimate CIFs non-parametrically from competing risks data, test equality across groups, and visualize estimated CIFs. The Fine and Gray model can be fit with *crr*() function (“cmprsk” package) which also allows for time-varying covariates. Predictions and visualization of CIFs for individuals with specified covariate values are allowed for *crr*-object. Alternatively, competing risk models can be fit with “riskRegression” package by employing different link functions between covariates and outcomes[46]. Regression on CSH can be performed treating competing events as censoring in any package that includes the Cox proportional hazards model, such as the “mstate” package[47] and the “survival” package[48].

The “mstate” package is particularly useful for analyzing competing risks data, as it can handle complex situations that involve multiple outcomes. This package covers all steps of the analysis of multi-state models (and competing risks models, as they are a special category of multi-state models), from model building and data preparation to estimation and graphical representation of the results. It can be applied to non- and semi-parametric models[49].

3.2. Analytical strategy

Figure 5 shows a flowchart that guides on analytical strategies depending on whether there are competing events or not. If there are no competing events, classical survival methods can be used. If there are competing events, an analytical approach should account them for. Then, depending on the goal, different methods can be applied. The CSH models are usually used to understand the association between a predictor and the event of interest. The SDH models can estimate the relationship between the predictor and the event of interest while accounting for the competing events. SDH models provide a convenient and direct calculation of CIFs and allow to predict the chance that an individual with given characteristics will experience the event of interest within a specified time period[15].

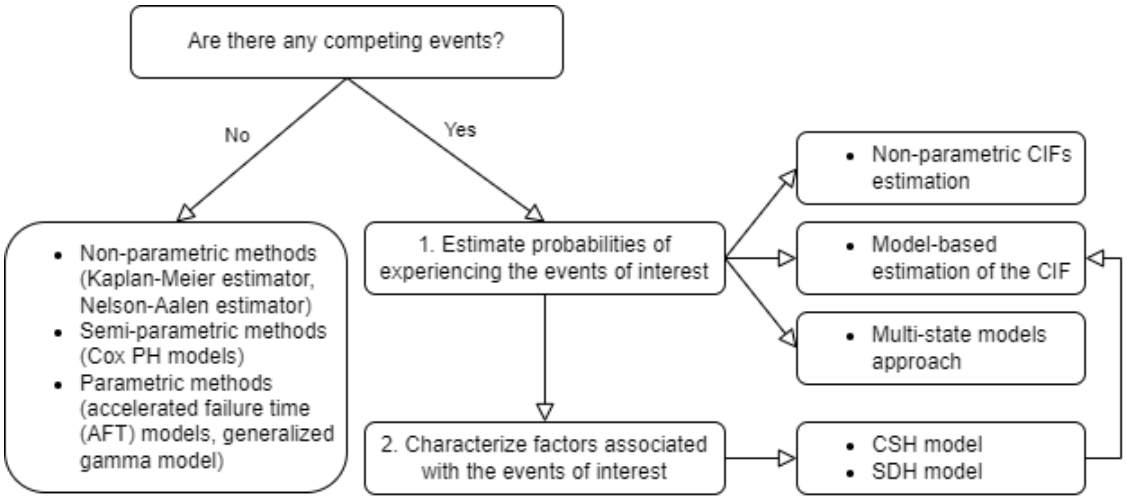

Figure 5 – Analytical strategies depending on whether there are competing events or not.

The competing events data analysis can be described as follows:

1. **Exploratory data analysis**

2. **Non-parametric CIF estimation**:
    a. Overall CIF estimation of marginal probability of death, transfer to HD, and renal transplantation.
    b. Subdistribution CIF estimation: separate estimates for each outcome for depending on:

i. whether a patient has diabetes or no
ii. whether a patient is male or female, etc.
iii. Gray's test for differences between two groups.

3. **Semi-parametric modeling**:
    a. CSH regression model:
        i. Model selection
        ii. Model diagnostic (assessing the PH assumption)
        iii. Model-based estimation of the CIF
    b. SDH (Fine and Gray) regression model:
        i. Model selection
        ii. Model diagnostic (assessing the PH assumption)
        iii. Model-based estimation of the CIF

4. **Multi-state model approach (if applicable)**:
    a. Multi-state model selection, states and transitions definition
    b. Estimation of the effect of prognostic factors on the transition rates:
        i. Consider "clock-forward" or "clock-reset" approach
        ii. Markov stratified hazards model
        iii. Markov proportional hazards model
        iv. State arrival extended Markov proportional hazards model.
    c. Prediction:
        i. Obtention of the patient-specific transition hazards
        ii. Obtention of the of the patient-specific probabilities of going to specific state or staying in specific state.

3.3. Data simulation

To illustrate the analysis and modeling process in the presence of competing events, we generated two competing risks datasets. The first dataset, *artPD*, was generated for competing risks modeling via the following algorithm:

1. Simulate failure times using random sampling from exponential distribution (Weibull or Gompertz distributions can be also used).

2. Simulate, using random sampling, from the vector of elements (0, 1, …, n) status variable which indicates the cause of failure (1, …, n) or if an individual was lost for follow-up (0=censoring).
3. Generate covariates (e.g., age, sex, diabetes).
4. Update failure times and status based on the effect of covariates.

The second dataset, *artIDM*, contains intermediate event and was generated to illustrate the multi-state model approach.

1. Simulate time-to-event for death and intermediate state (peritonitis) using random sampling from exponential distribution (Weibull or Gompertz distributions can be also used).
2. Simulate status variable for absorbing state (death) using the random sampling from the vector of elements (0=censoring, 1=death).
3. Simulate status variable for intermediate state (peritonitis) using random sampling from the vector of elements (0=censoring, 1= peritonitis).
4. Generate covariates (e.g., age, sex, diabetes).
5. Update failure times and status based on the effect of covariates.
6. If necessary, remove implausible observations, e.g., where time of an intermediate event is larger than of death or lost for follow-up.

3.4. Competing risks modeling, simulated data

Non-parametric CIF estimation

We start with overall CIF estimation for the death, transfer to HD, and renal transplantation. The estimated marginal probabilities of each outcome by month are shown in Figure 6 and Table 1.

Next, we obtain separate estimates of the cumulative incidence for each outcome for patients who have diabetes and do not have it. The results are shown in Figure 7. The same can be repeated for other sub-groups, for example, male vs. female, or ≤ 45 years old vs. > 45 years old. Note that we cannot draw any conclusive findings based on simulated data.

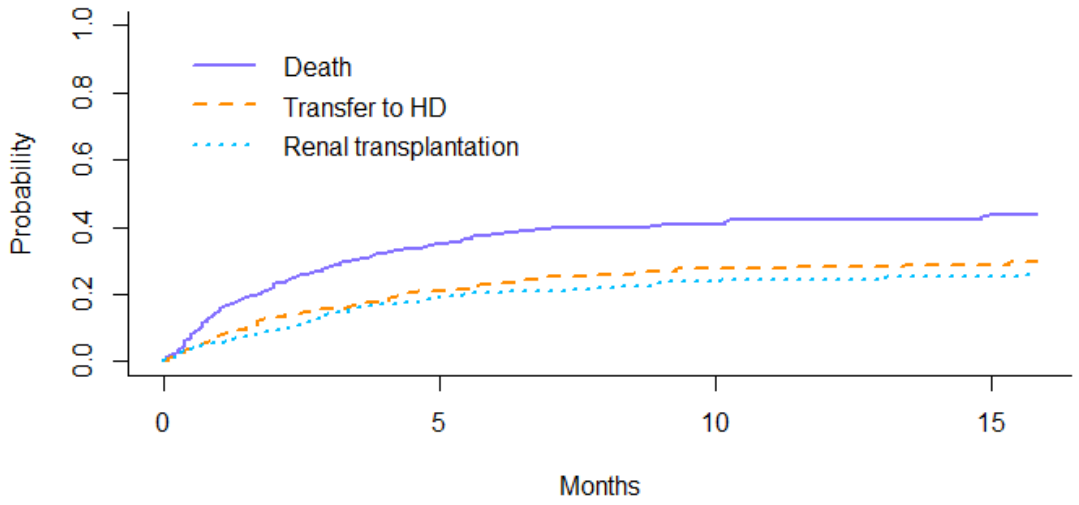

Figure 6 – Cumulative incidence for each outcome, patients on PD, simulated data.

Table 1: The overall CIF estimation of each outcome by months, patients on peritoneal dialysis

Outcome	**CIF,** estimate (variance)		
	months		
	5	**10**	**15**
Death	0.3546 (0.0007)	0.4077 (0.0008)	0.4354 (0.0009)
Transfer to HD	0.2108 (0.0005)	0.2758 (0.0007)	0.2897 (0.0008)
Renal transplantation	0.1948 (0.0005)	0.2377 (0.0006)	0.2516 (0.0007)

Abbreviations: CIF, cumulative incidence function; HD, haemodialysis

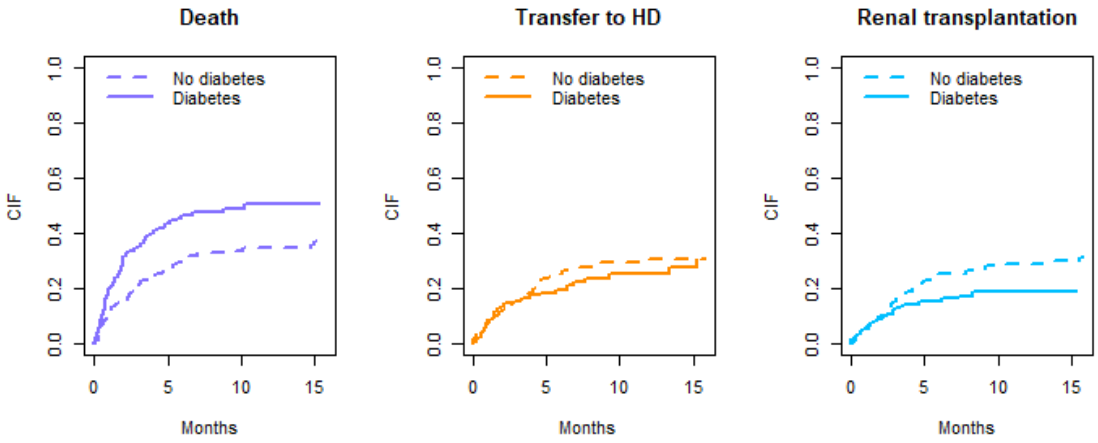

Figure 7 – Cumulative incidence for each outcome, patients on peritoneal dialysis, by diabetes (yes vs. no).

A formal test for differences between two groups of patients can be performed using the Gray's test. The test statistics for differences in incidence of each outcome, along with *p*-values, are presented in Table 2.

Table 2: Gray's test for differences between two groups of PD patients, by diabetes (yes vs. no)

Outcome	**Gray's test statistic**	**df**	***p*-value**
Death	9.697	1	0.002
Transfer to HD	0.349	1	0.555
Renal transplantation	3.389	1	0.066

Abbreviations: df, degrees of freedom; HD, haemodialysis

For death outcome, *p*-value of 0.002 indicates a statistically significant difference between cumulative incidence functions of patients without diabetes versus patients with diabetes. For the other two outcomes, Transfer to HD and Renal transplantation, *p*-values are larger than 0.05 indicating that there is no statistically significant difference (with a significance level of 0.05) in cumulative incidence among the two groups.

