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Title: Modelling survival data from hepatorenal syndrome acute kidney injury

Author: Alba Morató Catafal

Advisor: Ferran Aguilar Parera

Supervisor: Klaus Langohr

Department: Statistics and Operation Research Department

University: Polytechnic University of Catalonia (UPC)

UNIVERSITAT POLITÈCNICA DE CATALUNYA
BARCELONATECH
Facultat de Matemàtiques i Estadística

UNIVERSITAT DE BARCELONA

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Master's degree in Statistics and Operations Research

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Modelling survival data from hepatorenal syndrome acute kidney injury

Alba Morató Catafal

Advisor: Ferran Aguilar Parera

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Abstract

Hepatorenal syndrome (HRS) is a common complication of advanced cirrhosis. It is characterised by renal failure and major disturbances in circulatory function and it is caused by intense vasoconstriction of the renal circulation. Liver transplantation is the treatment of choice for HRS. However, it is not always possible owing to the short survival expectancy. Also, in the last years it has also been proved that the syndrome can be reversed by the simultaneous administration of albumin and arterial vasoconstrictors such as terlipressin. This treatment improves the survival rate and may also serve as a bridge to liver transplantation. The main aim of this study is to assess the survival of HRS patients that are being treated with albumin, vasopressors or both of them and check whether their response to those treatments is determinant for their survival.

Although the main objective is to assess mortality, the follow up of the subjects included may end due to death, transplant or end of the study. That is why in order to assess survival an approach with competing risks will be used. This will allow us to see how the age, being treated with albumin and the creatinine levels seem to have an increasing effect on the hazard while the serum albumin levels seem to have a decreasing effect.

However, since this approach does not allow to include all the information that we would want (such as the response to treatment) some other models will also be introduced. Firstly, time-varying variables will be introduced in the models. Although time-varying competing risks models have to be interpreted with caution, we will estimate the treatment with vasopressors, some etiology of cirrhosis indicators and some other variables such as the INR, bilirrubin and presence of ascites seem to have an effect on the hazard.

Next, landmark models will be explained and used. Here the treatment with albumin, the INR, the total bilirubin and the etiology of cirrhosis will seem to have a significant effect on the hazard, by making it increase. Also we will see how time seems to have an effect on the hazard of death.

To end, multi-state models will also be seen. In this case we will obtain separate hazard estimates for those subject that were responding to treatment and those who were not. We will see how for the responders the treatment with vasopressors, the etiology of cirrhosis, the levels of bilirrubin and the presence of ascites have an increasing effect on the hazard. For the ones responding, the variables that are estimated to have a significant effect on this increase are again some etiologies of cirrhosis, the INR, the creatinine levels and the presence of hepatic encephalophaty.

Finally, in the conclusions and discussion section the results obtained will be compared and discussed.

Keywords— survival, hazard, competing, landmark, multi-state, cirrhosis, kidney, hepatorenal

Abbreviations

Term	Abbreviation
Acute decompensation	AD
Acute kidney injury	AKI
Acute on chronic liver failure	ACLF
Acute tubular necrosis acute kidney injury	ATN-AKI
C-reactive protein	CRP
Creatinine	Creat
Cumulative incidence function	CIF
European foundation for the study of chronic liver failure	EF-Clif
Hazard ratio	HR
Heart rate	HR
Hepatorenal syndrome	HRS
Hepatorenal syndrome acute kidney injury	HRS-AKI
International normalized ratio	INR
Kaplan-Meier estimator	KM
Master's degree in statistics and operations research	MESIO
Mean arterial pressure	MAP
Neutrophil gelatinase-associated lipocalin	NGAL
Non alcoholic fatty liver disease	NAFLD
Non alcoholic steatohepatitis	NASH
Partial pressure of arterial carbon dioxide	PaCo2
Partial pressure of arterial oxygen	PaO2
White blood cells	WBC

Contents

Chapter 1

Motivation and introduction

1.1 Motivation

During my academic life I have seen some of the basic concepts on survival analysis, however, I have never had the opportunity to use these techniques on real data. This is why for my final semester of the Master's degree in Statistics and Operations Research (MESIO) I thought it would be a great opportunity to enroll on the subject of survival analysis and, simultaneously, apply those techniques - and some other ones not seen in the subject- to a real problem through this final project. This way, I could not only learn the theory and practice seen during the course but also face the issues that often arise from real data and get a more complete view of the topic. To do so, I have been working with the European Foundation for the study of chronic liver failure (EF-Clif) in order to analyze data of patients with hepatorenal syndrome.

Being able to analyze real data is not only a great opportunity to learn, but also is a way to contribute so that the results of this study can somehow provide new insights of the disease and can, hopefully, be applied by clinicians. In this aspect, EF-Clif's final objective is to improve the quality of life and to increase the survival of patients with liver cirrhosis. In this case, this objective is specifically focused on patients with hepatorenal syndrome.

1.2 Context and justification

Acute kidney injury (AKI) is a relatively frequent problem, occurring in approximately 20% of hospitalized patients with cirrhosis. It consists on an abrupt (48 hours) reduction in kidney function. Its most common causes in cirrhosis are prerenal azotemia (volume-responsive prerenal AKI), acute tubular necrosis, and hepatorenal syndrome (HRS). Among these, HRS is the one associated with the worst survival rates (Martín–Llahí et al., 2011) and it is the one we will focus on in this project.

As it has been just introduced, hepatorenal syndrome is a common complication of advanced cirrhosis. It is characterised by renal failure and major disturbances in circulatory function and it is caused by intense vasoconstriction of the renal circulation. The diagnosis of HRS is currently based on the exclusion of other causes of renal failure and its prognosis is very poor, particularly when there is rapidly progressive renal failure.

Liver transplantation is the treatment of choice for HRS, with a 3-year probability of survival of 60% (Gonwa et al., 1995). However, it is not always possible owing to the short survival expectancy (Garcia-Tsao, Parikh, & Viola, 2008). Also, in the last years it has also been proved that the syndrome can be reversed by the simultaneous administration of albumin and arterial vasoconstrictors such as terlipressin. This treatment improves the survival rate and may also serve as a bridge to liver transplantation.

AKI can be classified into structural or functional, defined respectively by structural damage as indicated by low tubular injury markers, and no structural damage but dysfunction of the liver indicated by low levels of

Major Criteria
Chronic or acute liver disease with advanced hepatic failure and failportal hypertension.
Low glomerular filtration rate, as indicated by serum creatinine of >1.5 mg/dL or 24-h creatinine clearance <40 mL/min.
Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs.
Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses (weight loss >500 g/d for several days in patients with ascites without peripheral edema or 1,000 g/d in patients with peripheral edema).
No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or less or increase in creatinine clearance to 40 mL/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline.
Proteinuria <500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.
Additional criteria
Urine volume <500 mL/d.
Urine sodium <10 mEq/L.
Urine osmolality greater than plasma osmolality.
Urine red blood cells <50 per high power field.
Serum sodium concentration <130 mEq/L.

Table 1.1: International Ascites Club's Diagnostic Criteria of Hepatorenal Syndrome.

serum creatinine. In this case, HRS-AKI is considered functional because it is mainly reversible after liver transplantation and kidneys from patients with cirrhosis and HRS can be safely transplanted to patients with end stage renal failure (Koppel et al., 1969).

HRS is often diagnosed by using the International Ascites Club criteria (Table 1.1). Some of these criteria are considered major criteria and must be present for the diagnosis of HRS. The remaining criteria, most of them based on urinary indices, are not necessary for the diagnosis but may provide useful supportive evidence. However, as it has already been mentioned, the diagnostic can be tricky but crucial, since the treatment for the different types of AKI is quite different: prerenal AKI needs diuretics withdrawal and plasma volume expansion, HRS-AKI is treated with vasocontrictors plus albumin and intrinsic AKI needs removal of nephrotoxic agents, restoration of kidney perfusion and/or renal replacement therapy. In addition, in the perspective of liver transplantation, HRS-AKI is reversible after transplant while ATN-AKI is not. This has relevant impact on transplant outcomes in term of morbidity and mortality (higher in ATN-AKI). Although some markers such as the fractional excretion of sodium or albuminuria are useful, they are not very accurate alone (Ariza et al., 2015; Belcher et al., 2014). This is why new biomarkers are being studied in order to have a better assessment of the syndrome.

Urinary biomarkers may be also useful to predict response to terlipressin and albumin. One of the most studied biomarkers is neutrophil gelatinase-associated lipocalin (NGAL). NGAL is a protein, which is produced by several cells and tissues such as white blood cells, kidneys, liver, lungs, etc. It is upregulated after ischemic and nephrotoxic AKI and it is detectable in urine within 3 hours after injury. Urinary NGAL can unveil the presence of some degree of tubular dysfunction. In addition, quinolinic acid, a downstream product of kynurenine pathway, which has shown to be associated with risk of AKI, could be useful for this purpose.

1.3 Aims

The main aim of this study is to assess the 28-day and 90-day mortality of HRS patients that are being treated with albumin, vasopressors or both of them and check whether their response to those treatments is determinant for their survival. This will be done through the following specific aims:

- Describe and understand the techniques for survival analysis and more specifically some of those used to model competing risks
- Perform a descriptive analysis of the sample of hepatorenal syndrome patients
- Describe the survival rates of these patients after 28 and 90 days after diagnostic
- Identify prognostic factors and describe how the survival rates interact with the treatment received (albumin and/or vasoconstrictors) and their responses to this treatment by using the techniques described
- Compare the results obtained by the different models

1.4 Data

The data used for this study comes from the PREDICT and the ACLARA cohorts.

The PREDICT cohort aims to identify predictors of the development of acute-on-chronic liver failure (ACLF) in patients hospitalized for an acute decompensation of cirrhosis without ACLF. It is composed of about 1200 patients across with Acute Decompensation (AD) at risk of developing ACLF in more than 10 centers in Europe. Its design consists of a prospective observation of these patients within three months to discover clinical, laboratory and patho-physiological predictors and mechanisms involved in the development and clinical course of ACLF, which might help to prevent and treat this illness. After the enrolment visit, the patients are stratified into two groups: Group 1 patients with high risk of ACLF development (CLIF-C AD score $\geq$ 60) and in Group 2 patients with low risk of ACLF (CLIF-C AD score <60). The whole cohort is followed for 3 months, while Group 1 is followed more closely. Since development of ACLF is an end-point in the case a subject developed it, a final visit 7-10 days after the development is planned. Additionally, data on liver transplantation, mortality, and causes of mortality at 3 months, 6 months and 12 months is collected for the whole cohort.

The ACLARA cohort aims to estimate the prevalence, epidemiology, characterization and mechanisms of ACLF in Latin America. It is composed of about 1300 patients with cirrhosis hospitalized for AD with and without ACLF across the 57 hospitals from the Latin America CLIF Consortium. Its design consists on a prospective follow-up observational investigation of these patients, obtaining clinical and standard laboratory data and samples for measuring circulating levels of inflammatory inducers and mediators, biomarkers of systemic circulatory dysfunction and oxidative stress, innate immune cell function and cell death and genotyping (obtained only at admission). Transcriptomics and metabolomics are obtained at admission, 8-10 days after admission and at discharge. The one-year clinical course (survival, liver transplantation and causes of death) is also recorded.

For this study we will use a subset of patients coming from these two cohorts that have been diagnosed of hepatorenal syndrome according to the International Club of Ascites Criteria and who have available urine samples at the time of diagnosis.

Both data sets include variables about the subjects demographics, medical history, laboratory data, treatments, etc. However, they do not include exactly the same variables. For this reason and because the data sets have not been designed for this concrete study the selection of the sample itself has been a challenge. This will be further explained next, in the methodology section.

1.4.1 Variables of interest

The response variable in the study is the time until an event, being this event either death or a liver transplant. In order to explain this response variable some covariates have been considered. On one hand, there would be

the variables such as the demographics of the patients or the etiology of the cirrhosis that have just measured once, since they do not change with time. These variables have been measured at the visit of inclusion. On the other hand, there are those variables that do change with time, such as treatments, results from physical examinations, clinical features and laboratory results and which have been measured at every visit (there are some exceptions leading to missing data). Let us introduce these two types of variables:

1.4.1.1 Baseline variables

Demographics

- Age: Age of the patient.
- Sex: Sex of the patient.

Etiology of cirrhosis

Dummy variables indicating whether the etiology of cirrhosis is due to:

- Alcohol
- Hepatitis B virus
- Hepatitis C virus
- Non alcoholic fatty liver disease (NAFLD) or Non-Alcoholic SteatoHepatitis (NASH)
- Cryptogenic
- Other
- Unknown

1.4.1.2 Time-varying variables:

Treatment

- Treatment with albumin: Dummy variable indicating whether the subject has been treated with albumin or not.
- Treatment with vasopressors: Dummy variable indicating whether the subject has been treated with vasopressors or not.

Physical examinations

- Mean Arterial Pressure (mmHg): Average arterial pressure throughout one cardiac cycle, systole, and diastole. Values over 70 may indicate circulation normal functioning while values under 70 imply circulation dysfunction (Jalan et al., 2014).
- Heart rate (bpm): Can be a predictor of some renal diseases (Böhm et al., 2015).

Clinical features

- Ascites: Dummy variable indicating whether the subject has ascites or not. This consists on having too much fluid in the abdomen due to cirrhosis.
- Hepatic encephalopathy: Dummy variable indicating whether the subject has hepatic encephalopathy or not. Hepatic encephalopathy is a nervous system disorder brought on by severe liver disease. When the liver does not work properly, toxins build up in the blood. These toxins can travel to the brain and affect brain function.
- Gastrointestinal bleeding: Dummy variable indicating whether the subject has gastrointestinal bleeding or not. May be a complication in patients with liver cirrhosis. It includes all forms of bleeding in the gastrointestinal tract, from the mouth to the rectum.
- Bacterial infection: Dummy variable indicating whether the subject has a bacterial infection or not. Serious and often fatal complication of patients with liver disease and can prove fatal either directly or by precipitation of gastrointestinal bleeding, renal failure, or hepatic encephalopathy (Wyke, 1989).

Laboratory

- International normalized ratio (INR): Test used to measure how quickly blood forms a clot, compared with normal clotting time. If there is serious liver disease and cirrhosis, the liver may not produce the proper amount of proteins and then the blood is not able to clot as it should. A high INR usually means that the liver is not working as well as it could because it is not making the blood clot normally ("INR (international normalized ratio)," n.d.). Values < 2 indicate coagulation normal functioning, values between 2 and 2.5 imply coagulation dysfunction and values over 2.5 imply coagulation failure (Jalan et al., 2014).
- Bilirubin (mg/dL): Values < 6 indicate liver normal functioning, values between 6 and 12 imply liver dysfunction and values over 12 imply liver failure (Jalan et al., 2014).
- Creatinine (mg/dL): Values < 2 indicate kidney normal functioning, values between 2 and 3.5 imply kidney dysfunction and values over 3.5 imply liver failure (Jalan et al., 2014).
- Albumin (g/dL): Protein made by the liver that helps keep fluid in the bloodstream so it does not leak into other tissues. It also carries various substances throughout your body, including hormones, vitamins, and enzymes. Low albumin levels can indicate a problem with your liver or kidneys.
- Hemoglobin (g/dL): Low levels of hemoglobin may indicate anemia, which may be caused by gastrointestinal bleeding or other symptoms of chronic liver failure.
- Sodium (mEq/L): Serum concentrations of sodium in patients with end-stage liver disease reflect a reduction in renal function, the underlying event that decreases survival (Lim et al., 2010).
- Total Cholesterol (mg/dL): Recent data suggest that disturbed hepatic cholesterol homeostasis and liver free cholesterol accumulation are relevant to the pathogenesis of some liver diseases (Arguello, Balboa, Arrese, & Zanlungo, 2015).
- CRP (mg/L): C-reactive Protein (CRP) is a protein made by the liver that has been found in elevated values in patients with chronic liver disease (Tilg et al., 1992).
- Leucocytes (x10^9/L): Also called white blood cells (WBC), they are the cells of the immune system that are involved in protecting the body against both infectious disease and foreign invaders. There are different types of blood cells.
- Lymphocytes (x10^9/L): Type of white blood cell, made in the bone marrow and generally found in lymph tissue and blood.
- Lymphocytes (%)
- Monocytes (x10^9/L): Largest type of white blood cells. Can differentiate into macrophages and conventional dendritic cells. As a part of the vertebrate innate immune system monocytes also influence the process of adaptive immunity.
- Monocytes (%)
- Neutrophils (x10^9/L): Most abundant type of white blood cells. They form an essential part of the innate immune system.
- Neutrophils (%)
- Immature neutrophils (%): A low percentage of immature neutrophils can indicate chronic infection. This is because, in the case of bacterial infection, mature neutrophils in the circulations migrate to the tissues in order to fight invading microorganisms. The bone marrow then responds to the decrease of the Neutrophil Count in the blood circulation by releasing stored mature neutrophils. However, as this storage becomes depleted, the bone marrow has to release neutrophils in its immature forms.
- PaO_2 (mmHg): Partial pressure of arterial oxygen. Indicator of the oxygenation of tissues, which may be decreased in several disease processes.
- $PaCO_2$ (mmHg): partial pressure of arterial carbon dioxide, it often serves as a marker of sufficient alveolar ventilation within the lungs.

1.4.2 Outline

This project consists of 4 chapters. In this first one, the data and the main objectives and motivations of the project have been introduced. Next, chapter 2 will describe the methods used in the project. First, an introduction to survival data analysis will be provided. This will be followed by the presention of some more specific techniques that can be used to model our data such as competing risk and multi-state models. The third chapter will explain the results obtained. It will start with a brief descriptive analysis of the data and next

the models introduced in the methodology section will be applied. Finally, in the conclusions and discussion section the results obtained will be compared and discussed.

Chapter 2

Methodology

2.1 Selection of the data

As it has been previously introduced, the selection of the sample has not been straightforward, since the data sets being used have not been designed for the exact purpose of this study and furthermore they do not include the exact same variables. For instance, just one of the data sets (the PREDICT one) included a variable indicating if a subject had hepatorenal syndrome or not. Since this variable had to be defined from other variables for the ACLARA data set, it was decided to use this same definition for both data sets. This way, we defined as subjects with hepatorenal syndrome those who were reported to be treated with albumin and/or vasopressors for HRS (this had been reported for both data sets) and those who were reported to have the syndrome (only reported in the PREDICT cohort). For those subjects we initially took the first visit when they had HRS as the diagnostic visit (although they could have developed it between visits). Additionally, knowing that HRS patients are expected to have high levels of creatinine, we checked the values of creatinine in the previous visits and realized that in some cases they had higher values of creatinine then. This would imply they were already showing the first symptoms of HRS in those previous visits. Therefore, for these subjects those visits were taken as the diagnostic visit. Following the same criteria, since the subjects are expected to have high creatinine values in the time of diagnostic, those having values lower than 1.5 mg/dL in the diagnostic visit were excluded.

The initial idea was to stratify the subjects depending on whether they were responsive to the treatment or not, as seen in other studies. This classification could be defined by whether the subjects ended up having healthy values of creatinine (lower than 1.5 mg/dL) or not. However, due to the characteristics of the data and the fact that it was not specifically designed for this study, not all subjects had the same number of follow-up visits. For that reason some of them did not have enough visits to lead to a conclusion or, what is the same, this variable could be censored in some cases. Furthermore, this would imply using values of the variable that are not basal to stratify the data, which is not good practice and, indeed, can lead to the so-called immortal time bias. What this bias implies is that to be a responder you have to survive to a minimum response time, this makes the individuals in the responder group immortal for some time (Putter, 2013). Some alternatives in order to study the response to treatment would be to include this variable as a time-varying covariate, to use landmark models, to use multi-state models, or the joint modelling of longitudinal and survival data. In this project the first three will be introduced, for further explanations check the survival analysis section (2.2).

Regarding the variables used to fit these kind of models, one option would be adapting the procedure suggested by Hosmer & Lemeshow (2000). However, since one of the objectives in this project is to compare all the models fitted, it has been decided to fit the models for all the variables presented in the previous section, in order to fit the same variables for all models and not decide which variables to include by just by looking at one model, which would probably favour that model.

Statistical software for data management

Since the raw data of the study is built and stored in SAS format, this software has been used for the primary steps of data retrieval and selection. More concretely, it has been used the 9.4 version of SAS.

SAS codes, as well as all the code from this project, are available in the online repository github.com/albamrt/HRS-survival .

2.2 Survival analysis

The methods introduced in the first introductory part of the current section (subsections 2.2.1, 2.2.2, 2.2.3) are mainly based on the explanations in In & Lee (2018), In & Lee (2019) and Klein & Moeschberger (2003). The following sections are mainly based on Austin & Fine (2017) (subsection 2.2.4), Austin, Latouche, & Fine (2020) (subsection 2.2.5) and Van Houwelingen & Putter (2011) (subsections 2.2.6 and 2.2.7).

Survival analysis is a branch of statistics focused on modelling the elapsed times until an event of interest, such as death in biological organisms and failure in mechanical systems. When dealing with this type of data, we often encounter two main problems: having not normally distributed data and having incomplete information, the so-called censored observations. Censored observations are due to not being able to follow some subjects until the event of interest. This can be because that person has not experienced the relevant outcome, such as relapse or death, by the time of the close of the study, because it has been lost to follow-up during the study period, because it has experienced a different event that has made further follow-up impossible, ... Therefore, we do have some information about them: they were alive until a certain point, but from there on we just do not know what happened.

To deal with this kind of data, we cannot use the classical statistical methods, we need to use special techniques of survival analysis. In this type of analysis, the outcome variable is the time until the event of interest, which has to be combined with the censoring variable, that indicates whether a subject has been followed until this event of interest or its track has been lost at some point.

The two most important functions in survival analysis are the survival and the hazard functions, which will be introduced in the following sections.

2.2.1 The survival function and the Kaplan-Meier estimator

Being T a non-negative random variable that measures the time until a certain event, the survival function $S(t)$, defines the probability that an individual survives beyond time t (that T is greater than t):

$$S(t) = P(T > t), \qquad 0 < t < \infty$$

In an ideal situation without censoring, this could be simply estimated by:

$$S(t) = \frac{\text{number of individuals with survival time} > t}{n}$$

However, because of the nature of these studies, we do usually have censored data. A very widely used method to deal with this problem is calculating and plotting a Kaplan–Meier curve, which is a non-parametric method of estimating the survival function.

Let $t_1 < t_2 < \ldots < t_k$ be the observed event times and $n = n_0$ the sample size at time 0, when no individuals have yet been censored or died. Let d_j be the number of individuals who have an event at time t_j, where $j = 1, \ldots, k$, and m_j the number of individuals censored in the interval $[t_j, t_{j+1})$. Then $n_j = (m_j + d_j) + \ldots + (m_k + d_k)$ is the number of individuals at risk just prior to t_j. Then, the Kaplan-Meier estimator of the survival function is defined as:

$$\hat{S}(t) = \prod_{j:t_j<t} \frac{n_j - d_j}{n_j}$$

and its standard errors can be estimated by using the Greenwood formula, which approximates the variance as:

$$\widehat{\mathrm{Var}}(\hat{S}(t)) = \hat{S}(t)^2 \prod_{j:t_j<t} \frac{d_j}{n_j(n_j - d_j)}$$

The Kaplan-Meier estimator allows to plot the Kaplan–Meier curve, which can be useful to compare survival times of two or a small number of groups. Confidence intervals can be plotted around the curves thanks to the variance obtained with the Greenwood formula.

Also, it is possible to compare the survival functions of two (or more) populations by using the log-rank test. This allows to test the null hypothesis that there is no difference between the populations in the probability of an event (e.g death) at any time point.

$$H_0 : S_1(t) = S_2(t),$$
$$H_a : S_1(t) \neq S_2(t)$$

The analysis is based on uncensored event times. For each time we calculate the observed number of deaths in each group and the number expected if there were in reality no differences between the groups. If a survival time is censored, that individual is considered to be at risk of dying in the week of the censoring but not in subsequent weeks. This way of handling censored observations is the same as for the Kaplan-Meier survival curve.

This way, the log-rank test statistic can be computed, for times t_j, where $j = 1, \ldots, k$, and groups $i = 1, 2$ as:

$$Z = \frac{\sum_{j=1}^{k} O_{i,j} - E_{i,j}}{\sqrt{\sum_{j=1}^{k} V_{i,j}}}$$

Where $O_{i,j}$ is the observed number of events in group i at time j, $E_{i,j} = N_{i,j}\frac{O_i}{N_j}$, where $N_{i,j}$ is the number of subjects at risk (who have not yet had an event or been censored) from group i at time j and $V_{i,j} = E_{i,j}\left(\frac{N_j - O_j}{N_j}\right)\left(\frac{N_j - N_{i,j}}{N_j - 1}\right)$.

The log-rank test is most likely to detect a difference between groups when the risk of an event is consistently greater for one group than another. It is unlikely to detect a difference when survival curves cross, that is why the survival curves should always be plotted (Bland & Altman, 2004).

Because the log-rank test is purely a test of significance it cannot provide an estimate of the size of the difference between the groups or a confidence interval. For these we must make some assumptions about the data. Common methods use the hazard ratio, including the Cox proportional hazards model, which will be described in the following sections.

2.2.2 The hazard, the cumulative hazard and the Nelson-Aalen estimator

Another way to describe survival data by means of the hazard function. It is usually denoted by $h(t)$ or $\lambda(t)$ and it is the instantaneous risk that an individual who is under observation at a time t has an event at that time. Put another way, it represents the instantaneous event rate for an individual who has already survived to time t. Supposing that an item has survived for a time t, then the probability that it will not survive for an additional time Δt is defined as:

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t)}{\Delta t \times S(t)} = \frac{f(t)}{S(t)}$$

It is related to the survival function in the following way:

$$h(t) = -\frac{d}{dt}\left[\log\big(S(t)\big)\right]$$

Although the relationship between these two functions allows to estimate one by having the other, it is difficult to estimate directly the hazard function. That is why the cumulative hazard $H(t)$, defined for an absolutely continuous variable in Equation (2.1), is often computed, because although it is more difficult to interpret, it is much easier to estimate.

$$H(t) = \int_0^\infty h(u)du \tag{2.1}$$

A way to interpret the cumulative hazard is as the cumulative force of mortality, or the number of events that would be expected for each individual by time t if the event were a repeatable process. However, it is usually just used as an intermediary measure for estimating $h(t)$ and as a diagnostic tool in assessing model validity (Clark, Bradburn, Love, & Altman, 2003). It also has a clear relationship with the survival function:

$$H(t) = -\log(S(t))$$

Or, what is the same:

$$S(t) = e^{-H(t)}$$

A simple nonparametric method for estimating $H(t)$ is the Nelson-Aalen estimator (Hosmer & Lemeshow, 2000), given by:

$$\hat{H}(t) = \sum_{t_i<t} \frac{d_i}{n_i}$$

with d_i the number of events at t_i and n_i the total individuals at risk at t_i.

Another approach to estimate the hazard is to assume that the survival times follow a specific mathematical distribution, which could have different shapes: it could be constant over time, strictly increasing, strictly decreasing or a combination of these (see Figure 2.1).

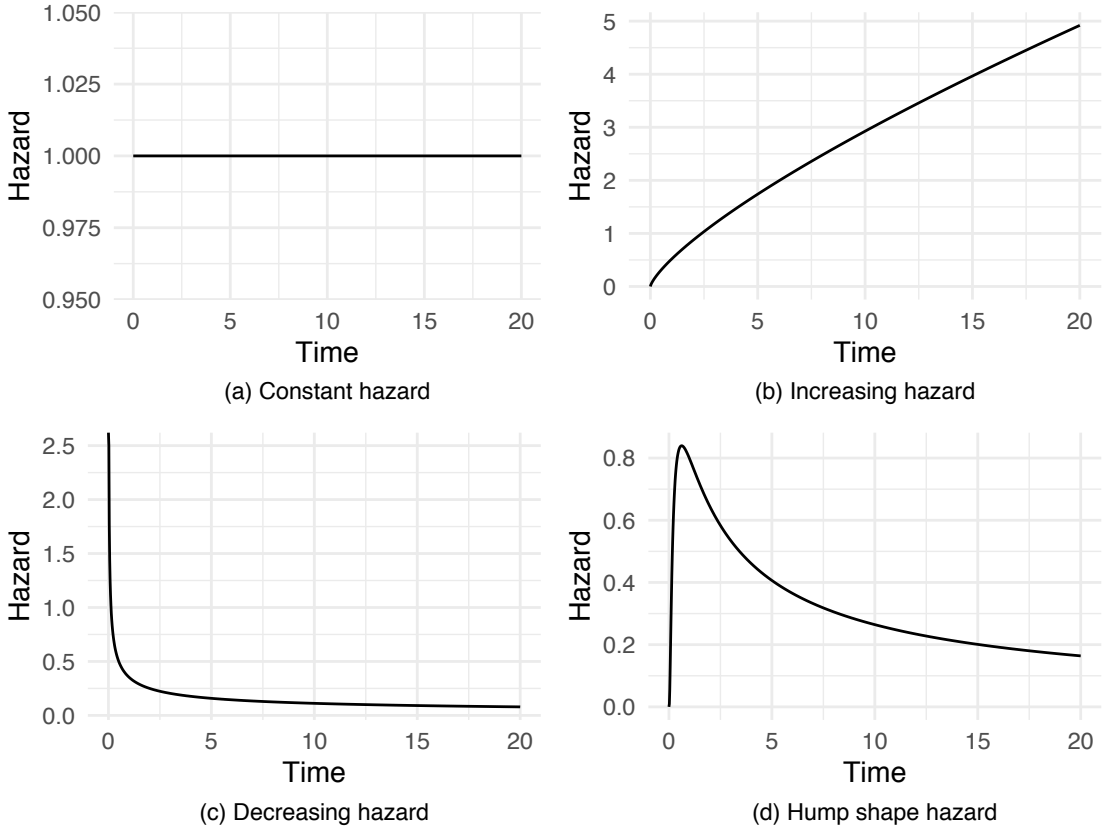

Figure 2.1: Parametric hazard functions.