Dataset characterization

The generated *artPD* dataset contains 400 observations of 6 variables. There are three different types of events (death, transfer to haemodialysis (HD), and renal transplantation) and three risk factors have been included: age, sex, and diabetes. The dataset also includes censored observations.

Coding:

- **id**: subject's ID number
- **sex**: refers to individual sex (1 = male (ref.), 2 = female)
- **age**: age at baseline (time point=0)
- **diabetes**: diabetes mellitus (Yes/No (ref.))
- **time**: time to event in months
- **status**: status of a subject (0 = censored, 1 = death, 2 = transfer to HD, 3 = renal transplantation).

The *artPD* dataset represents hypothetical study that involved 400 patients enrolled in PD program. The simple median follow-up time was only 1.7 months, whereas the potential follow-up time calculated using the "reverse" Kaplan-Meier method[10] was 7.3 months (range 0-15.8 months). The types and numbers of events and the patient's characteristics are summarized in Table 3 and Table 4, respectively.

Competing risks model for the PD patients' survival analysis study is shown in Figure 8. It has an initial state (start peritoneal dialysis program) and three different endpoints (absorbing states with no transitions between them).

Table 3: Types of events in *artPD* dataset

Outcome	**n**	**%**
Death	140	19.5
Transfer to haemodialysis	89	12.4
Renal transplantation	77	10.7
Censored	94	23.5

Table 4: Baseline characteristics of patients in *artPD* and *artIDM* datasets

Patient's characteristic		**n**	**%**
Gender	Male	186	46.5
	Female	214	53.5
Age (years)	N	400	100.0
	mean (SD)	49.58 (15.50)	
	Median (Q1-Q3)	49.00 (40.75 - 59.25)	
	Min-Max	7.00 – 94.00	
Diabetes	Yes	197	49.3
	No	203	50.7

Abbreviations: Max, maximum; Min, minimum; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation

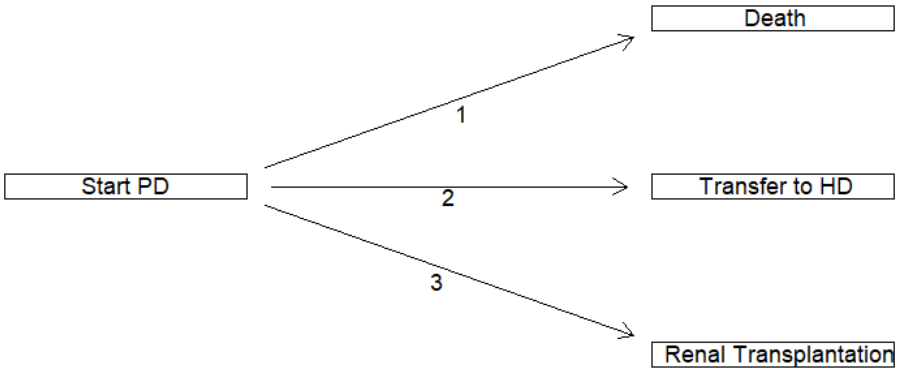

Figure 8 – A competing risks situation in the PD patients' survival analysis study.

Semi-parametric regression models

For a cause-specific hazards regression model, we use "mstate" package. We start with creating the transition matrix based on a competing risks model shown in Figure 8. Since there is one initial state and three absorbing states, the transition matrix is as follows:

from\to	event − free	death	transfer to HD	renal transpl.
event − free	NA	1	2	3
death	NA	NA	NA	NA
transfer to HD	NA	NA	NA	NA
renal transpl.	NA	NA	NA	NA

After converting the data into a long format and adding transition-specific covariates, we run CSH regression model with separate covariate effects for three outcomes. The crude and adjusted hazard ratios with confidence intervals and respective *p*-values are summarized in Table 5.

Since we deal with simulated data, we omit the step of model selection and consider only the full one:

$$h_c(t, X) = h_{0c}(t)exp[\beta_{1c}Sex + \beta_{2c}Age + \beta_{3c}Diabetes] ,$$

where $c = 1,2,3$ is event type and for the specific event type while the other two types of events are censored. The hazard ratios will be defined as (by example of variable Sex):

$$HR_c(Sex = Female\ vs. Sex = Male(Ref.) = exp[\beta_{1c}] .$$

The next step is assessing the PH assumption. The function *cox.zph*() from "survival" package performs a statistical test on PH assumption. It tests the correlation between the Schoenfeld residuals and survival time (or ranked survival time).

Table 6 shows that the *p*-value is only significant for age in case of transfer to HD indicating the potential violation of PH assumption for this variable. The global test (last row in Table 6) tests the PH assumption for all predictors simultaneously. It is not significant for any type of outcome suggesting that the PH assumption is satisfied.

Table 5: Parameter estimates in cause-specific hazards regression model, simulated data

Outcome	**Variable**		**Unadjusted model**		**Adjusted model**	
			HR (95% CI)	***p***	**HR (95% CI)**	***p***
Death	Age		1.01 (1.00-1.02)	0.050	1.01 (1.00-1.02)	0.067
	Sex	Female	1.24 (0.89-1.74)	0.204	1.27 (0.90-1.78)	0.168
		Male	1	-	1	-
	Diabetes	Yes	1.70 (1.21-2.38)	0.002	1.71 (1.22-2.40)	0.002
		No	1	-	1	-
Transfer to HD	Age		1.01 (1.00-1.02)	0.199	1.01 (1.00-1.02)	0.209
	Sex	Female	1.10 (0.72-1.67)	0.671	1.08 (0.71-1.65)	0.721
		Male	1	-	1	-
	Diabetes	Yes	1.04 (0.68-1.58)	0.872	1.03 (0.68-1.57)	0.888
		No	1	-	1	-
Renal transpl.	Age		1.00 (0.98-1.01)	0.664	1.00 (0.98-1.01)	0.763
	Sex	Female	0.77 (0.49-1.21)	0.251	0.76 (0.48-1.20)	0.237
		Male	1	-	1	-
	Diabetes	Yes	0.79 (0.49-1.26)	0.324	0.78 (0.49-1.25)	0.297
		No	1	-	1	-

Abbreviations: CI, confidence interval; HD, haemodialysis; HR, hazard ratio

Table 6: Correlation between
the Schoenfeld residuals and ranked survival time

Variable	**df**	**Outcome**					
		Death		**Transfer to HD**		**Renal transpl.**	
		chisq	***p*-value**	**chisq**	***p*-value**	**chisq**	***p*-value**
age	1	1.191	0.28	4.896	0.03	0.0004	0.98
sex	1	0.604	0.44	0.616	0.43	0.045	0.83
diabetes	1	2.378	0.12	0.033	0.86	0.713	0.40
GLOBAL	3	3.917	0.27	5.369	0.15	0.742	0.86

Abbreviations: chisq, chi-square statistic; df, degrees of freedom; HD, haemodialysis

Figure 9 shows the Schoenfeld residuals plotted against each individual's failure for all variables for death outcome. Plots for event types 2 and 3 are given in Figure 26 and Figure 27 (Annex 1). From the graphical inspection, there is a pattern of changing residuals across failure times for some of the covariates, indicating a potential violation of the PH assumption.

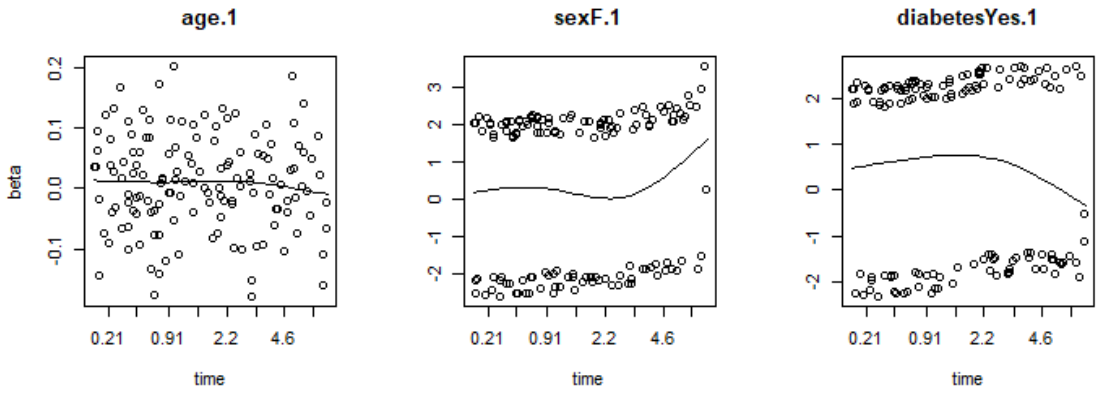

Figure 9 – Schoenfeld residuals plotted against failure time (graphical assessment of the PH assumption), CSH model, death, simulated data.

In case of Schoenfeld residuals showing a potential violation of the PH assumption, one can try to fit a time-dependent model or a stratified Cox model. Another possible solution is to try to transform the covariate that violates the proportional assumption or use a different model[7].

Now we can obtain the predicted cumulative incidences for each outcome and compare them for individuals with diabetes and without diabetes given that, for example, an individual is 60 years old male (Figure 10).

Nonlinearity, which refers to an incorrectly specified functional form in the parametric part of the model, poses a potential issue in Cox regression similar to linear and generalized linear models. In order to identify nonlinearity, the martingale residuals can be plotted against covariates, and can also be used to create component-plus-residual (or partial-residual) plots, following the approach used in linear and generalized linear models[50].

Figure 11 shows the plots of martingale residuals and partial residuals against the age for the regression of time to first event on age. Nonlinearity is not an issue for sex and diabetes since these covariates are dichotomous factors. Similar to the plots of Schoenfeld residuals, smoothing these plots is also important for interpretation. The smooth curves depicted in Figure 11 are generated using local linear regression with the

lowess() function. By setting *iter* = 0, a non-robust smooth is chosen, which is typically recommended for plots that may be banded[50]. It seems that nonlinearity is very slight in this case.

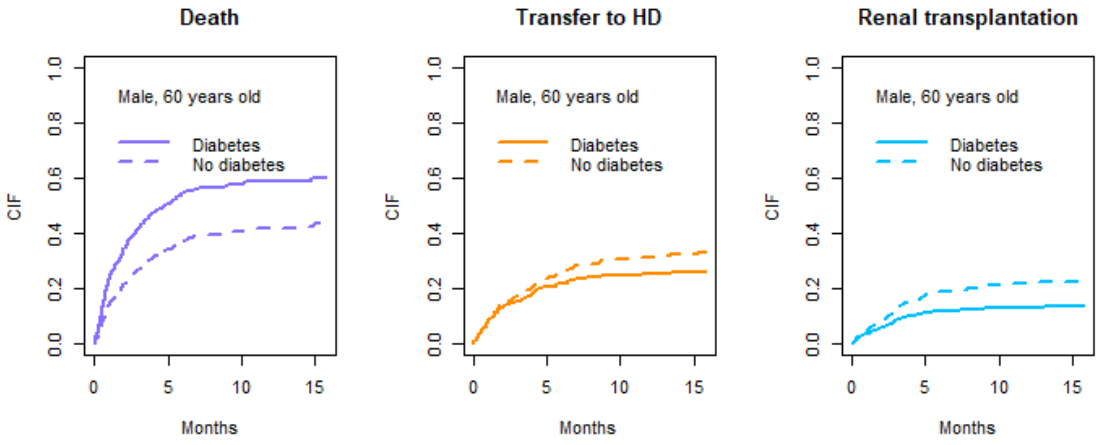

Figure 10 – CICs for 60 years old male individuals with diabetes vs. without, based on CSH model, simulated data.