2.2.3 The Cox model

However, nor the Nelson-Aalen estimator nor the Kaplan-Meier allow one to include regressors in the analysis. This is where the Cox (semi-parametric) proportional hazards model comes in. It is a survival analysis regression model that describes the relation between the event incidence, as expressed by the hazard function and a set of covariates (Clark et al., 2003). The model is written as:

$$h(t) = h_0(t) \exp(\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p) \tag{2.2}$$

where the hazard function $h(t)$ is dependent on a set of p covariates $(x_1, x_2, \ldots, x_p)$, whose impact is measured by the size of the respective coefficients $(\beta_1, \beta_2, \ldots, \beta_p)$. The term h_0 is called the baseline hazard, and is the value of the hazard if all the x_i are equal to zero (the quantity exp(0) equals 1). We could also write the model as:

$$h(t) = h_0(t) \exp(\beta_1 x_1) \exp(\beta_2 x_2) \cdots \exp(\beta_p x_p)$$

So, basically, there is a baseline hazard that varies with time and some covariates that act multiplicatively on the hazard at any point in time. The key assumption of this model is that the hazard of the event in any group is a constant multiple of the hazard in any other. This assumption implies that the hazard curves for the groups should be proportional and cannot cross. Derived from these characteristics, we call $\exp(\beta_i)$ hazard ratios. A value of β_i greater than zero, or equivalently a hazard ratio greater than one, indicates that

as the value of the ith covariate increases the event hazard increases and thus the length of survival decreases. However, this proportionality assumption is strong and therefore we need to verify that it holds.

Verification of proportionality assumption can be done mainly by two approaches. The first one consists on graphical visualization of the Schoelfeld residuals, which basically compare the observed covariate value for individuals that failed minus its expected value (therefore there is one value per individual per covariate). Under the hypothesis of proportionality, these residuals are expected to be randomly distributed and have a constant slope through time around zero. This can be inspected visually or by fitting a regression line and testing whether the slope equals zero. Another approach would be defining new explicative variables as $Z_2(t) = Z_1 g(t)$, being $g(t)$ a know function (usually $g(t) = \ln(t)$) and fitting a new model including Z_1 and Z_2. The coefficient associated to Z_2 is expected to not be significantly different than 0, meaning that there is no change through time. More about this topic in Gomez, Julia, & Langohr (2011).

However, sometimes time to event data has to be thought as a multi-state process. This would be the case of our data, where we can have more than one possible outcome. Depending on how many states are defined the data can be described either as a competing risks situation or as a multi-state one (being the first a concrete case of the second). If we considered 2 possible endpoints: a subject could die or that person could receive a transplant, then, the situation could be modeled as a competing risks one (see Figure 2.2). In the case of the multi-state model, we could also include as states the response or non-response to the treatment (see last case of 2.2). In contrast, in the competing risk model we should include the response to the treatment as a covariate in the model. And, since the response to the treatment is a variable that can only be observed through time, and not on a baseline level, it should be included in the model as a time-varying covariate. This will be further seen in the following sections.

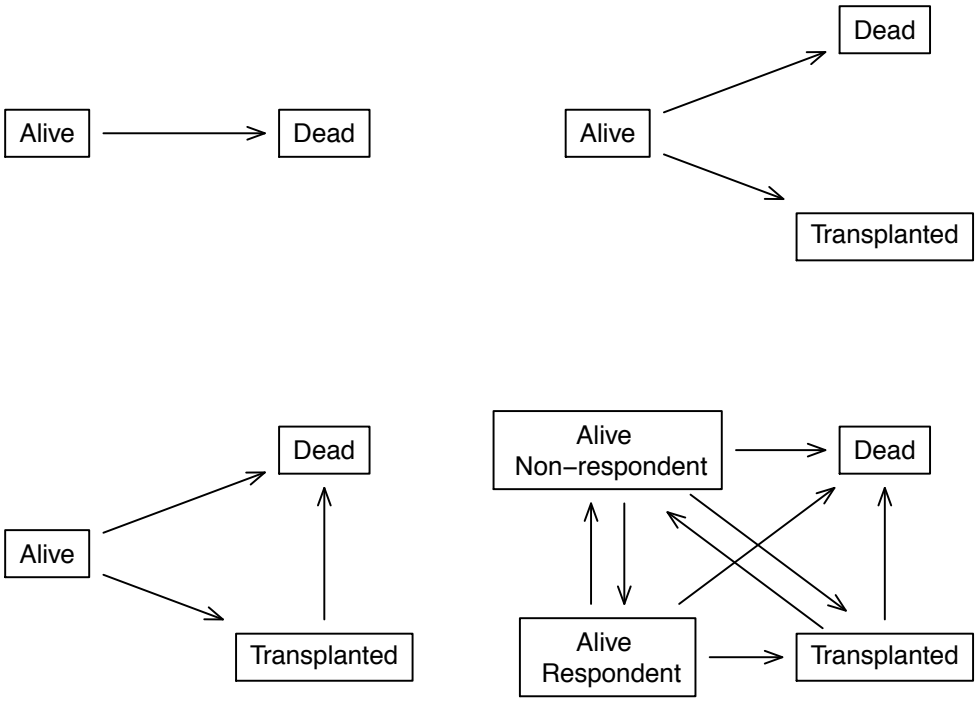

Figure 2.2: Four multi-state models. The upper left panel depicts simple survival, the upper right depicts competing risks with receiving a transplant and dead as competing risks, the lower left panel is a multi-state transplant-death model and the lower right is a multi-state model including four states: being alive and responding to treatment, being alive but not responding to treatment, receiving a transplant and dead.

2.2.4 Competing risks, the cause-specific hazard model and Fine and Gray's model

Competing risks are said to be present when a patient is at risk of more than one event, such as death from different causes, and the occurrence of one of these mutually excluding events will prevent any other event from ever happening (Gichangi & Vach, 2005). As we have already introduced, we could consider our case as such, having death and liver transplants as competing events. In this case, in practice, it is not true that the two events are mutually exclusive, since death can still happen after a transplant. However, it kind of makes sense to make that assumption especially by the way our data is organized, since the subjects are not followed after a transplant, so we do not any information after that.

For this type of data, using the classical survival techniques, which assume noninformative censoring, such as the Kaplan-Meier estimator would lead to biased results. Since it estimates the probability of the event of interest in the absence of competing risks, which is generally larger than that in the presence of competing risks, it usually leads to overestimate the rate of the event, especially when the rate of the competing risk is high (Alipour, Shokri, Yasari, & Khodakarim, 2018; Austin, Lee, & Fine, 2016). This is why the cumulative incidence function (CIF) is used instead.

This cumulative function for the kth cause is defined as $\text{CIF}_k(t) = P(T \leq t, D = k)$, where D is a variable

denoting the type of event that occurred. It denotes the probability of experiencing the kth event before time t and before the occurrence of a different type of event. The CIF has the desirable property that the sum of the CIF estimates of the incidence of each of the individual outcomes will equal the CIF estimates of the incidence of the composite outcome consisting of all of the competing events. Although in the absence of competing risks there is a direct correspondence between the hazard and incidence functions, this does not hold in the presence of competing risks, where it is important to specify whether risk denotes the hazard of an event (ie, the rate of the occurrence of the event in those still at risk of the event) or the incidence of the event (ie, the probability of the occurrence of the event).

Because of this, 2 different types of hazard functions are of interest: the cause-specific hazard function (2.3) and the subdistribution hazard function (2.4).

$$h_k^{cs}(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, D = k | T \geq t)}{\Delta t} \tag{2.3}$$

$$h_k^{sd}(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, D = k | T \geq t \cup (T < t \cap K \neq k))}{\Delta t} \tag{2.4}$$

The cause-specific hazard function for a given event type is the instantaneous rate of occurrence of the given type of event in subjects who are currently event-free. In practice, this means that all causes of death other than the one being studied are treated as censoring. 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.

Basically, both models can be estimated as seen in Equation (2.2), by adjusting the risk set (more information on how to do this in practice in Section 2.2.8).

Note that for the subdistribution hazard function, we are considering the rate of the event in those subjects who are either currently event-free or who have previously experienced a competing event. So, the main difference between both models is that in the case of the cause-specific hazard, individuals are removed from the risk set when any type of event occurs; whereas for the subdistribution one an individual is removed from the risk set when an event of the focal type occurs or when the individual is truly censored. However, when a competing event occurs, the individual remains in the risk set. Fine and Gray acknowledge that this is "unnatural" because, in fact, those who experience competing events are no longer actually at risk of the focal event. But it's necessary in order to get a model that correctly predicts cumulative incidence functions.

In fact, this is the main point of the subdistribution model (also been described as the CIF regression model): when a covariate is associated with an increase in the subdistribution hazard function, it will also be associated with an increase in the incidence of the event. On the contrary, when using a cause-specific hazard model in the presence of competing risks, it is incorrect to infer that if a given variable is associated with an increase in the hazard function, it will also be associated with an increase in the incidence of the event of interest. What can actually be interpreted from this model is that an increase in variable x is associated to an increase of the hazard of event k in subjects who are alive (Austin & Fine, 2017).

As it is also mentioned in Austin & Fine (2017):

> "(...) cause-specific hazard model is more appropriate for addressing etiological questions (eg, is a given risk factor or characteristic associated with the rate of the occurrence of the outcome in subjects who are currently event-free) while the Fine-Gray model is more appropriate for addressing questions around incidence and prognosis (eg, what is an individual's probability of experiencing the outcome within a given duration of time)."

This is because the cause-specific hazard function denotes the instantaneous rate of the primary outcome in those subjects who are currently event free, so a regression coefficient from this model can be interpreted as the relative effect of the corresponding covariate on the relative increase in the rate of the occurrence of the primary event in subjects who are currently event free. On the contrary, clinical prediction models and risk-scoring systems are interested in estimating the absolute incidence of the event of interest, which is given by the subdistribution hazard model.

Therefore, they suggest that depending on the clinical question one model or the other should be used. However, they also mention an alternative approach, consisting on fitting both the cause-specific and the subdistribution hazard models, for both the primary outcome and for the competing events in order to develop a greater understanding of the relationship between covariates and outcomes (being careful in interpreting the regression coefficients from the subdistribution hazard model correctly). This is the approach taken in the project.

2.2.5 Time-varying covariates

Time-varying coavriates are present when a given covariate changes over time during the follow-up period, which is a common phenomenon in clinical research. For example, the effect of smoking on cancer risk has been extensively studied. However, the smoking status is ever changing during the follow-up period. Such a covariate can be considered as a time-varying covariate.

There are two types of time-varying covariates: internal and external. The internal ones are related to the subjects and depend on the fact that they are alive. The external ones are typically related to external factors, not depending on the subjects and therefore, their status. An example of an internal covariate would be any clinical feature of the subject while an example of an external could be any variable related to pollution, climate, ...

A way of modelling these kind of covariates is by extending the general hazard model for failure time proposed by Cox:

$$h(t|Z(t)) = h_0(t)\exp(\boldsymbol{\beta}'\boldsymbol{x} + \boldsymbol{\gamma}'\boldsymbol{X}(t))$$

where $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ are coefficients of time-fixed and time-varying covariates respectively and $\boldsymbol{Z}(t) = [x_1, x_2, \ldots, x_p, X_1(t), X_2(t), \ldots, X_q(t)]$, being $x_1, \ldots, x_p$ the time-fixed covariates and $X_1(t), \ldots, X_q(t)$ the time-varying covariates.

From this model we obtain a non-constant hazard ratio defined as:

$$\widehat{\text{HR}} = \frac{h(t;\boldsymbol{Z}(t))}{h(t;\boldsymbol{Z}(t)^*)} = \frac{h_0(t)\exp(\boldsymbol{\beta}'\boldsymbol{x} + \boldsymbol{\gamma}'\boldsymbol{X}(t))}{h_0(t)\exp(\boldsymbol{\beta}'\boldsymbol{x}^* + \boldsymbol{\gamma}'\boldsymbol{X}(t)^*)} = \exp(\boldsymbol{\beta}'\boldsymbol{x}^* + \boldsymbol{\gamma}'\boldsymbol{X}(t)^*)$$

Time-dependent Cox models are especially appropriate for external covariates, since those vary as a function of time but are independent of the failure time. The other main approach to model time-varying covariates would be joint modeling of longitudinal and survival data, which is beyond the scope of this project.

In our case, an option would be fitting a competing risks model with time-varying covariates in order to allow this 'dynamic prediction'. This could be done either by fitting a cause-specific model or a subdistribution one. However, in Austin et al. (2020), the authors explain how often the results of the subdistribution model with time-varying covariates are misinterpreted, since one would think that the coefficients for the time-varying covariates could be directly associated with the CIF or the risk of the event, but this does not hold, as it will now be explained.