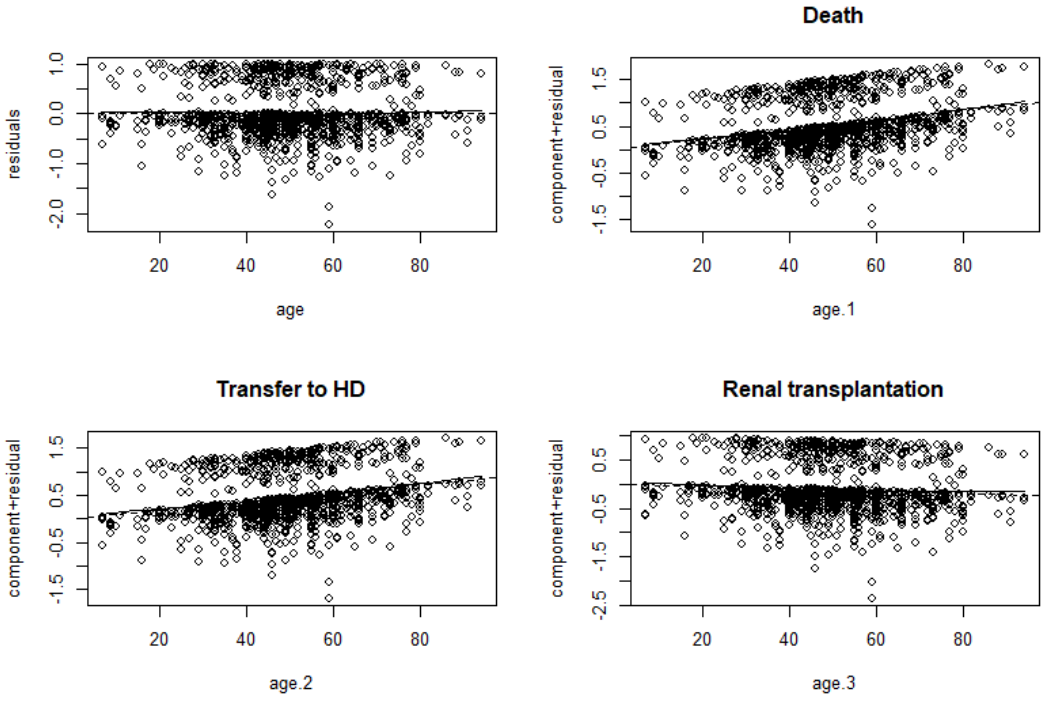

Figure 11 – Martingale-residual plots (top-left) and component-plus-residual plots (top-right and bottom) for the covariate *age*.

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To fit Fine and Gray (SDH) regression model we use *crr*() function from the 'cmprsk' package. In the simplest form it requires a vector of follow-up times, a vector of status

with a code for each failure type or censoring, and a matrix of fixed covariates (design matrix). To include categorical variables into model we need to carefully code it numerically with the help of design matrix. For the full model design matrix is as follows:

	age	sexF	diabetesYes
1	59	1	1
2	7	1	1
3	32	1	1
4	51	0	1
…	…	…	…
400	53	1	1

The crude and adjusted hazard ratios are summarized in Table 7.

Again, as in CSH model considered above, we omit the step of best fitted model selection and consider only the full one.

Table 7: Parameter estimates in SDH (Fine and Gray) regression model, simulated data

Outcome	**Variable**		**Unadjusted model**		**Adjusted model**	
			HR (95% CI)	***p***	**HR (95% CI)**	***p***
Death	Age		1.01 (1.00-1.02)	0.120	1.01 (1.00-1.02)	0.120
	Sex	Female	1.22 (0.87-1.69)	0.250	1.23 (0.88-1.71)	0.230
		Male	1	-	1	-
	Diabetes	Yes	1.65 (1.18-2.29)	0.003	1.65 (1.18-2.29)	0.003
		No	1	-	1	-
Transfer to HD	Age		1.00 (0.99-1.02)	0.650	1.00 (0.99-1.02)	0.650
	Sex	Female	0.97 (0.64-1.47)	0.900	0.97 (0.64-1.47)	0.890
		Male	1	-	1	-
	Diabetes	Yes	0.83 (0.55-1.25)	0.360	0.83 (0.55-1.25)	0.360
		No	1	-	1	-
Renal transpl.	Age		0.99 (0.98-1.00)	0.130	0.99 (0.98-1.00)	0.110
	Sex	Female	0.66 (0.42-1.03)	0.067	0.66 (0.42-1.02)	0.063
		Male	1	-	1	-
	Diabetes	Yes	0.60 (0.38-0.95)	0.029	0.58 (0.37-0.93)	0.024
		No	1	-	1	-

Abbreviations: CI, confidence interval; HD, haemodialysis; HR, hazard ratio

To perform model diagnostic we use the output of the crr() function that also provides a matrix of Schoenfeld residuals. Plotting the *j*-th column of this matrix against the vector of unique failure times allows for the evaluation of the lack of fit over time in the

corresponding predictor. Schoenfeld residuals plots given in Figures 28-30 (Annex 1) show evidence of a non-constant local average in some cases, e.g., for variable age at renal transplantation.

The fitted Fine and Gray model can be used to predict new observations with given combinations of covariates. For illustration purposes, we create a new dataset containing two patients (as in the example for CSH model above). The design matrix for a new dataset is as follows:

	age	sexF	diabetesYes
1	60	0	1
2	60	0	0

For prediction we use the fitted model for each outcome (*crr*() object), the *predict*() function, and the design matrix containing covariate combinations. Then the generic function *plot*() can be applied to draw CIF for each observation (Figure 12).

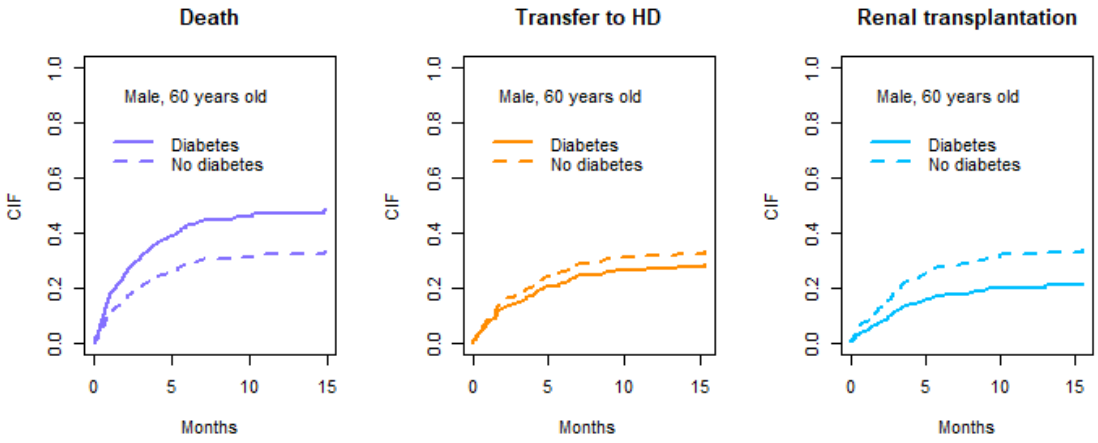

Figure 12 – CIFs for 60 years old male individuals with diabetes vs. without, based on a SDH model, simulated data.

3.5. Multi-state model approach

Now we consider a common multi-state situation known as the illness-death model. Based on our simulated data (*artPD* dataset), this model cannot be applied since we have only one observed type of event for an individual. For demonstrative purposes, we generated another data, *artIDM* dataset, with one more outcome which represents the occurrence of at least one episode of peritonitis.

Dataset characterization

The generated *artIDM* dataset contains 534 observations of 8 variables. There are two types of events: death and peritonitis and three predictors: age, sex, and diabetes. The dataset also includes censored observations.

Coding:

- **id**: subject's ID number
- **sex**: refers to individual sex (1 = male (ref.), 2 = female)
- **age**: age at baseline (time point=0)
- **diabetes**: diabetes mellitus (Yes/No(ref.))
- **ptime**: time to peritonitis in months
- **pstatus**: status of a subject (0 = censored, 1 = peritonitis)
- **dtime**: time to death in months
- **dstatus**: status of a subject (0 = censored, 1 = death)

The types and numbers of events and the patient's characteristics are summarized in Table 8 and Table 9 respectively. The model to be considered has one initial state (Start PD), one intermediate transient state (Peritonitis) and one absorbing state (Death). Here, the 'illness' state corresponds to a peritonitis episode.

Table 8: Types of events in *artIDM* dataset

Outcome	**n**	**%**
Peritonitis, no death	105	19.7
Death without peritonitis	154	28.8
Death after peritonitis	158	29.6
Free of any event	117	21.9

The graphical representation of the model is given in Figure 13. There are three possible transitions:

- **Transition I**: Start PD → Peritonitis (1 → 2)
- **Transition II**: Start PD → Death (1 → 3)
- **Transition III**: Peritonitis → Death (2 → 3).

Table 9: Baseline characteristics of patients in *artIDM* dataset

Patient's characteristic		**n**	**%**
Sex	Male	249	46.6
	Female	285	53.4
Age (years)	N	400	100.00
	mean (SD)	47.95 (16.05)	
	Median (Q1-Q3)	48.00 (36.00 - 59.00)	
	Min-Max	0.00 – 99.00	
Diabetes	Yes	256	47.9
	No	278	52.1

Abbreviations: Max, maximum; Min, minimum; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation

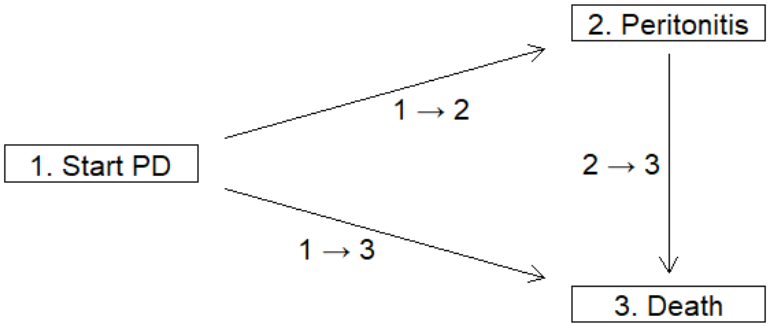

Figure 13 – A 3-state model (illness-death model) for the PD patients' survival analysis study

Estimation

The first step in a multi-state model analysis with "mstate" package is to set up the transition matrix which specifies possible direct transitions (those with NA are impossible) and assigns numbers to the transitions for future reference. For the illness-death model presented in Figure 13, the transition matrix is as follows:

from\to	Start PD	Peritonitis	Death
Start PD	NA	1	2
Peritonitis	NA	NA	3
Death	NA	NA	NA

Then we prepare data in a long format specifying the names of the covariates that we are interested in modeling and add transition-specific covariates. After having prepared

the data in long format, we can estimate the covariate effects using Cox regression using the *coxph*() function of the "survival" package.

First, we consider the model without any proportionality assumption on the baseline hazards. Using the "clock forward" approach and assuming a Markov model, we will use Cox's PH model for each of the transition hazards separately. The hazard for the $i \rightarrow j$ transition for an individual with covariate vector z is then given by:

$$h_{ij}(t|z) = h_{ij,0}(t)\exp\left[\beta_{ij}^{\intercal} z\right],$$

where $h_{ij,0}(t)$ is the baseline hazard of the $i \rightarrow j$ transition, β_{ij} is the vector of regression coefficients that describe the effect of z on transition $i \rightarrow j$. The estimates of β_{ij}, their standard errors and *p*-values are presented in Table 10 (stratified hazards column).

Table 10: Parameter estimates in stratified hazards and PH Markov models, "clock forward" approach, simulated data

		Markov			
		stratified hazards		**proportional hazards**	
		HR (95% CI)	***p***	**HR (95% CI)**	***p***
1 → 2 transition					
Age		0.99 (0.99-1.00)	0.128	-	-
Sex	Female	1.12 (0.88-1.43)	0.368	-	-
	Male	-	-	-	-
Diabetes	Yes	0.94 (0.74-1.20)	0.620	-	-
	No	-	-	-	-
1 → 3 transition					
Age		1.01 (1.00-1.02)	0.051	1.01 (1.00-1.02)	0.118
Sex	Female	0.90 (0.66-1.25)	0.537	0.96 (0.70-1.32)	0.785
	Male	-	-	-	-
Diabetes	Yes	1.08 (0.78-1.48)	0.645	1.05 (0.77-1.45)	0.743
	No	-	-	-	-
2 → 3 transition					
Age		1.02 (1.01-1.03)	0.001	1.02 (1.01-1.03)	<0.001
Sex	Female	0.89 (0.65-1.23)	0.485	0.89 (0.65-1.23)	0.478
	Male	-	-	-	-
Diabetes	Yes	1.41 (1.03-1.93)	0.034	1.47 (1.07-2.02)	0.017
	No	-	-	-	-

Abbreviations: CI, confidence interval; HR, hazard ratio

The estimated cumulative baseline hazards for this model are shown in Figure 14 (left plot). We may assume the baseline hazards to be proportional for the transitions 1 → 3 and 2 → 3. This is equivalent to grouping these two transitions based on the state of arrival and using the occurrence of the intermediate event as a time-dependent covariate.

The estimates of β_{ij}, their standard errors and p-values are presented in Table 10 (proportional hazards column). The right plot of shows the estimated baseline cumulative hazards for all three transitions in this model. A comparison of the right plot with the left one in Figure 14 suggests that the proportionality assumption of the baseline hazards for the 1 → 3 and 2 → 3 transitions is reasonably fulfilled.

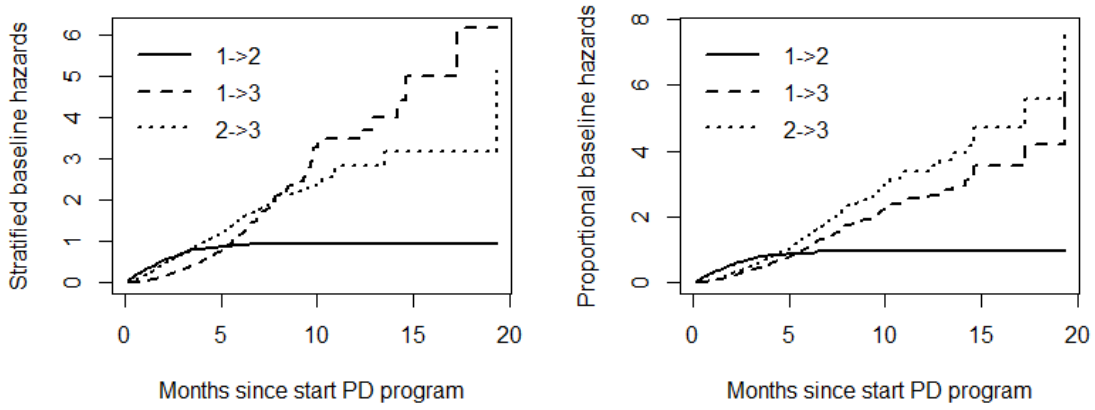

Figure 14 – Baseline cumulative hazard curves for the illness-death model: stratified baseline hazards (left plot); proportional baseline hazards of the 1 → 3 and the 2 → 3 transitions (right plot).

Error! Not a valid bookmark self-reference. contains parameter estimates with standard errors and *p*-values for the state arrival extended Markov model. Table 19 and Table 20 in Annex 2 contain the results for the “clock reset" approach, for the same three models.

Note that the difference in parameter estimates between the two approaches is quite small. Clinical context is typically the primary factor in determining whether to choose the “clock forward” or “clock reset” approaches. For the prediction, we will use the “clock forward” Markov proportional hazards model.

Table 11: Parameter estimates in state arrival extended Markov model, "clock forward" approach, simulated data

		State arrival extended Markov proportional hazards model	
		HR (95% CI)	***p***
1 → 3 transition			
Age		1.01 (1.00-1.02)	0.115
Sex	Female	0.95 (0.69-1.31)	0.774
	Male	-	-
Diabetes	Yes	1.06 (0.77-1.45)	0.737
	No	-	-
2 → 3 transition			
Age		1.02 (1.01-1.03)	<0.001
Sex	Female	0.89 (0.65-1.22)	0.474
	Male	-	-
Diabetes	Yes	1.50 (1.09-2.06)	0.013
	No	-	-

Abbreviations: CI, confidence interval; HR, hazard ratio

Prediction

To obtain prediction probabilities in the context of the Markov multi-state models, two steps are involved:

1. Obtain patient-specific transition hazards based on the estimated model parameters, baseline transition hazards and the covariate values of a patient of interest, with the help of the *msfit*() function.
2. Based on the patient-specific transition hazards, obtain transition probabilities with the help of the *probtrans*() function.

Figure 15 shows the (conditional) probabilities of going to a specific state before or at time *t* or staying in a specific state until time *t*. From bottom to top, the probabilities are shown as follows:

- Alive, peritonitis or a probability of transition 1 → 2
- Death after peritonitis or a probability of transition 2 → 3
- Death without peritonitis or a probability of transition 1 → 3

- Alive, no peritonitis or a probability of staying in state 1.

Figure 16 shows the survival probabilities without distinction between before or after peritonitis (the time of prediction was at Start PD).

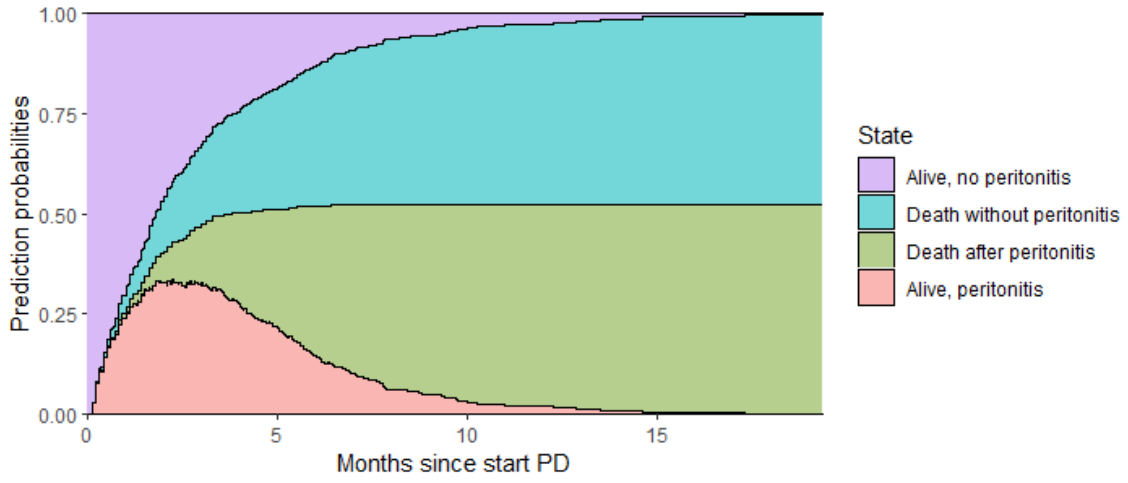

Figure 15 – Stacked prediction probabilities at time = 0 for a 60 years old male individual without diabetes.

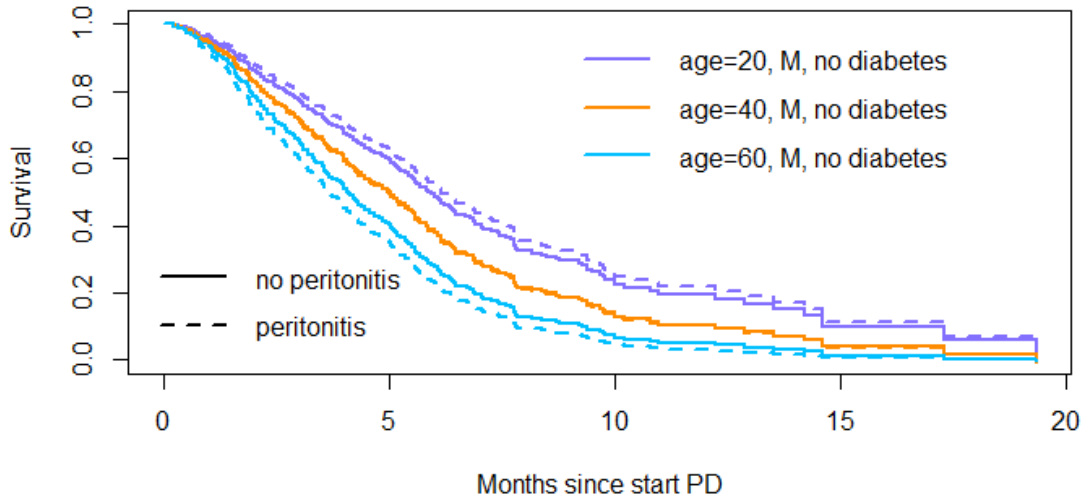

Figure 16 – Predicted survival probabilities for male patients of three different ages without diabetes, given peritonitis (dashed lines) and given no peritonitis (solid lines).

4. Application to real data

4.1. Data description

The data used in this chapter are derived from the records of patients who were part of the peritoneal dialysis program at the Peritoneal Dialysis Unit of the Nephrology Department of the University Hospital Center of Santo António. The data include information on all prevalent patients in the program between October 1985 (program start date) and May 2023. The information provided for each patient includes sociodemographic and clinical information assessed at program admission (gender, age, follow-up time, observed event, and diabetes).

The work developed in this project is an integral part of the semi-annual quality control evaluation of the Peritoneal Dialysis Unit at the Santo António University Hospital Center, regarding major outcomes such as patient survival and technique survival. The present project has been approved by the Ethics Committee of the Santo António University Hospital Center, complying with all ethical principles for clinical research stated in the Helsinki Declaration.