It is known that in the absence of competing risks the survival is related to the cumulative hazard function such that $S(t) = \exp(-H(t))$, and therefore the CIF can be defined as $\text{CIF}(t) = 1 - \exp(-H(t))$. But in presence of competing risks and time-varying covariates the CIF is defined as:

$$\text{CIF}_k(t|\boldsymbol{X}(s), s \leq t) = P(T \leq t|\boldsymbol{X}(s), s \leq t)$$

And the subdistribution hazard can be written as:

$$h_1(t|\boldsymbol{X}(s), s \leq t) = h_{10}(t)\exp(\boldsymbol{X}(t)\boldsymbol{\beta})$$

Consequently, we have that:

$$\text{CIF}_1(t|\boldsymbol{X}(s), s \leq t) = 1 - \exp\Big(-\int_0^t h_1(s|\boldsymbol{X}(u), u \leq s)du\Big) = 1 - \exp\Big(-\int_0^t h_{10}(s)e^{\boldsymbol{X}(s)\boldsymbol{\beta}}ds\Big)$$

In the case of external time-varying covariates, $\boldsymbol{X}(t)$ is known even when a subject is not under observation and the above integral can be evaluated at any point and has a clear probabilistic meaning. However, in general, we can no longer make simple claims that a covariate that has an effect on the subdistribution hazard of the outcome has an effect of the same direction on the cumulative incidence of the outcome, as it depends on the entire history of the time-varying covariate.

An alternative would be to use the landmark (conditional) approach.

2.2.6 Landmarking

Putter (2013) explains how this approach actually emerged from the debate on the effect of response to chemotherapy on survival (Anderson, Cain, & Gelber, 1983) and its common for the analysis for two groups: a "responder" and a "non-responder" one to compare survival between these two groups, which has from the beginning been our objective. But since, as already mentioned, at baseline we do not know who will be the responders or the non-responder subjects and, when studying survival, it is not allowed to make groups based on something that will happen in the future. That is why the landmark approach emerged with the objective of dynamic prediction of survival.

Landmarking simply consists of choosing a set of landmark time points and splitting the data on these points. The response at those fixed points in time is considered and the patients with events (or censored) before landmark are removed from the analysis. This allows to compute the probability of survival using the preferred method given the sample at risk at that time, so it can be adapted, in the case of competing risks, to both the cause-specific and subdistribution model. For a single landmark s the Cox model would be estimated as:

$$h_s(t|\boldsymbol{X}(s)) = h_{s,0}(t)\exp(\boldsymbol{x}(s)'\boldsymbol{\beta}_s(t)), \quad \text{for} \quad t \geq s$$

This could be used, for example, to model the probability of survival until 90 days given that subjects are alive after one week. Alternatively, they can be fitted for multiple landmarks. In Van Houwelingen & Putter (2011), the sliding landmark model is introduced. This is defined as the simple Cox model applied for all individuals at risk at $t = t_{LM}$ and ignoring any event after $t = t_{LM} + w$ (Equation (2.5)).

$$h_s(t|\boldsymbol{x}, t_{LM}, w) = h_0(t|t_{LM}, w)\exp(\boldsymbol{x}'\boldsymbol{\beta}_{LM}), \quad \text{for} \quad t_{LM} \leq t \leq t_{LM} + w \tag{2.5}$$

Although this approach is a very convenient and useful way to obtain a dynamic prediction without having to fit a model with complicated time-varying effect, it requires a separate Cox model to be fitted at each time-point t_{LM} for which a prediction is required. This is not very practical and hard to communicate to clinical users. In order to obtain more smooth and simple models, landmark supermodels were introduced. Those consist of unifying landmarks models over different time points into one unique model.

This can be achieved by computing all the separate prediction models and smoothing them by local smoothers like "loess" or by fitting some regression models to the predictions with the landmark t_{LM} as explanatory variable. In Van Houwelingen & Hans (2007), a different approach is presented that allows the use of existing survival software to obtain a prediction model that can be applied over a range of prediction times. It is based on the construction of a "super prediction data set". This way, super models with landmark-specific baseline hazards are obtained. This will be further explained in the following sub-section.

2.2.6.1 Super model with landmark-specific baseline hazards by stratifying

In order to build a super prediction data set the following steps must be followed:

1. Fix the prediction window w;

2. Select a set of prediction time points $s_1, \ldots, s_L$;

3. Create a prediction data set for each $t_{LM} = s_l$ by truncation and administrative censoring;

4. Stack all those data sets into a single "super prediction data set".

Since the selection of the set of prediction time-points needs a weighting of those, the simplest approach is selecting an interval $[s_1, s_L]$ and taking an equidistant grid of points on the interval. In this large data set, the subsets corresponding to a given prediction time $t_{LM} = s_l$ are labeled as "strata".

This way, the models can be fitted with standard procedures (say the `coxph` function of the `survival` package) by just adding the landmark value as a stratification term. This allows to fit separate baseline hazard functions for each strata but unique coefficients for each variable (and not one for each landmark) The model equation would look like follows:

$$h(t|\boldsymbol{x}, t_{LM} = s, w) = h_0(t|s, w)\exp(\boldsymbol{x}'\boldsymbol{\beta}), \quad \text{for} \quad s \leq t \leq s + w$$

This first approach based on stratified analysis produces nice smooth landmark dependent effects. However, they give separate estimated baseline hazards for each stratum. This smoothness could be modeled in a more direct way as seen in the next sub-section.

2.2.6.2 Super model with landmark-specific baseline hazards by using landmark as a covariate

As mentioned, the smoothness could be modeled more directly as:

$$h_{s0}(t_i) = h_0(t)\exp(\boldsymbol{\theta}(s))$$

where $\theta(s) = \sum_{j=1}^{m_h} \eta_j g_j(s)$, for proper basis functions $g_j(s)$ standardized by $g_j(s_1) = 0$.

This model can be fitted by applying a Cox model without stratification with main effects for the stratum variable s modeled by $\boldsymbol{\theta}(s)$ and interaction of s with the covariates modeled by $\boldsymbol{\beta}(s)$. It is advisable for this kind of data to remove trends in the covariates before fitting the models.

For further information about these models, Van Houwelingen & Putter (2011) can be checked.

2.2.7 Multi-state models

A multi-state model is used to model a process where subjects transition from one state to the next. It consists of different states (indicated by boxes) and transitions (indicated by arrows). Patients experience a transition when they pass from one state to the other. For instance, a standard survival curve can be thought of as a simple multi-state model with two states (alive and dead) and one transition between those two states. In these kind of models it is important to compute and plot estimates of p(t), which is a vector containing the probability of being in each of the states at time t. These can generally be computed by using the Aalen-Johansen estimate.

Mathematically the estimate is simple. For each unique time where an event occurs, form the transition matrix $T(t)$ with elements or rates of $h_{ij}(t)$, which is the fraction of subjects who transition from state i to j at time t, among those in state i just prior to time t. Then:

$$p(t) = p(0)\prod_{s \leq t} T(s)$$

where $p(0)$ is the initial distribution of subjects.

Each of the possible transitions from one state to another has an associated transition hazard which is the instantaneous risk of a transition from one state (state i) to another (state j) at time t. If T denotes the time of reaching state j from state i, we denote the hazard rate (transition intensity) of the $i \to j$ transition by:

$$h_{ij}(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T \leq t + \Delta t | T \geq t)}{\Delta t}$$

In this kind of models there are two main approaches to define t: the 'clock forward' and the 'clock reset' approaches. In the 'clock forward' approach time t refers to the time since the patient entered the initial state. In the 'clock reset' one time t in $h_{ij}(t)$ refers to the time since entry in state i; in this case the clock is reset to 0 each time the patient enters a new state.

A property that is often assumed in practice is that the multi-state model is a Markov model. Loosely speaking, the Markov property states that the future depends on the history only through the present. For a multi-state model this means that, given the present 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.

In order to estimate the effect of prognostic factors on the transition rates in multi-state models, transition-specific Cox models can be used. This means that Cox's proportional hazards model is fitted for each of the transition hazards separately. The hazard for transition $i \to j$ for a subject with covariate vector Z is then given by

$$h_{ij}(t|\boldsymbol{Z}) = h_{ij,0}(t) \exp(\boldsymbol{\beta}'_{ij} \boldsymbol{Z})$$

where $h_{ij,0}$ is the baseline hazard of transition $i \to j$ and $\boldsymbol{\beta}_{ij}$ is the vector of regression coefficients that describe the effect of $\boldsymbol{Z}$ on transition $i \to j$. In practice, this implies just subsetting the rows for the transitions $i \to j$ (having the data in long format) and fitting a Cox regression model for the selected data; for further information on how to do so one can check Putter, Fiocco, & Geskus (2007).

2.2.8 Statistical software for survival analysis

For the descriptive and survival analyses, the R statistical programming language has been used, in its 4.1.2 version.

CIFs can be estimated in R using the `cuminc` function in the `cmprsk` package (Gray, 2020).

Cause-specific hazard models can be fitted by estimating the conventional Cox proportional hazards model by simply treating those subjects who experience a competing event as being censored at the time of the occurrence of the competing event. In R, one can use the `coxph` function in the `survival` package (Therneau & Grambsch, 2000).

Subdistribution hazard models can be fitted in R by using the `FGR` function in the `riskRegression` package (Gerds, Ohlendorff, & Ozenne, 2021). Alternatively, they can also be fitted by using the `coxph` function of the `survival` package by previously preparing the data with the `finegray` function of the same package.

About landmarking, the `coxph` function can also be used, by preparing the data with the `cutLM` function of the `dynpred` package (Putter, 2015).

Finally, transient hazards for the multi-state models can also be fitted with the `coxph` function.

All the R codes from the section can be found in the online repository github.com/albamrt/HRS-survival.

Chapter 3

Results

3.1 Descriptive analysis

Our database contains information about 269 subjects. Considering dying and receiving a transplant as the two possible outcome events, it can be seen that among our subjects, 94 died while 112 received a transplant (Figure 3.1). Our main objective is to find out which of the variables introduced previously can be associated with death. But before doing so, let us just take a look at the values of these variables. As it has already been introduced, first only basal values of the variables will be used, to later on include time-varying covariates. Let us then start by having a look at the basal values of these variables.

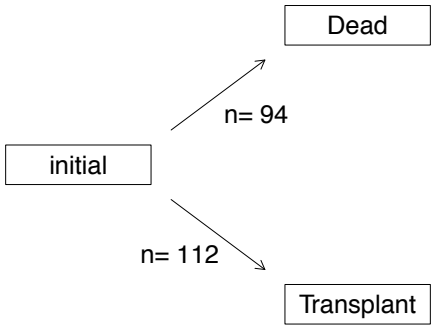

Figure 3.1: Number of subjects for the two possible outcomes: death and transplant.

3.1.1 Basal characteristics of the population

Some basal characteristics from the visit of diagnostic of the patients are presented in this section. In Table 3.1 the basal values for the continuous variables are summarized. There we can not only see how these variables are distributed but also which of them include missing values and in what percentage. In that aspect, we can see that some of these continuous variables show a pretty large amount of missing data. For instance, there is about 75% of missing data for the variables Pao_2 and $PaCO_2$. This is due to the fact that only patients on mechanical ventilation have this information. Total cholesterol has more than 65% missing data too due to not being reported by the doctors, since cholesterol is not on the main scores for liver functioning. Regarding cell populations, the missing data is of almost 40% for the percentage of immature neutrophils, more than 25% for monocytes, almost 20% for lymphocytes and monocytes (density and percentage) and 13% for the percentage of lymphocytes and monocytes. This is because although the levels of leucocytes are almost always reported, only in few cases more complete information about cell types is analysed. Finally, the CRP also contains

almost 20% of missing information. This is due to the fact that the test to obtain it is pretty expensive and generally only those patients that are in the intensive care unit have it tested. These variables just mentioned have been removed from posterior analyses due to a significant amount (larger than 5%) of missing data.

There are some other variables that also contain missing values but in a much lower percentange, such as albumin (4.83%), sodium (0.74%) and leucocytes (1.49%). Since all of them have less than 5% of missing cases, they have been kept in the analyses.

Regarding the values of the variables, we can observe how our subjects' age goes from 18 to 84 years old, with a mean age of around 60 years old. About the clinical variables, it can be seen that, as expected due to the inclusion criteria, the mean value of creatinine is 2.71, with all cases with values greater than 1.5, which would imply kidney dysfunction. On the contrary, the mean and median values for the INR are lower than 2 and the third quantile is around 2, implying that most of the sample do not show coagulation dysfunction, at least at diagnostic time and the mean and median values of MAP are around 79, also reflecting normal function of circulation for most subjects at diagnostic time. The median value for bilirubin is around 3 and the third quantile is of almost 8, indicating that more than half of the sample show normal functioning of the liver, but some do show liver failure and liver dysfunction.

Table 3.1: Descriptive analysis of continuous variables.

	% missing	Mean	Sd	Min	1st Q	Median	3rd Q	Max
Age (yr)	0.00	59.16	10.45	18.00	54.00	60.00	66.00	84.00
Albumin (g/dL)	4.83	2.97	0.75	1.20	2.45	2.90	3.50	4.91
Total Bilirubin (mg/dL)	0.00	8.09	10.75	0.36	1.49	3.21	7.79	48.50
Total Cholesterol (mg/dL)	65.43	76.88	38.47	7.34	50.19	71.00	96.00	185.33
Creatinine (mg/dL)	0.00	2.71	1.10	1.50	1.90	2.44	3.10	7.27
CRP (mg/L)	19.33	68.06	116.66	0.48	17.83	40.30	84.70	997.00
Hemoglobin (g/dL)	0.00	9.30	2.10	4.30	7.70	8.90	10.60	16.70
Heart rate (bpm)	1.12	81.47	16.66	49.00	70.00	79.00	92.00	155.00
Immature neutrophils (%)	43.87	1.54	4.00	0.00	0.00	0.00	0.90	25.00
INR	0.00	1.98	1.42	0.96	1.40	1.68	2.08	16.00
Lymphocytes ($\times 10^9$/L)	19.33	0.94	0.64	0.10	0.50	0.84	1.20	4.85
Lymphocytes (%)	13.01	11.82	7.44	1.00	6.03	10.05	16.00	47.20
MAP (mmHg)	0.00	79.53	13.19	43.67	70.67	79.33	87.67	118.33
Monocytes ($\times 10^9$/L)	25.65	0.83	0.54	0.02	0.42	0.74	1.08	3.45
Monocytes (%)	13.01	9.70	5.24	0.30	6.40	9.00	12.17	50.20
Sodium (mEq/L)	0.74	133.12	7.42	106.40	128.00	133.00	138.00	152.00
Neutrophils ($\times 10^9$/L)	17.84	7.31	5.83	0.00	3.40	6.00	9.85	36.00
Neutrophils (%)	19.33	74.86	15.33	0.00	66.35	76.68	83.92	184.44
PaCO2 (mmHg)	74.72	32.47	10.10	19.00	25.65	31.00	35.82	78.70
PaO2 (mmHg)	75.09	102.64	60.06	44.60	72.00	89.40	113.35	418.00
Leucocyte ($\times 10^9$/L)	1.49	9.33	6.20	0.90	5.02	7.68	12.40	39.20

The summary for the basal levels of the categorical variables can be seen in Table 3.2. In this case, none of the categorical variables present missing values at diagnostic time. We can see how most of the sample (68.77%) are men. Regarding the treatment, at diagnostic time 82.16% are treated with albumin, while 45.35% are treated with vasopressors. It can also be seen how the most frequent etiology for cirrhosis is alcohol, followed by NAFLD/NASH and the Hepatitis C virus one. Note that one subject can be associated to multiple etiologies, therefore the sum of the percentages of the etiology variables can exceed 100. Regarding ascites, they are present on the 84.01% of subjects, 10.04% are reported to present gastrointestinal bleeding and 59.48% show bacterial infection.

Table 3.2: Descriptive analysis of categorical variables.

	% yes	% missing
Female sex	31.23	0
Treatment with albumin	82.16	0
Treatment with vasopressors	45.35	0
Etiology of cirrhosis - Alcohol	61.71	0
Etiology of cirrhosis - Hepatitis B virus	3.72	0
Etiology of cirrhosis - Hepatitis C virus	11.90	0
Etiology of cirrhosis - NAFLD/NASH	19.70	0
Etiology of cirrhosis - Cryptogenic	8.92	0
Etiology of cirrhosis - Other	8.55	0
Ascites	84.01	0
Hepatic encephalopathy	50.56	0
Gastrointestinal bleeding	10.04	0
Bacterial infection	59.48	0

3.1.2 Variables along visits

In some of the analyses presented in this project the values along time of these variables are going to be used. Let us then see how they vary depending on time. Figure 3.2 shows the trajectories for the continuous variables by subject. Also, in the top-right corner of each plot there is the total number of missing data for that variable. It can be seen how the percentages of missing data for each variable along time is pretty similar to the ones obtained for their basal values.

A part from this, some observations can be made from the plots. By looking at right extreme of the x axis we can observe how those subjects that live longer tend to have low values of creatinine, CRP, INR, leucocytes or bilirrubin. For the mean arterial presion it looks like those subjects who live longer show values of about 80 mmHg.

Plots for the categorical variables can be found in Figure 3.3. Here, the absolute frequency of each category of the variables can be seen through time. This allows to see how the total absolute frequencies decrease through time (with death, censor or transplant of subjects) and how both categories (yes/no) are related. Also, the orange line shows the proportion of 'yes' (relative to the number of cases in each time point).

In general, we see that most subjects' etiology of cirrhosis is alcohol-related, followed in frequency by NAFLD/NASH. However, from those patients that are observed for the most time, very few have alcohol-related cirrhosis, while a very large number of them have NAFLD/NASH-related cirrhosis. About the other variables it can be seen that, among the subjects who are observed for the longer times, all have bacterial infection.

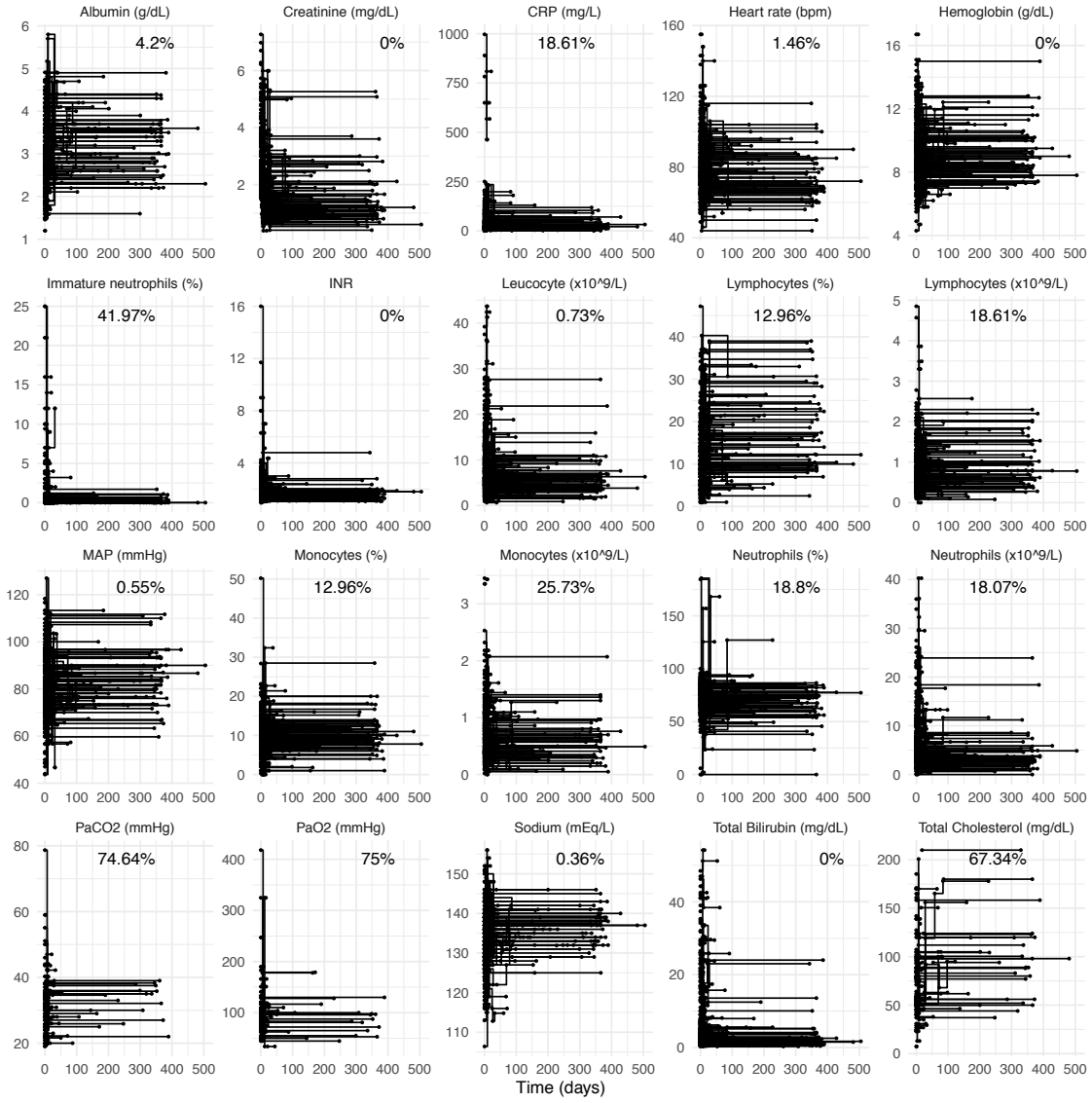

Figure 3.2: Values of continuous variables in every visit for each subject. In the top right the total percentage of missing data is indicated.

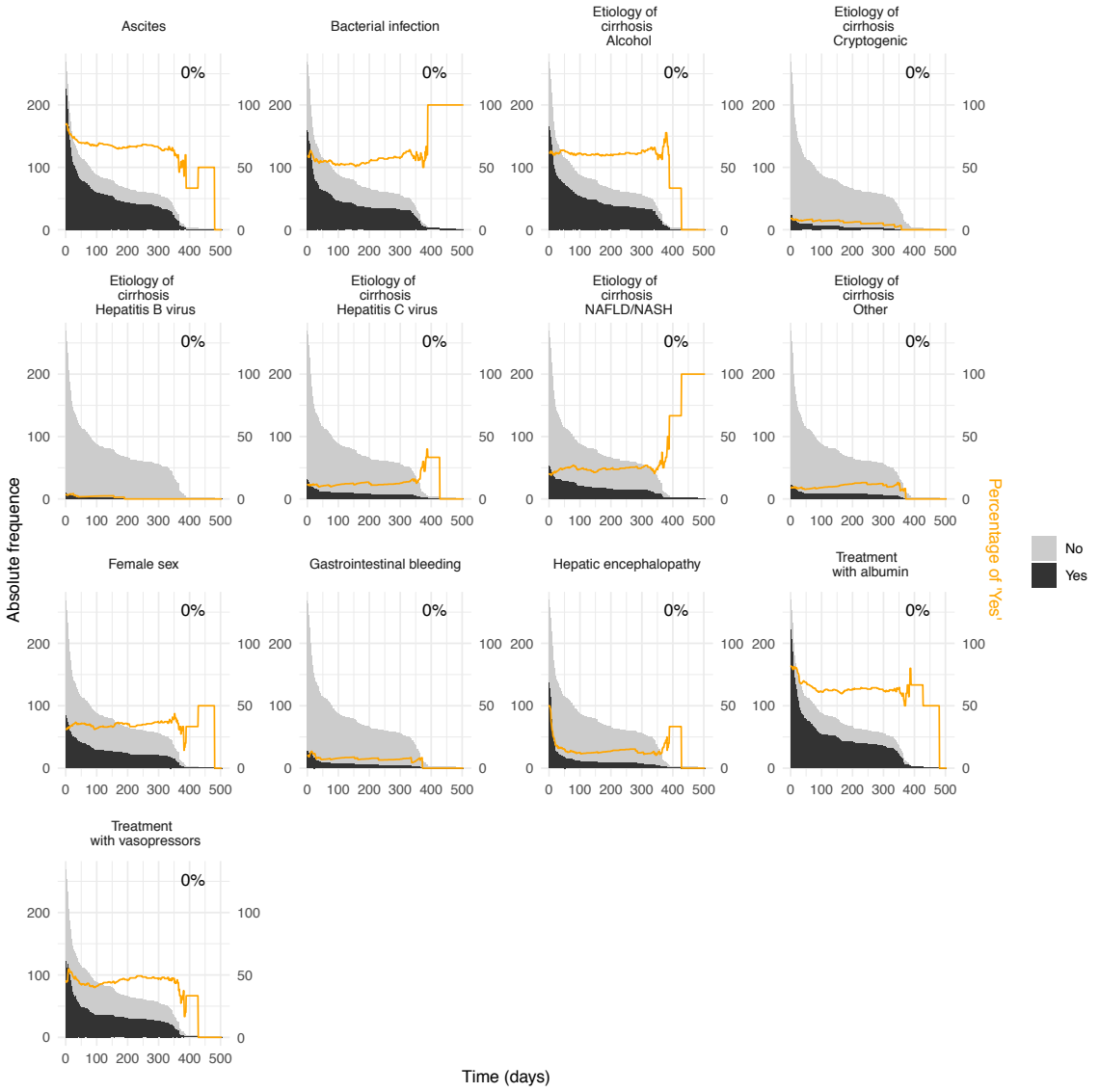

Figure 3.3: Absolute frequences of categorical variables through time. In the top right the total percentage of missing data is indicated.

3.2 Survival analysis

As it has just been introduced in the previous section, the main objective of this project is to find out which of the variables that have just been introduced can be associated with death.

In this section the survival techniques described in the 'Methods' section are going to be applied. To start with, in Table 3.3 we can see a basic description about how many subjects are reported to die, how many are reported to have a liver transplant and how many are censored. It can be observed that the most frequent events are transplants, for the 41.64% of our sample. The second most frequent event is death, for the 34.94% of the sample. Finally, up to the 23.42% of our data set has censorship, which is why we need to apply survival analysis techniques.

Table 3.3: Absolute and relative frequence of the two events (death and liver transplant) and censored observations.

Event	n	%
Censored	63	23.42
Dead	94	34.94
Transplant	112	41.64

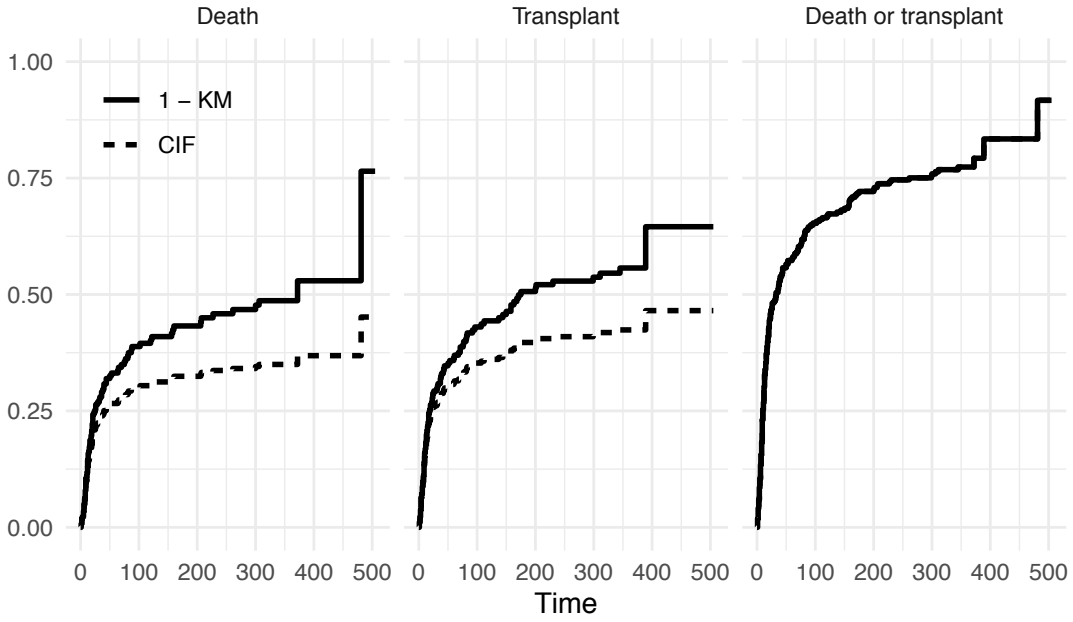

Figure 3.4: Comparison of the Kaplan-Meier and cumulative incidence function estimates.

As we have already mentioned, in presence of competing risks (as it is the case) Kaplan-Meier estimates would lead to overestimating the rate of the event. Figure 3.4 shows both the Kaplan-Meier and the cumulative incidence estimate for death and transplant and it can be seen how, as expected, the Kaplan-Meier estimation is much higher than the cumulative incidence one. The only case where the Kaplan-Meier and the CIF coincide is in the case when any of the two events are considered as endpoints (a situation without competing risks).