The initial PD dataset included 736 patients. Among them, 14 patients (1.90%) had recovery of renal function and 1 patient (0.14%) had missing observation of the event time. The number of individuals with missingness in any covariate was 3 (0.41%). We assume that the potential impact of these 18 patients (2.45%) is negligible (< 5%), and we may ignore them in the analysis (complete-case approach)[51].

The dataset for complete-case analysis involved 718 patients enrolled in PD program, 55.4% women (n = 398). The mean age was 49.6 years (SD = 15.8 years), 22.4% of the patients had diabetes (Table 12). The simple median follow-up time was only 22.7 months, whereas the potential follow-up time calculated using the “reverse” Kaplan-Meier method[10] was 172 months (range 0.1-188.3 months).

The types and numbers of events are summarized in Table 13. Transfer to HD was the most common outcome followed by renal transplantation. At the end of the study period, 8.9% of the patients were still on PD or were lost to follow-up.

Table 12: Baseline characteristics of patients

Patient's characteristic		**n**	**%**
Gender	Male	320	44.6
	Female	398	55.4
Age	N	718	100
	mean (SD)	49.62 (15.79)	
	Median (Q1-Q3)	49.73 (37.15 - 61.97)	
	Min-Max	15.22 - 87.87	
Diabetes	Yes	161	22.4
	No	557	77.6

Abbreviations: Max, maximum; Min, minimum; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation

Table 13: Types of events in PD data

Outcome	**n**	**%**
Death	140	19.5
Transfer to haemodialysis	312	43.5
Renal transplantation	202	28.1
Censored	64	8.9

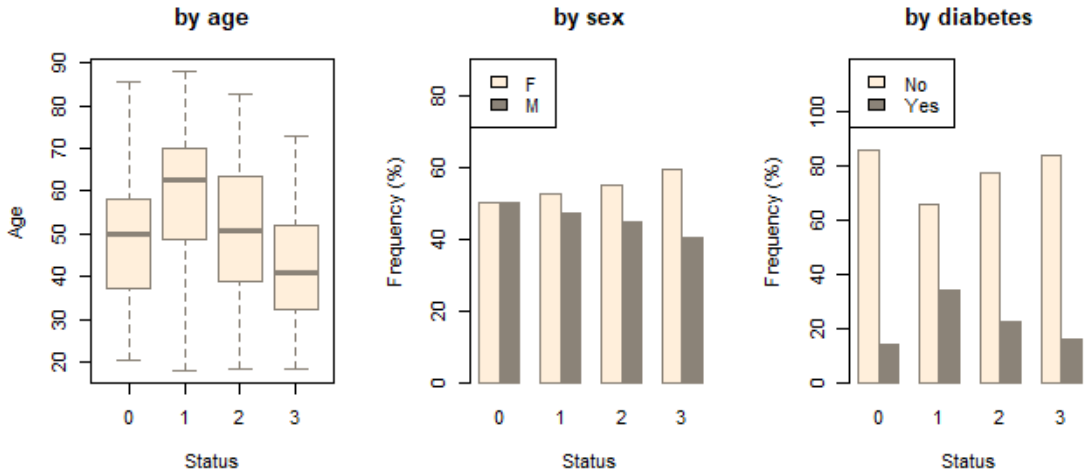

Figure 17 – Distributions of outcomes (Status) by baseline characteristics of patients: 0 = censored, 1 = death, 2 = transfer to HD, 3 = renal transplantation.

Distributions of outcomes by baseline characteristics are shown in Figure 17. Younger patients were more likely to discontinue PD due to renal transplantation compared to

those who discontinued PD for other reasons (death, transfer to HD). Patients who had died during the study period tended to be older. Females experienced any type of event more frequently than males, while the frequency of staying alive or being lost to follow-up is almost equal for both genders. As the majority of patients did not have diabetes, they experienced all events more frequently compared to those with diabetes.

4.2. Non-parametric CIF estimates

Overall CIF estimates

Figure 18 and Table 14 summarize the overall CIF estimates for each outcome taking competing risks into account. For example, the probabilities of transfer to HD by 50, 100 and 150 months after starting PD were 0.35, 0.45 and 0.47, respectively.

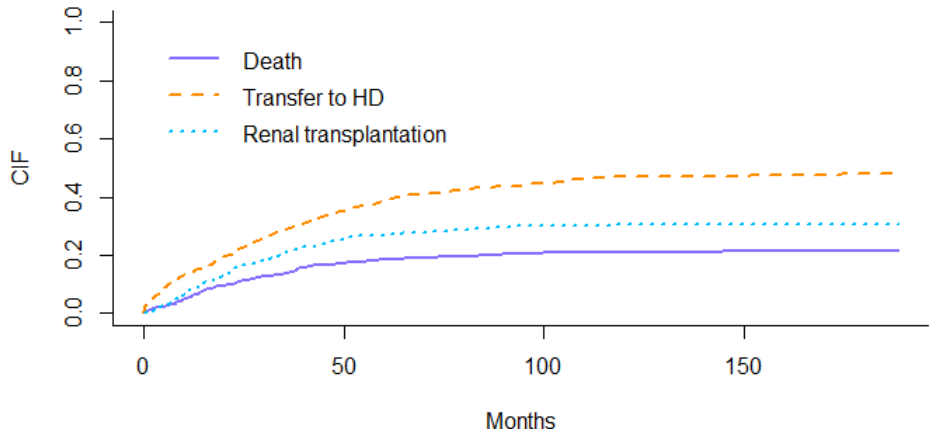

Figure 18 – Cumulative incidence for each outcome, patients on PD, real data.

Table 14: The overall CIF estimation of each outcome by months, patients on PD, real data.

Outcome	**CIF,** estimate (variance)		
	months		
	50	**100**	**150**
Death	0.1723 (0.0002)	0.2084 (0.0003)	0.2128 (0.0003)
Transfer to HD	0.3512 (0.0003)	0.4459 (0.0004)	0.4727 (0.0004)
Renal transplantation	0.2556 (0.0003)	0.3016 (0.0003)	0.3056 (0.0003)

Figure 19 displays the CIC for the occurrence of each type of event, obtained using two different methods: one that takes competing risks into account and the other based on the complement of the Kaplan-Meier method. The implementation of a competing risks approach yields a lower estimate of cumulative incidence for all events. The differences between the incidences, as computed using the two methods, become more pronounced with time of follow-up. Essentially, the Kaplan-Meier method incorrectly overestimates the actual probability of an event occurrence, and this difference grows as the duration of follow-up increases.

Subdistribution CIF estimates

Subgroup analyses were performed using Gray's test calculating the cumulative incidence for each type of event by the variables sex, age group and diabetes.

Considering transfer to HD as an event of interest, none of the factors were statistically significant (see Table 15). When considering the competing events, death and renal transplantation, age groups and diabetes were statistically significant (p-values are less than 0.05). Figure 20 and Figure 21 show the cumulative incidence curves for the death and renal transplantation in the two age groups and by diabetes (no vs. yes). It can be seen that the cumulative incidence for older patients is higher in case of death ($p < 0.001$) and lower in case of renal transplantation ($p < 0.001$) compared to younger patients. The cumulative incidence is higher for patients with diabetes in case of death ($p < 0.001$) and lower in case of renal transplantation compared to patients who did not have diabetes ($p = 0.024$).

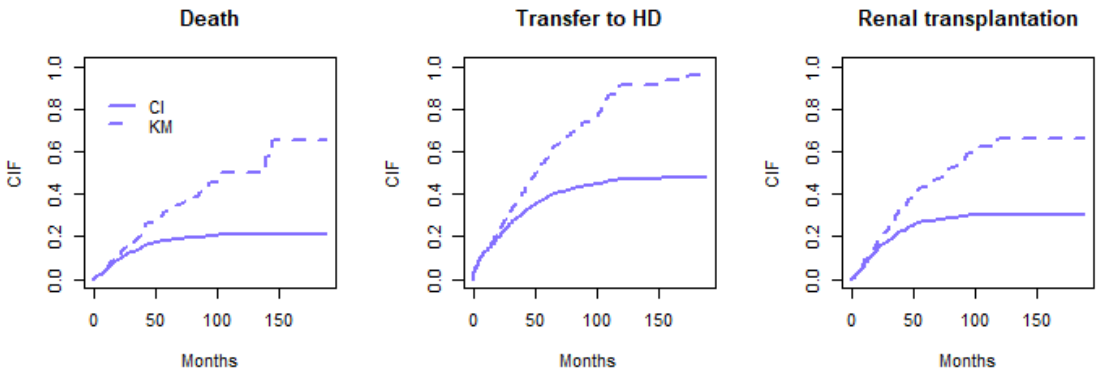

Figure 19 – The complement of the Kaplan-Meier estimate and the cumulative incidence estimate for each outcome, patients on PD, real data.

Table 15: Gray's test for differences between two groups of PD patients, real data

Outcome	Subgroup analysis by	Gray's test statistic	df	*p*-value
Death	age (<55 vs. ≥55 years old)	61.681	1	<0.001*
	sex (male vs. female)	0.721	1	0.396
	diabetes (no vs. yes)	13.107	1	<0.001*
Transfer to HD	age (<55 vs. ≥55 years old)	0.323	1	0.570
	sex (male vs. female)	0.049	1	0.825
	diabetes (no vs. yes)	0.124	1	0.725
Renal transplantation	age (<55 vs. ≥55 years old)	57.583	1	<0.001*
	sex (male vs. female)	1.540	1	0.215
	diabetes (no vs. yes)	5.064	1	0.024*

Footnotes: * Statistically significant at the .05 level.

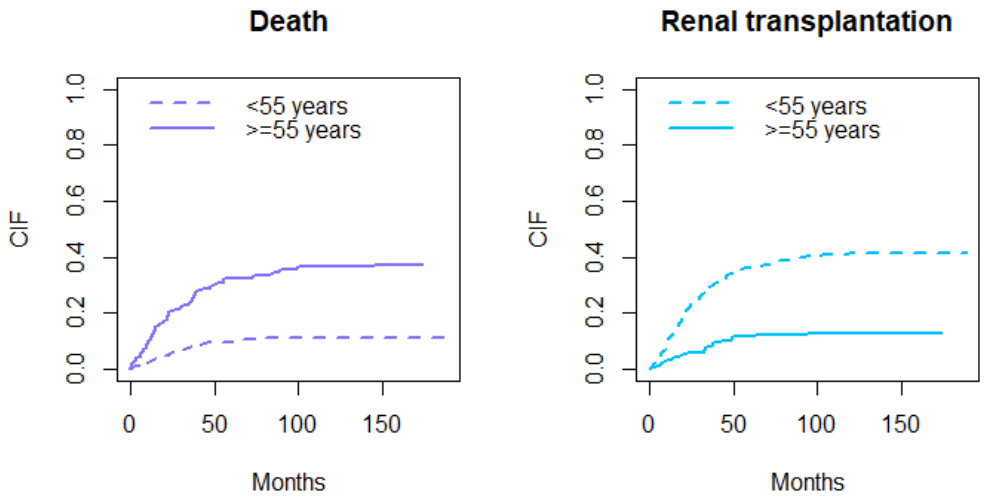

Figure 20 – CICs for death and renal transplantation outcomes by age group.