Therefore, in order to describe the survival rates of these patients after 28 and 90 days after diagnostic we can look at the cumulative incidence function at those time points. Just by looking at Figure 3.4 it can be seen that most events do happen in the beginning. More concretely, for the event of death the value of the CIF at 28 days is of 0.22 while at 90 days is of 0.3. In the case of transplants, the CIF at 28 days is of 0.26 while at 90 days is of 0.34. Finally, in the case of any of the two events, its value is of 0.48 at 28 days and of 0.65 at 90 days.

In order to model this data, two main approaches will be seen: including just the basal characteristics of the population and including time-varying covariates in order to perform dynamic predictions.

In the first case, a competing risks model will be fitted, just with values at the time of diagnostic of hepatorenal syndrome.

In the second case, three models will be seen. First, time-varying variables will be introduced through time-varying competing risks models. Second, the same will be done by using landmarking. Finally, a multi-state

model will be fitted, where not only dead and transplant will be contemplated as states but also two states regarding whether a subject has responded to the treatment or not will be introduced.

3.2.1 Competing risks with basal variables

In this section the data will be fitted by using competing risks. Formally, this would be the same as using a multi-state model with three states: alive, transplant and dead; considering transplant and dead as absorbing states. Here, the simple case of basal covariates will be seen.

Two different methods have been introduced in order to estimate competing risks: the subdistribution or cumulative incidence function (just seen in the plot) and the cause-specific model. Both will be fitted here, in order to gain a greater insight of the data; however, it should be taken into account that since our main objective is prediction, the main model we should be looking at is the subdistribution one, or what is the same, Fine and Gray's model.

The results from Fine and Gray's model can be seen in Table 3.4. Citing Austin & Fine (2017):

> "The exponentiated regression coefficient from a Fine-Gray subdistribution hazard model denotes the magnitude of the relative change in the subdistribution hazard function associated with a 1-unit change in the given covariate. Therefore, one is reporting the relative change in the instantaneous rate of the occurrence of the event in those subjects who are event-free or who have experienced a competing event."

Focusing on death as endpoint, it can be observed that for some variables the estimated 95% confidence intervals of the hazard ratios include 1, indicating that those variables do not show an effect on the subdistribution function. However, some do have significant effects. For instance, the subdistribution hazard ratio for the values of albumin and its associated confidence intervals are 0.73 (0.54, 0.99). This indicates that an increase of 1g/dL of albumin would suppose a decrease in the subdistribution hazard ratio of the 37% . However, the treatment with albumin seems to have the contrary effect, having an estimate increase in the subdistribution hazard of almost 3 times. This could be related to the concrete characteristics of the patients who receive this treatment and not to the treatment per se. Finally, the NAFLD/NASH and cryptogenic etiologies of cirrhosis also seem to make the subdistribution hazard increase in 1 and 3 units respectively. This can be interpreted as evidence that these variables have an influence on the rate of death in subjects who are either event-free (still alive) or who have experienced a competing event (those who have received a transplant). Also, this can be translated in this variables having an effect on the cumulative incidence function of death (although the magnitude of this effect can not be directly inferred from these results).

In Table 3.5 the results from the cause-specific model are reported. In this case, and again citing Austin & Fine (2017):

> "The exponentiated regression coefficient from a cause-specific hazard model denotes the magnitude of the relative change in the cause-specific hazard function associated with a 1-unit change in the covariate. Therefore, the cause-specific hazard ratio denotes the relative change in the instantaneous rate of the occurrence of the primary event in subjects who are currently event-free".

In this case, the variables that show a significant effect on the cause-specific hazard ratio of death are age, treatment with albumin and the albumin and creatinine levels. Again, the treatment with albumin and its level seem to have contrary effects, having the first an increasing effect on the cause-specific hazard function and the second one a decreasing effect. Regarding the age, it also has a greater-than-one cause-specific hazard ratio estimation, with an estimate of 1.035, indicating that an increase of 10 units in this variable would suppose an increase of the 41.2% in the cause-specific hazard. Finally, higher creatinine levels also make the cause-specific hazard ratio increase. This means that these variables are associated with a change in the rate of death in those who were currently alive.

So, it looks like the effects found in both models are not so different. However, there are some variables that seem to be relevant (significant) in one of the models and not in the other one. For instance, the NAFLD/NASH and cryptogenic etiologies of cirrhosis seem to have an effect on the cumulative incidence function of death but

Table 3.4: Fine and Gray model for time-fixed (basal) variables for different endpoints.

	Death			Transplant			Death or transplant		
	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%
Age (yr)	1.00	0.98	1.03	1.04	1.01	1.06	1.05	1.03	1.06
Female sex	1.05	0.64	1.71	0.82	0.50	1.36	0.76	0.54	1.06
Treatment with albumin	3.86	1.55	9.60	0.64	0.39	1.03	1.55	1.04	2.32
Treatment with vasopressors	0.93	0.56	1.53	1.21	0.77	1.92	1.03	0.73	1.45
Etiology of cirrhosis - Alcohol	1.41	0.65	3.06	0.89	0.36	2.19	1.02	0.53	1.95
Etiology of cirrhosis - Hepatitis B virus	1.65	0.59	4.66	0.66	0.16	2.72	0.87	0.34	2.26
Etiology of cirrhosis - Hepatitis C virus	1.79	0.75	4.27	0.82	0.37	1.82	1.34	0.77	2.32
Etiology of cirrhosis - NAFLD/NASH	2.06	1.03	4.11	0.49	0.19	1.30	0.86	0.43	1.73
Etiology of cirrhosis - Cryptogenic	3.14	1.14	8.62	0.57	0.16	1.98	1.38	0.61	3.10
Etiology of cirrhosis - Other	1.57	0.53	4.66	0.94	0.29	3.03	1.18	0.55	2.53
MAP (mmHg)	1.00	0.98	1.02	0.99	0.97	1.01	0.98	0.97	1.00
Heart rate (bpm)	1.00	0.98	1.01	1.00	0.99	1.02	1.00	0.99	1.01
Hemoglobin (g/dL)	1.06	0.91	1.22	0.95	0.86	1.05	1.03	0.96	1.11
Leucocyte ($\times 10^9$/L)	0.98	0.93	1.03	1.02	0.98	1.06	1.01	0.98	1.04
INR	1.03	0.85	1.25	1.11	0.99	1.23	1.16	1.06	1.27
Albumin (g/dL)	0.73	0.54	0.99	1.09	0.80	1.50	0.81	0.65	1.02
Total Bilirubin (mg/dL)	1.03	1.00	1.05	1.02	1.00	1.04	1.05	1.03	1.06
Creatinine (mg/dL)	1.05	0.87	1.27	1.01	0.84	1.23	1.05	0.92	1.20
Sodium (mEq/L)	1.01	0.98	1.05	0.99	0.96	1.02	1.00	0.98	1.02
Ascites	1.51	0.75	3.03	1.28	0.63	2.58	1.43	0.88	2.32
Hepatic encephalopathy	1.20	0.73	1.96	0.99	0.65	1.52	1.32	0.94	1.85
Gastrointestinal bleeding	1.53	0.73	3.21	0.51	0.25	1.06	0.65	0.39	1.10
Bacterial infection	0.88	0.53	1.44	1.13	0.74	1.74	1.11	0.80	1.53

Table 3.5: Cause-specific model for time-fixed (basal) variables for different endpoints.

	Death			Transplant			Death or transplant		
	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%
Age (yr)	1.04	1.01	1.06	1.06	1.03	1.09	1.05	1.03	1.07
Female sex	0.94	0.56	1.55	0.71	0.44	1.14	0.79	0.56	1.12
Treatment with albumin	4.53	1.90	10.84	1.01	0.61	1.67	1.66	1.09	2.52
Treatment with vasopressors	0.87	0.52	1.44	1.21	0.77	1.92	1.04	0.74	1.46
Etiology of cirrhosis - Alcohol	1.15	0.52	2.52	0.88	0.37	2.08	1.05	0.59	1.86
Etiology of cirrhosis - Hepatitis B virus	1.10	0.29	4.12	0.52	0.13	2.09	0.82	0.32	2.08
Etiology of cirrhosis - Hepatitis C virus	1.90	0.84	4.30	1.10	0.51	2.37	1.45	0.84	2.50
Etiology of cirrhosis - NAFLD/NASH	1.36	0.66	2.82	0.46	0.19	1.10	0.81	0.47	1.41
Etiology of cirrhosis - Cryptogenic	2.74	0.98	7.67	0.73	0.22	2.46	1.50	0.69	3.25
Etiology of cirrhosis - Other	1.19	0.38	3.73	1.01	0.34	2.99	1.16	0.54	2.48
MAP (mmHg)	0.99	0.97	1.01	0.98	0.96	1.00	0.98	0.97	0.99
Heart rate (bpm)	1.00	0.99	1.02	1.00	0.99	1.02	1.00	0.99	1.01
Hemoglobin (g/dL)	1.08	0.96	1.22	0.98	0.88	1.09	1.03	0.95	1.11
Leucocyte ($\times 10^9$/L)	0.99	0.95	1.04	1.03	0.99	1.07	1.01	0.98	1.05
INR	1.15	0.99	1.34	1.17	1.04	1.31	1.16	1.06	1.27
Albumin (g/dL)	0.69	0.49	0.98	0.92	0.68	1.25	0.81	0.65	1.02
Total Bilirubin (mg/dL)	1.05	1.03	1.08	1.05	1.02	1.07	1.05	1.03	1.07
Creatinine (mg/dL)	1.13	0.93	1.39	1.03	0.86	1.24	1.06	0.93	1.21
Sodium (mEq/L)	1.02	0.98	1.05	0.99	0.96	1.02	1.00	0.98	1.03
Ascites	1.71	0.83	3.50	1.50	0.78	2.88	1.58	0.97	2.55
Hepatic encephalopathy	1.54	0.93	2.55	1.24	0.80	1.92	1.36	0.98	1.89
Gastrointestinal bleeding	1.43	0.68	3.03	0.49	0.22	1.06	0.80	0.47	1.35
Bacterial infection	1.09	0.67	1.78	1.16	0.74	1.83	1.14	0.82	1.58

not not to be so important for the rate of death in those who were currently alive. The contrary happens for the age and the creatinine levels.

As mentioned previously (2.2.4), the variables having an effect on the cause-specific hazard model are factors that have an effect on the occurrence of the outcome in subjects who are currently event-free, being more appropriate for addressing etiological questions, while the Fine-Gray model significant effects are more related to the individual's probability of experiencing the outcome within a given duration of time, being more appropriate for addressing questions around incidence and prognosis.

3.2.2 Competing risks with time-varying covariates

However, since the previous models are built with basal variables, the treatments that were not administered from the first visit and the response to treatment could not be included so its effect could not be estimated. This can be solved by using time-varying covariates. However, as already mentioned, competing risk models including time-varying covariates have to be interpreted with caution since there are many pitfalls in such analysis. Most of those pitfalls can be circumvented by the landmark analysis to be seen later. Nevertheless, time-dependent Cox-models can give relevant insight in the data.

We have already seen that, specially the subdistribution model has to be interpreted with caution, since it no longers reflects the cumulative incidence function.

In Table 3.6 the cause-specific model is reported. In this case the treatment with albumin does not show a significant effect (although its HR estimate > 1) but the treatment with vasopressors does (with a cause-specific hazard ratio of 1.69). Again, this may be due to the fact that subjects being treated with vasopressors are worse than those without this treatment. Also, some variables related to cirrhosis show a significative effect in increasing the cause-specific hazard ratio. These are the alcohol related cirrhosis ($HR_{cs} = 2.13$), the hepatitis C virus one ($HR_{cs} = 2.37$), the NAFLD/NASH one ($HR_{cs} = 2.14$) and the cryptogenic etiology of cirrhosis ($HR_{cs} = 5.96$). Some laboratory-related variables also seem to be important in this case. A unit increase in INR seems to increase the cause-specific hazard by 24%, while a 1mg/dL increase in bilirrubin seems to increase it by a 5%. Finally, the presence of ascites is estimated to double the cause-specific hazard of death.

The fit of Fine and Gray's model with the exact same (time-varying) variables can be seen in Table 3.7. Here, the results have to be interpreted with caution. In this case it will only be used in order to compare it to the cause-specific model. Here, the treatment with albumin seems to significantly increase the subdistribution hazard, as well as the NAFLD/NASH cirrhosis etiology and the cryptogenic one. Also, similarly to the just seen cause-specific model, the INR also seems to make the subdistribution hazard increase.

In both cases the response to treatment was estimated not to be significant for the models. However, as it can be seen in Figure 3.5 its estimated effect in the cumulative cause-specific hazard is greater (reducing by 76% the cause-specific hazard) than in the subdistribution one. However, as already mentioned (2.2.5) in the case of intern time-varying covariates these results have to be interpreted with caution. That is why in the next section landmark models are going to be used.

Table 3.6: Time-dependent Cox cause-specific model regression with time-varying covariates for different endpoints.

	Death			Transplant			Death or transplant		
	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%
Age (yr)	1.02	1.00	1.05	1.05	1.02	1.07	1.04	1.02	1.05
Female sex	1.03	0.62	1.71	0.81	0.51	1.31	0.91	0.65	1.28
Response to treatment (creat < 1.5 mg/dL)	0.57	0.30	1.09	0.56	0.30	1.04	0.58	0.37	0.90
Treatment with albumin	2.00	0.95	4.22	0.53	0.32	0.88	0.88	0.59	1.32
Treatment with vasopressors	1.69	1.03	2.79	1.72	1.07	2.78	1.67	1.19	2.36
Etiology of cirrhosis - Alcohol	2.13	1.01	4.51	0.92	0.39	2.21	1.47	0.84	2.57
Etiology of cirrhosis - Hepatitis B virus	0.96	0.30	3.05	0.42	0.12	1.50	0.61	0.26	1.43
Etiology of cirrhosis - Hepatitis C virus	2.37	1.12	5.04	1.00	0.48	2.09	1.53	0.92	2.55
Etiology of cirrhosis - NAFLD/NASH	2.14	1.04	4.40	0.47	0.19	1.17	1.05	0.60	1.82
Etiology of cirrhosis - Cryptogenic	5.96	2.10	16.89	0.90	0.27	2.96	2.35	1.09	5.05
Etiology of cirrhosis - Other	1.89	0.61	5.83	1.04	0.35	3.06	1.48	0.70	3.14
MAP (mmHg)	1.00	0.98	1.02	0.97	0.96	0.99	0.98	0.97	1.00
Heart rate (bpm)	1.01	1.00	1.03	1.02	1.01	1.03	1.02	1.01	1.03
Hemoglobin (g/dL)	1.02	0.89	1.17	1.01	0.89	1.14	1.02	0.93	1.12
Leucocyte ($\times 10^9$/L)	0.99	0.95	1.03	1.04	1.00	1.07	1.02	0.99	1.04
INR	1.24	1.09	1.42	1.02	0.87	1.20	1.13	1.02	1.24
Albumin (g/dL)	0.76	0.54	1.07	0.88	0.64	1.22	0.82	0.65	1.04
Total Bilirubin (mg/dL)	1.05	1.03	1.08	1.05	1.03	1.07	1.05	1.03	1.07
Creatinine (mg/dL)	1.18	0.94	1.48	0.98	0.79	1.23	1.06	0.91	1.25
Sodium (mEq/L)	1.01	0.97	1.05	0.98	0.94	1.01	0.99	0.97	1.02
Ascites	2.09	1.01	4.32	1.43	0.80	2.52	1.77	1.13	2.76
Hepatic encephalopathy	1.41	0.83	2.38	1.41	0.85	2.34	1.42	0.99	2.03
Gastrointestinal bleeding	1.07	0.53	2.13	1.06	0.55	2.06	1.05	0.65	1.68
Bacterial infection	0.74	0.46	1.21	1.24	0.78	1.98	0.97	0.69	1.35

Table 3.7: Time-dependent Fine and Gray's regression with time-varying covariates for different endpoints.