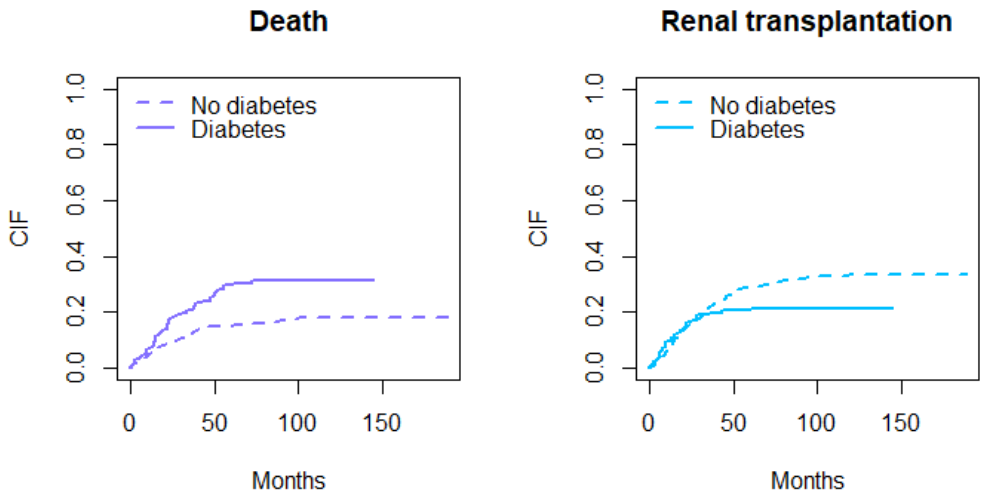

Figure 21 – CICs for death and renal transplantation outcomes by diabetes.

4.3. Semi-parametric regression models

Cause-specific hazards regression model

Table 16 gives a summary of the unadjusted and adjusted effects of covariates for each outcome based on the cause-specific hazard models. In the unadjusted models (univariable), it was observed that the variable age was significant for the death and renal transplantation outcomes. Variable diabetes was significant for the death and transfer to HD outcomes. These effects of age and diabetes remained significant in the adjusted (multivariable) model. Variable sex was non-significant for any of the outcomes considered and remained non-significant when adjusted for age and diabetes.

Table 16: Parameter estimates in cause-specific hazards regression model, real data

Outcome	**Variable**		**Unadjusted model**		**Adjusted model**	
			HR (95% CI)	***p***	**HR (95% CI)**	***p***
Death	Age		1.04 (1.03, 1.06)	<0.001*	1.04 (1.03, 1.06)	<0.001*
	Sex	Female	0.93 (0.67, 1.30)	0.665	1.30 (0.92, 1.83)	0.140
		Male	1	-	1	-
	Diabetes	Yes	2.35 (1.65, 3.33)	<0.001*	2.03 (1.42, 2.88)	<0.001*
		No	1	-	1	-
Transfer to HD	Age		1.00 (1.00, 1.01)	0.472	1.00 (0.99, 1.01)	0.608
	Sex	Female	1.01 (0.80, 1.26)	0.960	1.07 (0.85, 1.34)	0.589
		Male	1	-	1	-
	Diabetes	Yes	1.38 (1.06, 1.81)	0.017*	1.38 (1.06, 1.81)	0.017*
		No	1	-	1	-
Renal transpl.	Age		0.96 (0.96, 0.97)	<0.001*	0.96 (0.96, 0.97)	<0.001*
	Sex	Female	1.23 (0.93, 1.63)	0.142	0.99 (0.74, 1.33)	0.970
		Male	1	-	1	-
	Diabetes	Yes	0.88 (0.60, 1.27)	0.488	1.07 (0.73, 1.57)	0.711
		No	1	-	1	-

Abbreviations: CI, confidence interval; HD, haemodialysis; HR, hazard ratio
Footnotes: * Statistically significant at the .05 level.

In the adjusted model, the risk of death increased with age (HR = 1.04, 95% CI = 1.03-1.06). The risk of death was also higher for patients with diabetes compared to those who did not have diabetes (HR = 2.03, 95% CI = 1.42-2.88). The risk of renal

transplantation decreased with age (HR = 0.96, 95% CI = 0.96-0.97). The risk of transfer to HD was higher for patients with diabetes compared to those who did not have diabetes (HR = 1.38, 95% CI = 1.06-1.81).

The check for possible interactions revealed a significant interaction between age and diabetes variables for renal transplantation. The HR for age was 0.97 in patients without diabetes and $0.97 \times 0.96 = 0.93$ in patients with diabetes. Thus, the risk of renal transplantation decreased with age for all patients, but for patients with diabetes, this decrease is more substantial. However, the PH assumption assessment showed the potential violation for the interaction term, that is why it was not included in the final model. All non-significant variables were also eliminated from the final model selected for further analysis.

Table 17 summarizes the results of a statistical test on correlation between the Schoenfeld residuals and ranked survival time for the final CSH model. All the *p*-values are greater than 0.05 suggesting that the PH assumption is satisfied for all variables in the model.

Table 17: Correlation between the Schoenfeld residuals and ranked survival time, CSH model, real data

Variable	**Outcome**								
	Death			**Transfer to HD**			**Renal transplantation**		
	chisq	**df**	***p***	**chisq**	**df**	***p***	**chisq**	**df**	***p***
age	1.26	1	0.26	-	-	-	0.644	1	0.42
sex	-	-	-	-	-	-	-	-	-
diabetes	1.68	1	0.19	0.02	1	0.89	-	-	-
GLOBAL	3.11	2	0.21	0.02	1	0.89	0.644	1	0.42

Abbreviations: chisq, chi-square statistic; df, degrees of freedom

From the graphical inspection of the Schoenfeld residuals plotted against each individual's failure (Figure 31 and Figure 32 in Annex 1), there is no pronounced pattern of changing residuals with time. The PH assumption appears to be supported for the age and diabetes for death, diabetes for transfer to HD and age for renal transplantation.

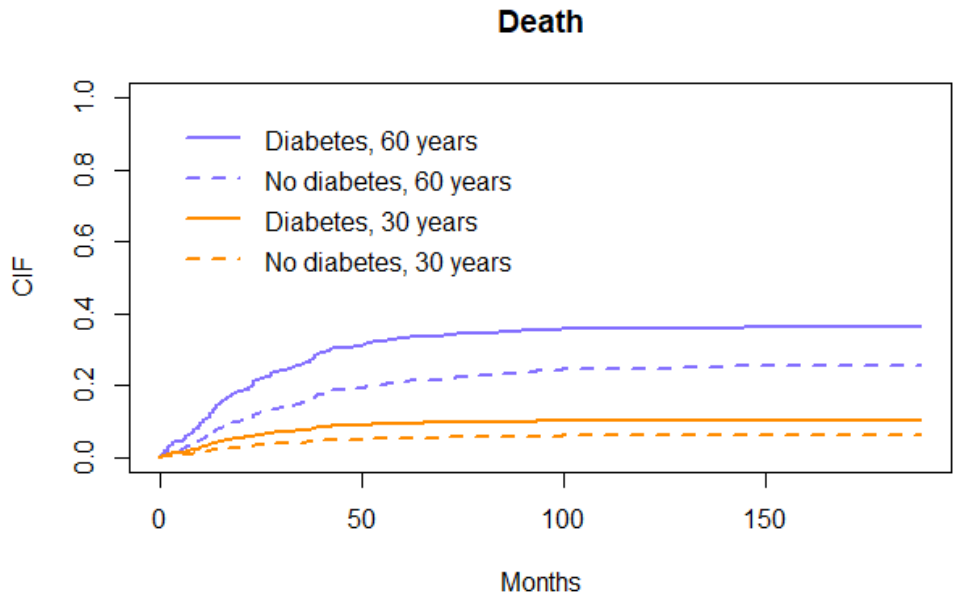

Figure 22 – Predicted CICs for death, based on a CSH adjusted model, real data.

The plots of martingale residuals and partial residuals against the age for the regression of time to first event on age (Figure 33, Annex 1) indicate that nonlinearity is very slight for the covariate age in the model of choice. The CICs predicted based on the CSH model are shown in Figure 22 and Figure 23.

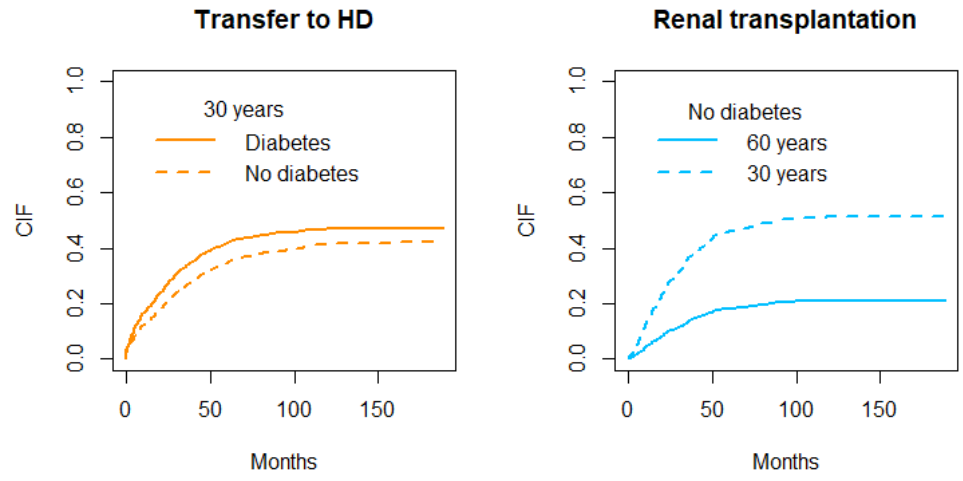

Figure 23 – CICs for transfer to HD and renal transplantation, based on a CSH model, real data.

Fine and Gray regression model

Table 18 gives a summary of the unadjusted and adjusted effects of covariates for each outcome based on the subdistribution hazard models. Variable diabetes was significant for the death and transfer to HD outcomes in unadjusted models and when adjusted for variables age and sex, remained significant for death, and became non-significant for renal transplantation. Just like in the CSH models, variable sex was non-significant for any of the outcomes considered and remained non-significant when adjusted for age and diabetes. All non-significant variables were also eliminated from the final model selected for further analysis.

The Schoenfeld residuals plots for age and diabetes in Figure 34 (Annex 1) do not show a monotonically increasing or decreasing pattern, and therefore it can be assumed that these variables are not time-dependent.

Table 18: Parameter estimates in subdistribution hazards regression model, real data

Outcome	**Variable**		**Unadjusted model**		**Adjusted model**	
			HR (95% CI)	***p***	**HR (95% CI)**	***p***
Death	Age		1.05 (1.04, 1.06)	<0.001*	1.05 (1.03, 1.06)	<0.001*
	Sex	Female	0.87 (0.63, 1.21)	0.410	1.15 (0.82, 1.63)	0.410
		Male	1	-	1	-
	Diabetes	Yes	1.94 (1.37, 2.74)	<0.001*	1.66 (1.17, 2.37)	0.005*
		No	1	-	1	-
Transfer to HD	Age		1.00 (1.00, 1.01)	0.160	1.00 (1.00, 1.01)	0.170
	Sex	Female	0.99 (0.79, 1.23)	0.920	1.02 (0.81, 1.28)	0.860
		Male	1	-	1	-
	Diabetes	Yes	1.06 (0.81, 1.39)	0.690	1.04 (0.79, 1.37)	0.760
		No	1	-	1	-
Renal transpl.	Age		0.96 (0.95, 0.97)	<0.001*	0.96 (0.95, 0.97)	<0.001*
	Sex	Female	1.20 (0.91, 1.58)	0.210	0.95 (0.71, 1.27)	0.72
		Male	1	-	1	-
	Diabetes	Yes	0.66 (0.45, 0.97)	0.035*	0.79 (0.53, 1.17)	0.24
		No	1	-	1	-

Abbreviations: CI, confidence interval; HD, haemodialysis; HR, hazard ratio
Footnotes: * Statistically significant at the .05 level.

Figure 24 shows that the effects of age for the cause-specific and subdistribution hazard models are quite close for the death and renal transplantation outcomes. The CICs predicted based on the SDH adjusted model shown in Figure 25 look very similar to the respective CICs predicted using the CSH adjusted model.

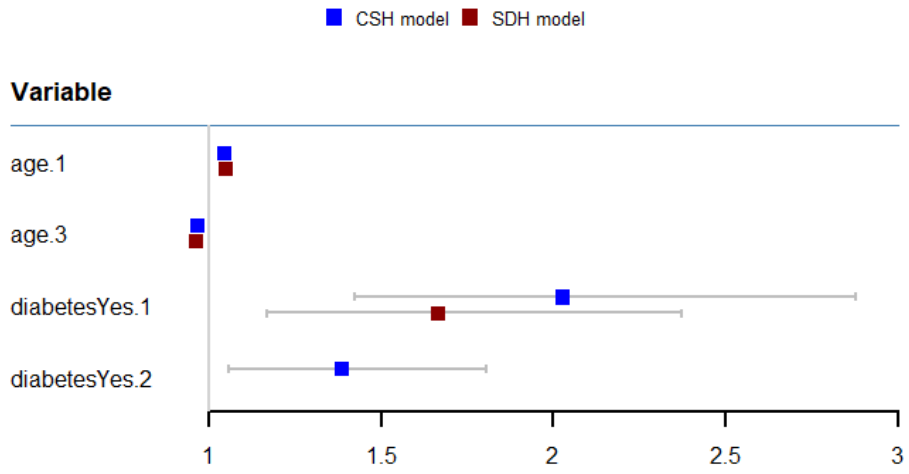

Figure 24 – Hazard ratios based on a CSH and SDH models, real data.

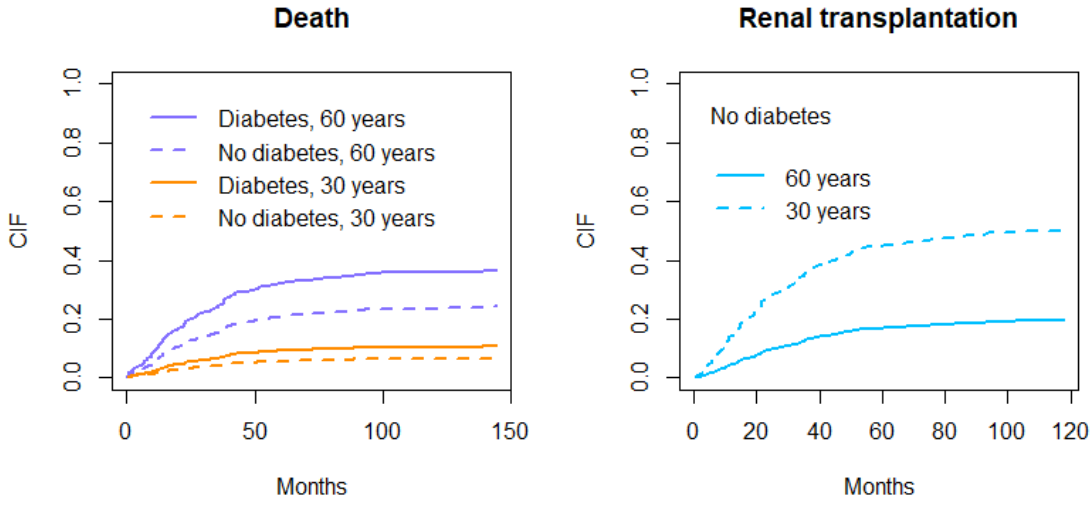

Figure 25 – CICs for death and renal transplantation, based on a SDH adjusted model, real data.

5. Final discussion

When analyzing competing risk data, it is important to present the results of both the event of interest and the competing events. Teixeira et al. (2013) concluded in their work[43] that a competing risk approach to estimating cumulative incidence in studies with multiple outcomes, specifically in PD studies, results in more rigorous estimates and is recommended. For a dominant risk, one can use either the CSH model or the SDH model. However, Lim et al. in their work[52] do not recommend the SDH model for a minor risk and claim that a CSH model is more appropriate in competing risk data analysis.

In this report, we presented results for covariate effects for each type of event in the available data, which were obtained based on real data, using both semi-parametric modeling approaches (CSH and SDH). Additionally, CICs were estimated non-parametrically (overall and by sex, age, and diabetes). It was also shown that the Kaplan-Meier method provides the wrongly overestimated probability of occurrence of all types of events.

The CSH model showed that:

- age and diabetes were the factors associated with a shorter time to death,
- diabetes was the only factor associated with a shorter time to transfer to haemodialysis,
- age was the only factor associated with a shorter time to renal transplantation.

The SDH model showed that:

- age and diabetes were the factors associated with a shorter time to death,
- none of the factors had a significant association with a shorter time to transfer to haemodialysis (in contrast to the CSH model, where diabetes was significant),
- diabetes was the only factor associated with a shorter time to renal transplantation (in contrast to the CSH model, where the only significant factor was age).

The difference between HR estimates obtained using CSH and SDH models can be attributed to the different interpretations of the regression coefficients in each model. The exponentiated coefficient from CSH regression model represents the magnitude of the relative change in the cause-specific hazard function related to a unit change in the covariate. Thus, the cause-specific HR denotes the relative change in the instantaneous rate of the occurrence of the primary event in subjects who are currently event-free. The exponentiated coefficient from SDH regression model represents the magnitude of the

relative change in the subdistribution hazard function related to a unit change in the covariate. Therefore, subdistribution HR denotes the relative change in the instantaneous rate of the occurrence of the event in subjects who are event-free or who have experienced a competing event[28].

Further work

A future line of research would be to:

- analyze more demographic and clinical characteristics to determine other important factors (e.g., income, education, comorbidities, and others), investigate the possible interactions for these variables and time-dependence if non-proportional hazards are observed;
- investigate, with the help of other multi-state models, how the presence of intermediate events (e.g., first peritonitis) affects the probabilities of the event of interest and competing events (as was described using the simulated data in Chapter 3).

Among the other approaches that can expand the study are joint models when the longitudinal outcome and survival endpoints are associated. One such study[40] on PD patients aimed to model longitudinal and survival data jointly in a competing risk context and presented an example of a dataset on peritoneal dialysis where death/transfer to hemodialysis was the event of interest and renal transplant was the competing event. Another study[53] proposed flexible multi-state structured additive regression (STAR) models combined with penalized splines (P-splines) to evaluate PD programs and adapted the concept of time-dependent ROC curves to a multi-state competing risks framework. Such an approach can result in important conclusions which cannot be obtained using standard statistical methodologies.

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Annexes

Annex 1. Residuals plots

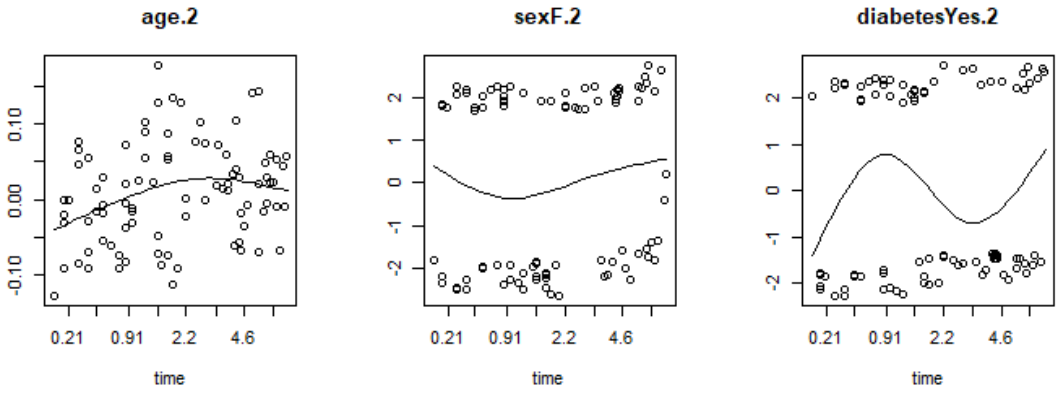

Figure 26 – Schoenfeld residuals plots for CSH model, transfer to HD, simulated data.

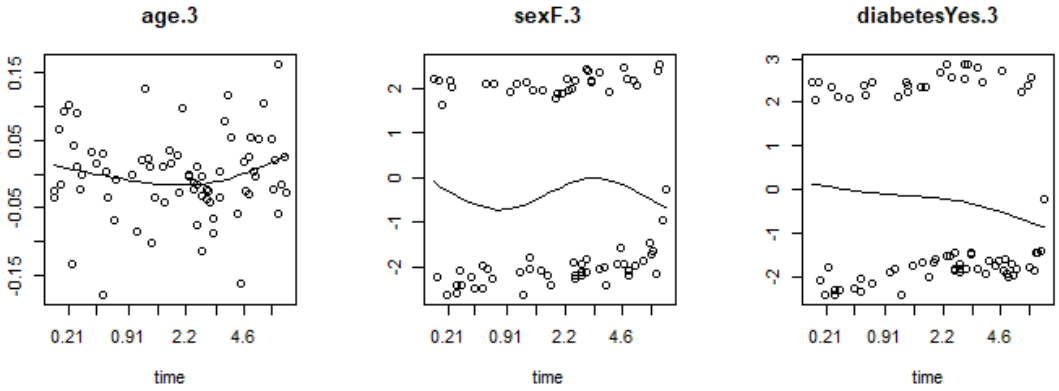

Figure 27 – Schoenfeld residuals plots for CSH model, renal transplantation, simulated data.

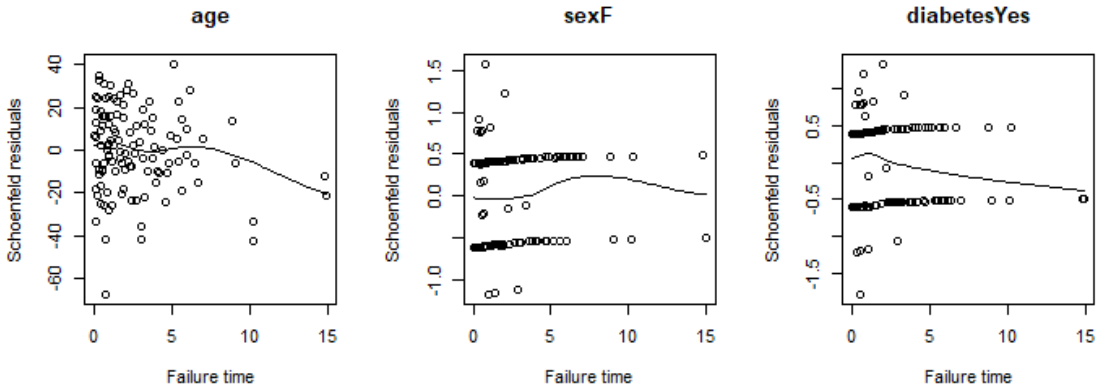

Figure 28 – Schoenfeld residuals plots for the Fine and Gray model, death, simulated data.