	Death			Transplant			Death or transplant		
	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%
Age (yr)	1.01	0.98	1.03	1.04	1.01	1.06	1.04	1.02	1.05
Female sex	1.11	0.68	1.83	0.89	0.56	1.40	0.91	0.65	1.28
Response to treatment (creat < 1.5 mg/dL)	1.06	0.56	2.01	0.96	0.52	1.76	0.58	0.37	0.90
Treatment with albumin	2.13	1.04	4.37	0.44	0.28	0.70	0.88	0.59	1.32
Treatment with vasopressors	1.49	0.89	2.47	1.57	0.99	2.46	1.67	1.19	2.36
Etiology of cirrhosis - Alcohol	2.06	1.00	4.27	0.79	0.33	1.89	1.47	0.84	2.57
Etiology of cirrhosis - Hepatitis B virus	1.78	0.54	5.86	0.54	0.16	1.82	0.61	0.26	1.43
Etiology of cirrhosis - Hepatitis C virus	2.16	0.94	4.99	0.84	0.39	1.81	1.53	0.92	2.55
Etiology of cirrhosis - NAFLD/NASH	2.62	1.35	5.09	0.42	0.16	1.15	1.05	0.60	1.82
Etiology of cirrhosis - Cryptogenic	4.79	1.87	12.27	0.50	0.16	1.60	2.35	1.09	5.05
Etiology of cirrhosis - Other	2.05	0.72	5.83	0.79	0.26	2.40	1.48	0.70	3.14
MAP (mmHg)	1.01	0.98	1.03	0.98	0.96	0.99	0.98	0.97	1.00
Heart rate (bpm)	1.00	0.99	1.02	1.02	1.00	1.03	1.02	1.01	1.03
Hemoglobin (g/dL)	0.97	0.82	1.15	0.99	0.90	1.10	1.02	0.93	1.12
Leucocyte ($\times 10^9$/L)	0.98	0.93	1.02	1.03	0.99	1.06	1.02	0.99	1.04
INR	1.23	1.05	1.43	0.85	0.70	1.03	1.13	1.02	1.24
Albumin (g/dL)	0.90	0.67	1.21	1.01	0.72	1.41	0.82	0.65	1.04
Total Bilirubin (mg/dL)	1.02	0.99	1.05	1.03	1.01	1.04	1.05	1.03	1.07
Creatinine (mg/dL)	1.18	0.94	1.48	0.92	0.74	1.13	1.06	0.91	1.25
Sodium (mEq/L)	1.02	0.99	1.06	0.97	0.94	1.00	0.99	0.97	1.02
Ascites	1.58	0.82	3.04	1.07	0.60	1.91	1.77	1.13	2.76
Hepatic encephalopathy	1.14	0.69	1.88	1.18	0.74	1.88	1.42	0.99	2.03
Gastrointestinal bleeding	0.87	0.42	1.78	1.10	0.57	2.12	1.05	0.65	1.68
Bacterial infection	0.65	0.40	1.06	1.37	0.89	2.11	0.97	0.69	1.35

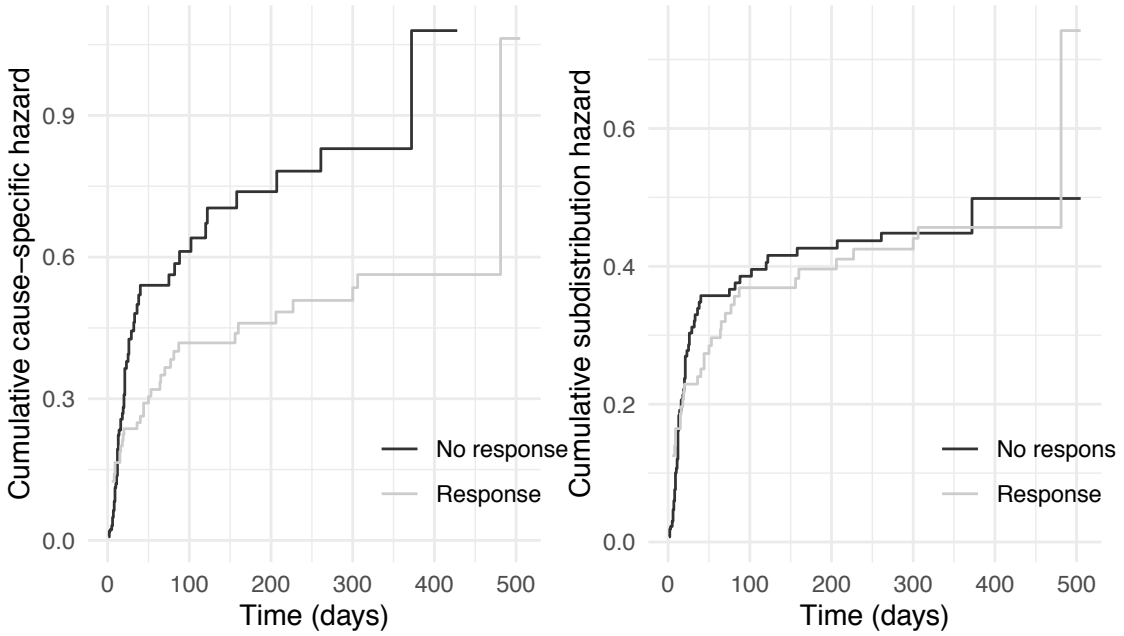

Figure 3.5: Predicted cumulative baseline cause-specific (left) and subdistribution (right) hazards for death stratified by response to treatment (defined as a time-varying covariate).

3.2.3 Competing risks with landmarks

As mentioned, landmarking may be a better alternative to fit competing risks models with time-varying covariates. The steps in Van Houwelingen & Putter (2011) have been followed in order to fit both the cause-specific and the subdistribution model with landmarks.

As we can see in Figure 3.4, the minimum time at which an event happens is day 1 and most events happen during the first 100 days. Also, we are especifically interested in the survival at 28 and 90 days. For those reasons, we are defining the landmark points as an equally spaced grid of 20 points ranging from $t_{LM} = 1$ to $t_{LM} = 100$, with a distance of 5 and a window of 100.

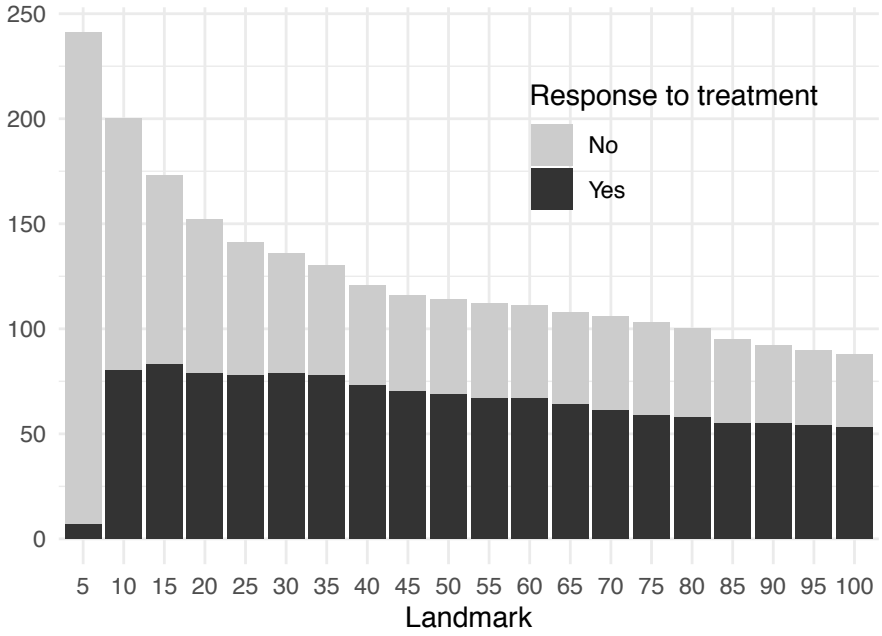

Figure 3.6: Stacked barplot of the distribution of responders and non-responders through the landmarks set.

Before looking at the fit of the model, it can be seen how responders and non-responders are distributed among the chosen landmarks (Figure 3.6).

The two types of super models introduced in the methods have been fitted. First, a super model has been fitted just by using a landmark super data frame and using the landmark indicator as a stratifying variable. After that, a model has been fitted without using landmarks as stratifying variables but using them as covariates in the model (directly and in a quadratic form). The results of the analyses are shown in Table 3.8.

In both cases the estimated hazard ratio for the response to treatment shows values under 1, which would mean that responding to treatment reduces these ratios. However, in both cases this effect does not seem to be significative. It is remarkable that the estimates in both models look quite similar. In both models the treatment with albumin, the INR and the total bilirubin seem to have a significant effect on the hazard, by increasing it. In the first model the etiology of cirrhosis related to hepatitis B virus was also estimated to have a increasing effect on the hazard while in the second model we see how the landmark component is also significant.

These results actually seem to go quite in line with what we had seen until now. However, it looks like the time-component variable is also adding to the model.

3.2.4 Multi-state models

Finally, in this section data will be modeled as if it was part of a multi-state process with 4 states: alive and responding to treatment, alive and non-responding to treatment, transplanted and death (last case of Figure 2.2). The first two states representing the subjects that are alive can transient to any other state, while the last two (transplant and death) are absorbing states. In this case, the 'transplant' state has to be absorbing because there is no data after this event, however, ideally, it would also be modeled as a transient state that could still lead to be alive or death. The results from this section include then another endpoint: the transition from non-responding to responding. This allows to determine which factors can predict a response to the treatment.

Table 3.8: Landmark super model Cox regressions.

	Death			Transplant			Death or transplant		
	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%
Super model 1									
Age (yr)	0.99	0.95	1.04	1.05	1.01	1.09	1.03	1.00	1.06
Female sex	0.50	0.20	1.28	1.30	0.64	2.62	0.89	0.50	1.57
Response to treatment (creat < 1.5 mg/dL)	0.46	0.17	1.22	0.55	0.18	1.64	0.53	0.26	1.04
Treatment with albumin	6.97	1.03	46.98	0.30	0.15	0.60	0.74	0.38	1.45
Treatment with vasopressors	0.65	0.24	1.73	2.23	1.02	4.86	1.25	0.66	2.35
Etiology of cirrhosis - Alcohol	2.66	0.89	7.96	0.62	0.05	8.22	2.06	0.72	5.92
Etiology of cirrhosis - Hepatitis B virus	5.21	1.01	26.92	0.18	0.02	1.26	1.02	0.25	4.20
Etiology of cirrhosis - Hepatitis C virus	3.10	0.79	12.19	0.53	0.12	2.35	1.31	0.43	3.99
Etiology of cirrhosis - NAFLD/NASH	3.08	0.93	10.20	0.15	0.01	2.51	0.91	0.34	2.39
Etiology of cirrhosis - Cryptogenic	4.27	0.76	24.12	0.47	0.02	9.44	1.93	0.49	7.66
Etiology of cirrhosis - Other	1.33	0.29	6.01	0.64	0.03	12.42	1.60	0.40	6.40
MAP (mmHg)	0.98	0.95	1.02	0.95	0.92	0.97	0.96	0.94	0.98
Heart rate (bpm)	1.01	0.99	1.04	1.04	1.01	1.06	1.03	1.01	1.05
Hemoglobin (g/dL)	0.85	0.66	1.10	0.98	0.80	1.21	0.95	0.80	1.12
Leucocyte ($\times 10^9$/L)	0.95	0.88	1.03	0.99	0.92	1.07	0.98	0.92	1.03
INR	1.41	1.15	1.72	1.18	0.89	1.56	1.21	1.00	1.47
Albumin (g/dL)	1.25	0.70	2.25	1.29	0.71	2.35	1.23	0.79	1.92
Total Bilirubin (mg/dL)	1.06	1.02	1.09	1.07	1.04	1.11	1.06	1.04	1.09
Creatinine (mg/dL)	0.76	0.48	1.21	1.10	0.75	1.59	1.02	0.76	1.37
Sodium (mEq/L)	1.00	0.93	1.07	0.94	0.90	0.99	0.98	0.94	1.02
Ascites	1.29	0.38	4.32	3.34	1.21	9.23	2.39	1.07	5.35
Hepatic encephalopathy	2.16	0.97	4.84	0.95	0.33	2.73	1.33	0.66	2.69
Gastrointestinal bleeding	0.71	0.21	2.41	0.46	0.16	1.27	0.53	0.23	1.23
Bacterial infection	1.44	0.62	3.33	1.02	0.46	2.25	1.15	0.67	1.97
Super model 2									
Age (yr)	1.00	0.96	1.04	1.05	1.01	1.10	1.03	1.00	1.06
Female sex	0.48	0.19	1.21	1.24	0.60	2.52	0.84	0.47	1.48
Response to treatment (creat < 1.5 mg/dL)	0.51	0.19	1.35	0.67	0.24	1.90	0.59	0.29	1.17
Treatment with albumin	6.91	1.05	45.40	0.33	0.16	0.66	0.80	0.41	1.55
Treatment with vasopressors	0.68	0.26	1.79	2.27	1.03	4.97	1.28	0.69	2.40
Etiology of cirrhosis - Alcohol	2.41	0.81	7.18	0.59	0.05	6.53	1.79	0.65	4.95
Etiology of cirrhosis - Hepatitis B virus	4.65	0.90	23.99	0.15	0.02	1.11	0.87	0.20	3.79
Etiology of cirrhosis - Hepatitis C virus	3.09	0.80	11.88	0.49	0.12	2.07	1.26	0.42	3.75
Etiology of cirrhosis - NAFLD/NASH	2.82	0.85	9.42	0.15	0.01	2.02	0.82	0.32	2.13
Etiology of cirrhosis - Cryptogenic	4.03	0.72	22.66	0.49	0.03	7.71	1.76	0.46	6.71
Etiology of cirrhosis - Other	1.19	0.27	5.22	0.60	0.04	9.72	1.37	0.36	5.25
MAP (mmHg)	0.98	0.95	1.02	0.95	0.92	0.97	0.96	0.94	0.98
Heart rate (bpm)	1.01	0.99	1.04	1.03	1.01	1.06	1.03	1.01	1.04
Hemoglobin (g/dL)	0.85	0.66	1.10	0.98	0.81	1.18	0.95	0.81	1.11
Leucocyte ($\times 10^9$/L)	0.95	0.88	1.03	0.99	0.93	1.07	0.98	0.92	1.03
INR	1.38	1.14	1.69	1.16	0.87	1.54	1.20	1.00	1.44
Albumin (g/dL)	1.25	0.70	2.23	1.36	0.76	2.42	1.25	0.81	1.93
Total Bilirubin (mg/dL)	1.06	1.02	1.09	1.07	1.04	1.11	1.06	1.04	1.09
Creatinine (mg/dL)	0.74	0.49	1.13	1.11	0.77	1.59	1.00	0.74	1.35
Sodium (mEq/L)	1.01	0.95	1.08	0.95	0.91	1.00	0.99	0.95	1.03
Ascites	1.30	0.39	4.34	3.30	1.16	9.36	2.35	1.04	5.29
Hepatic encephalopathy	2.12	0.95	4.75	0.93	0.34	2.57	1.28	0.64	2.57
Gastrointestinal bleeding	0.72	0.21	2.44	0.42	0.15	1.14	0.52	0.23	1.19
Bacterial infection	1.49	0.64	3.46	1.03	0.48	2.21	1.19	0.70	2.02
s	1.06	1.04	1.08	1.05	1.03	1.07	1.05	1.04	1.07
s^2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure 3.7 shows the Aalen-Johansen estimations of the transition probabilities from responding and non-responding states to death and transplant. We can observe how the transition probability from responding to the treatment to death is lower than the one from the non-responding state. On the contrary, in the case of transplant, those individuals coming from the responding state have a higher transition probability of entering the transplant state.