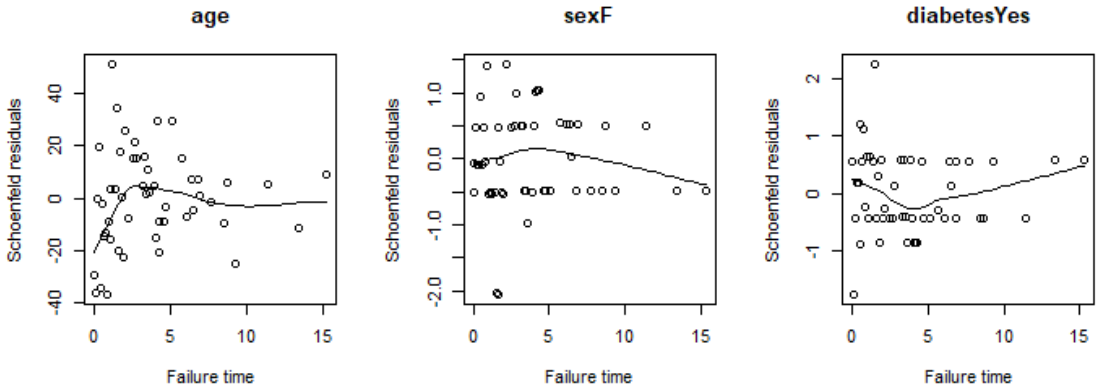

Figure 29 – Schoenfeld residuals plots for the Fine and Gray model, transfer to HD, simulated data.

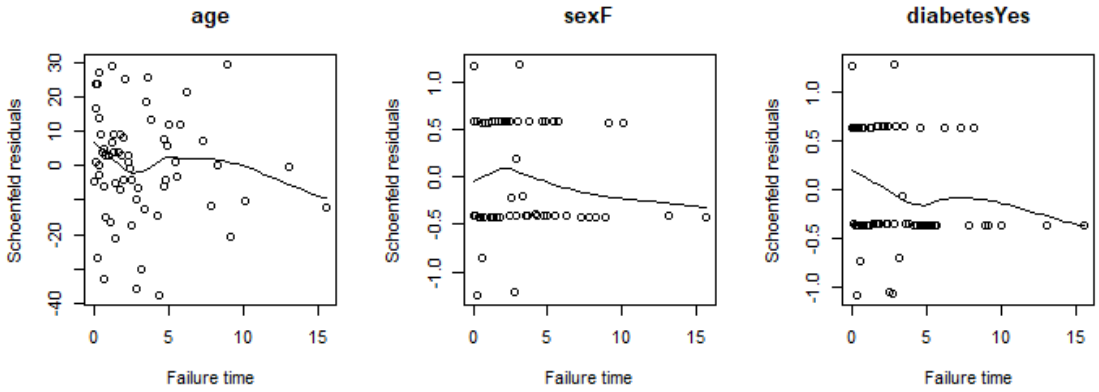

Figure 30 – Schoenfeld residuals plots for the Fine and Gray model, renal transplantation, simulated data.

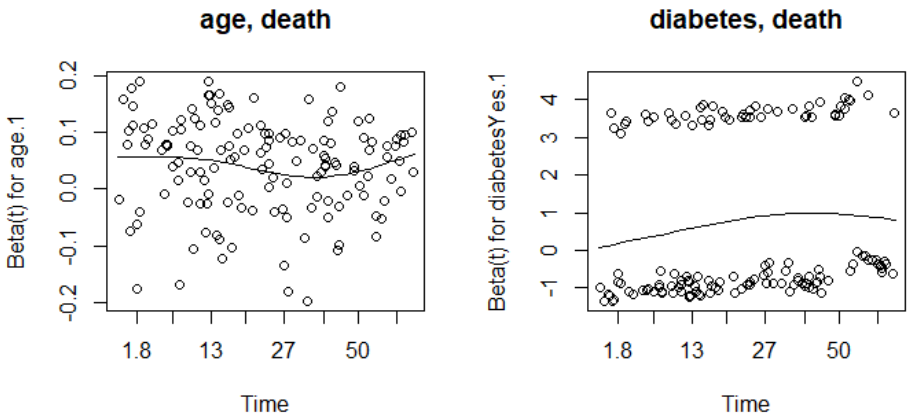

Figure 31 – Schoenfeld residuals plots for CSH model, death, real data.

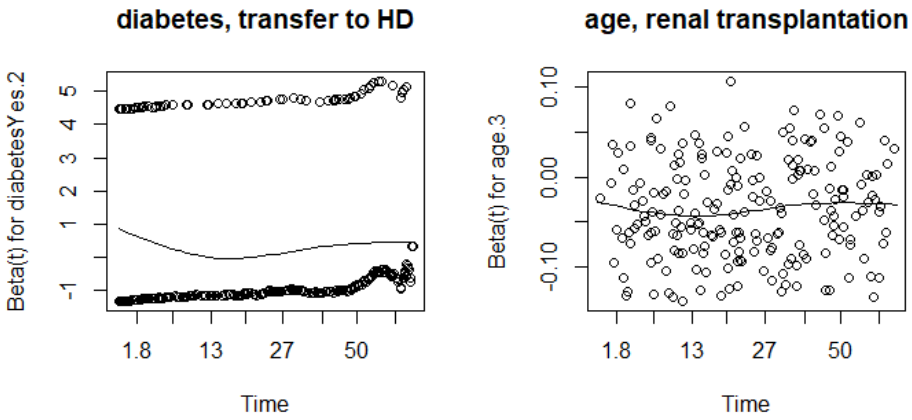

Figure 32 – Schoenfeld residuals plots for CSH model, real data.

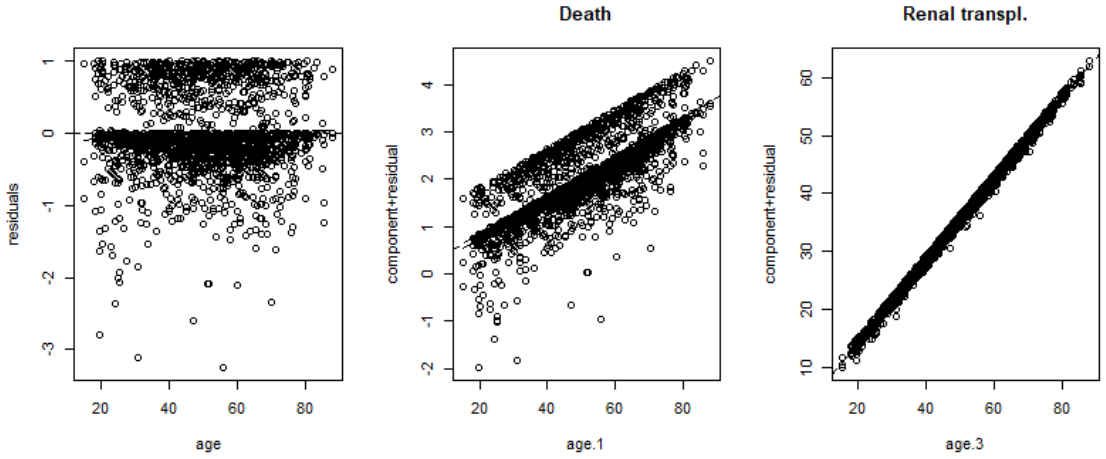

Figure 33 – Martingale-residual plot (left) and component-plus-residual plots (middle and right) for the covariate age, CSH model, real data.

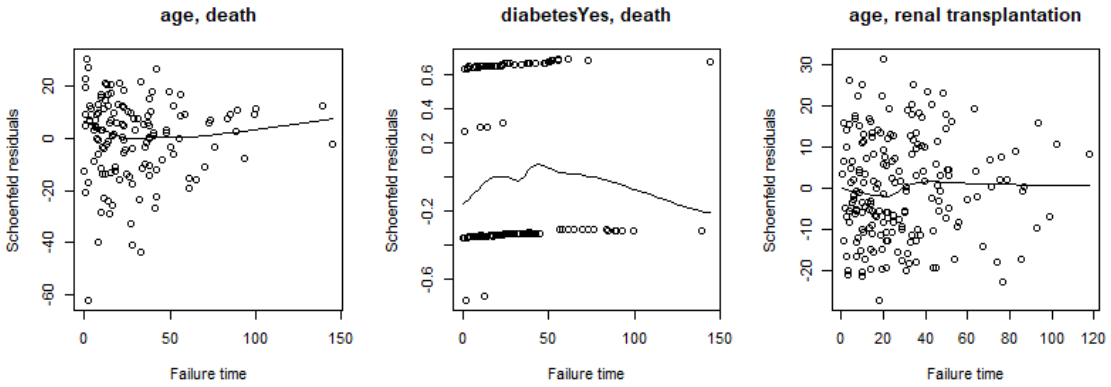

Figure 34 – Schoenfeld residuals plots for the Fine and Gray model, real data.

Annex 2. Parameter estimates in Markov models, “clock reset" approach

Table 19: Parameter estimates in state arrival extended Markov model, “clock reset” approach, simulated data

		Markov			
		stratified hazards		**proportional hazards**	
		HR (95% CI)	***p***	**HR (95% CI)**	***p***
1 → 2 transition					
Age		0.99 (0.99-1.00)	0.128	-	-
Sex	Female	1.12 (0.88-1.43)	0.368	-	-
	Male	-	-	-	-
Diabetes	Yes	0.94 (0.74-1.20)	0.620	-	-
	No	-	-	-	-
1 → 3 transition					
Age		1.01 (1.00-1.02)	0.051	1.01 (1.00-1.02)	0.107
Sex	Female	0.90 (0.66-1.25)	0.537	0.96 (0.70-1.32)	0.812
	Male	-	-	-	-
Diabetes	Yes	1.08 (0.78-1.48)	0.645	1.05 (0.77-1.45)	0.749
	No	-	-	-	-
2 → 3 transition					
Age		1.02 (1.01-1.03)	0.001	1.02 (1.01-1.03)	<0.001
Sex	Female	0.90 (0.66-1.24)	0.525	0.88 (0.64-1.21)	0.434
	Male	-	-	-	-
Diabetes	Yes	1.39 (1.02-1.91)	0.040	1.51 (1.10-2.07)	0.011
	No	-	-	-	-

Table 20: Parameter estimates in state arrival extended Markov model, "clock reset" approach, simulated data

		State arrival extended Markov proportional hazards model	
		HR (95% CI)	***p***
1 → 3 transition			
Age		1.01 (1.00-1.02)	0.106
Sex	Female	0.96 (0.70-1.32)	0.806
	Male	-	-
Diabetes	Yes	1.05 (0.77-1.45)	0.747
	No	-	-
2 → 3 transition			
Age		1.02 (1.01-1.03)	<0.001
Sex	Female	0.89 (0.64-1.22)	0.453
	Male	-	-
Diabetes	Yes	1.49 (1.09-2.05)	0.013
	No	-	-