In Table 3.9 the transitions from non-responding and responding states to death are modeled. In Table 3.10 there can be seen the models for the transitions from these states to the transplant one. And finally, in this case it is also possible to model the transition from the non-responding to the responding state, which can be found in Table 3.11.

When considering the transitions to death it looks like the importance of the variables depends on whether one comes from the responding or from the non-responding state. For instance, in the non-responding case it looks like the treatment with vasopressors, the alcoholic, NAFLD/NASH and cryptogenic etiologies of cirrhosis, the levels of bilirrubin and the presence of ascites have an increasing effect on the transition probability. However, in the case of respondents, the variables that are estimated to have a significant effect on this increase are the hepatitis C virus and cryptogenic related cirrhosis, the INR, the creatinine levels and the presence of hepatic encephalophaty.

Although the transitions from these states to the transplant one is also interesting, next, let us focus in the transition from the non-responding to the responding state, which can give us some more insight on whether there are some characteristics of the patients that make them more responsive to the treatment. In this case the results are a bit disappointing in the sense that two variables appear to be significant for the model: the alcoholic etiology of cirrhosis, making the transition probability increase; and the creatinine levels, making the transition probability decrease. In the case of this second variable this was expected, since the higher the response group is defined by having creatinine values over 1.5mg/dL, so having higher values (although under 1.5), could mean that there is already a tendence and makes it more possible to exceed that value.

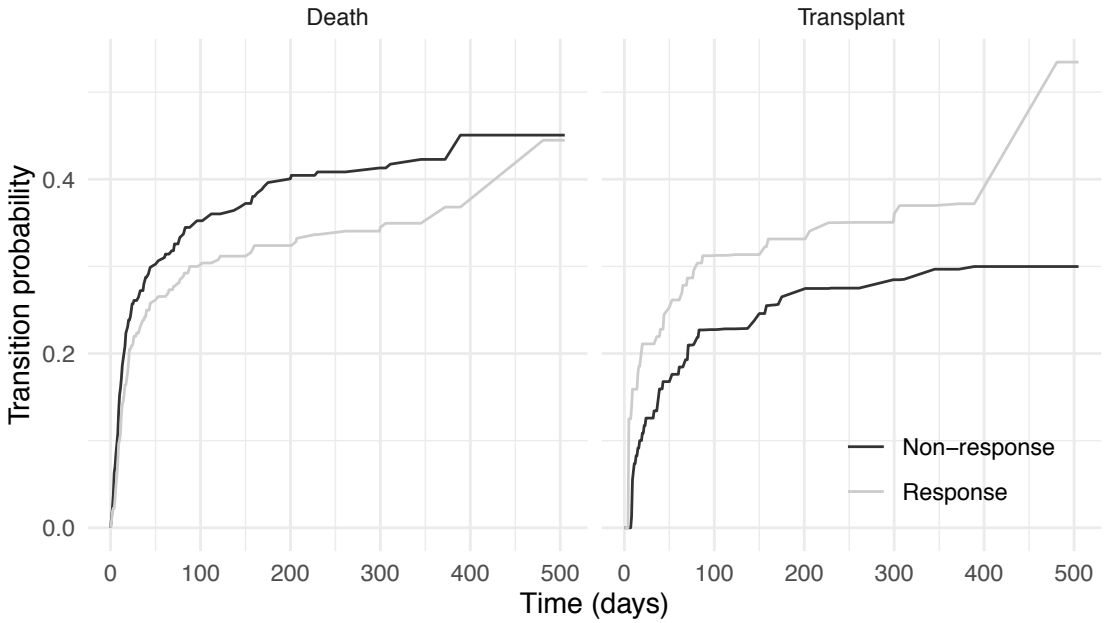

Figure 3.7: Aalen-Johansen estimations of transition probabilities to death and transplant, from responding and non-responding to treatment.

Table 3.9: Multi-state Cox models for transition probabilities from non-responding and responding states respectively to death.

	Non-responding to death			Responding to death		
	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%
Age (yr)	1.04	1.00	1.07	0.96	0.90	1.03
Female sex	1.38	0.74	2.57	0.41	0.14	1.23
Treatment with albumin	2.72	0.92	8.06	0.71	0.17	2.93
Treatment with vasopressors	2.20	1.15	4.21	2.05	0.69	6.12
Etiology of cirrhosis - Alcohol	2.96	1.18	7.47	4.51	0.77	26.38
Etiology of cirrhosis - Hepatitis B virus	0.70	0.17	2.91	3.34	0.24	46.70
Etiology of cirrhosis - Hepatitis C virus	2.60	0.97	6.96	5.38	1.27	22.73
Etiology of cirrhosis - NAFLD/NASH	2.86	1.14	7.18	3.66	0.69	19.51
Etiology of cirrhosis - Cryptogenic	9.86	2.56	38.03	10.27	1.08	97.33
Etiology of cirrhosis - Other	3.04	0.79	11.63	0.00	0.00	Inf
MAP (mmHg)	0.99	0.96	1.02	1.01	0.96	1.07
Heart rate (bpm)	1.01	1.00	1.03	0.99	0.95	1.03
Hemoglobin (g/dL)	1.04	0.90	1.20	0.71	0.48	1.03
Leucocyte ($\times 10^9$/L)	1.01	0.97	1.06	0.92	0.81	1.05
INR	1.17	1.00	1.38	2.76	1.57	4.86
Albumin (g/dL)	0.64	0.42	0.98	1.19	0.49	2.87
Total Bilirubin (mg/dL)	1.07	1.03	1.10	1.00	0.95	1.06
Creatinine (mg/dL)	1.12	0.88	1.43	29.03	2.67	315.30
Sodium (mEq/L)	1.01	0.97	1.06	0.98	0.90	1.07
Ascites	2.99	1.12	7.99	1.52	0.37	6.26
Hepatic encephalopathy	0.94	0.50	1.79	4.83	1.46	15.95
Gastrointestinal bleeding	1.05	0.47	2.37	0.34	0.04	2.90
Bacterial infection	0.94	0.49	1.80	0.75	0.30	1.86

Table 3.10: Multi-state Cox models for transition probabilities from non-responding and responding states respectively to transplant

	Non-responding to transplant			Responding to transplant		
	exp(coef)	2.5%	97.5%	exp(coef)	2.5%	97.5%
Age (yr)	1.04	1.01	1.07	1.11	1.04	1.18
Female sex	0.87	0.48	1.58	0.80	0.29	2.23
Treatment with albumin	0.54	0.29	1.01	0.17	0.06	0.52
Treatment with vasopressors	1.29	0.73	2.29	4.98	1.72	14.40
Etiology of cirrhosis - Alcohol	1.04	0.35	3.08	0.48	0.06	3.75
Etiology of cirrhosis - Hepatitis B virus	0.50	0.13	1.97	0.00	0.00	Inf
Etiology of cirrhosis - Hepatitis C virus	0.85	0.33	2.24	0.11	0.01	1.11
Etiology of cirrhosis - NAFLD/NASH	0.40	0.13	1.29	0.28	0.05	1.48
Etiology of cirrhosis - Cryptogenic	0.89	0.19	4.09	0.38	0.03	4.61
Etiology of cirrhosis - Other	0.64	0.15	2.73	1.14	0.12	10.62
MAP (mmHg)	0.98	0.96	1.00	0.93	0.89	0.97
Heart rate (bpm)	1.01	1.00	1.03	1.07	1.03	1.12
Hemoglobin (g/dL)	1.00	0.87	1.16	0.91	0.61	1.34
Leucocyte ($\times 10^9$/L)	1.02	0.98	1.07	1.03	0.95	1.11
INR	1.01	0.82	1.24	1.42	0.76	2.65
Albumin (g/dL)	0.87	0.59	1.29	0.95	0.43	2.09
Total Bilirubin (mg/dL)	1.05	1.03	1.08	1.05	1.00	1.10
Creatinine (mg/dL)	1.06	0.85	1.33	1.14	0.14	9.00
Sodium (mEq/L)	0.97	0.94	1.01	1.01	0.93	1.09
Ascites	1.60	0.73	3.48	2.19	0.63	7.67
Hepatic encephalopathy	1.32	0.73	2.37	1.83	0.51	6.54
Gastrointestinal bleeding	0.94	0.43	2.07	1.93	0.41	9.18
Bacterial infection	1.63	0.91	2.94	0.71	0.24	2.15

Table 3.11: Multi-state Cox models for transition probabilities from non-responding state to responding one.

	Non-responding to responding		
	exp(coef)	2.5%	97.5%
Age (yr)	0.98	0.96	1.00
Female sex	1.43	0.90	2.27
Treatment with albumin	0.98	0.57	1.66
Treatment with vasopressors	0.60	0.37	0.98
Etiology of cirrhosis - Alcohol	1.71	0.82	3.59
Etiology of cirrhosis - Hepatitis B virus	0.64	0.08	4.96
Etiology of cirrhosis - Hepatitis C virus	1.12	0.52	2.41
Etiology of cirrhosis - NAFLD/NASH	1.21	0.60	2.43
Etiology of cirrhosis - Cryptogenic	1.82	0.64	5.21
Etiology of cirrhosis - Other	1.53	0.59	3.99
MAP (mmHg)	1.00	0.98	1.02
Heart rate (bpm)	1.00	0.98	1.01
Hemoglobin (g/dL)	1.04	0.93	1.17
Leucocyte ($\times 10^9$/L)	0.98	0.94	1.02
INR	1.11	0.95	1.30
Albumin (g/dL)	1.06	0.79	1.43
Total Bilirubin (mg/dL)	1.00	0.97	1.02
Creatinine (mg/dL)	0.74	0.56	0.97
Sodium (mEq/L)	0.98	0.95	1.01
Ascites	1.17	0.64	2.15
Hepatic encephalopathy	1.06	0.67	1.67
Gastrointestinal bleeding	1.69	0.92	3.10
Bacterial infection	1.42	0.90	2.22

Chapter 4

Conclusions and discussion

The main objective of this project was to assess the 28-day and 90-day mortality of HRS patients that are being treated with albumin, vasopressors or both of them and check whether their response to those treatments is determinant for their survival. This has been done by using four types of models.

The first model seen (3.2.1) consisted of using competing risks models on data from the time of diagnostic. In this model the survival and prognostic factors have been studied but the response to treatment could not be included in the model, since this variable could not be assessed at basal level and, although stratifying these models by time-dependent variables is not an uncommon practice, this can actually lead to bias. In these case two sub-models have been introduced: the cause-specific model and the subdistribution one.

The second model (3.2.2) consisted of including time-dependent covariates in the competing risk methods already seen. An advantage of these models is the possibility to include dynamic variables such as the response to treatment. However, some assumptions of the classic competing risks models do not hold and therefore they have to be interpreted with caution.

The third type of model (3.2.3) that was introduced was the landmark model and super-model. In this case, these models have been estimated by using super data frames, splitting our data in equally spaced time intervals and either stratifying by a variable identifying those landmarks, which would lead to different baseline hazards for each landmark, or introducing these variable as a covariate in the model, leading to a unique baseline hazard and an estimation of the effect of the landmark covariate. Here, again the response to treatment could be included and the model assumptions hold. However, these models are not so intuitive to understand and interpret.

The last model that has been seen (3.2.4) is the multi-state model. In this case, the response to treatment could also be included. However, this has been done by introducing it not as a covariate but as a state in the model. So, contrary to the competing risks models seen previously where the subjects could only go from the alive state to either death or receiving a transplant, here they are modeled to be transiting four possible states. All the subjects start from the same state: not responding to treatment and from there they can potentially go to any of the three other states: response to treatment, receiving a transplant, or dying. If they go to the response to treatment state, they still can go to any of the three other states. However, the other two states (death and transplant are considered to be absorbing states, meaning that once they enter there they cannot transient to any other state. This model allows not only to include the response to treatment variable, which we are interested in but also to model it as one of the endpoints of the model. Therefore, not only the variables associated to dying or receiving a transplant can be identified but also the ones to responding to treatment.

Although the models seen have some differences and the interpretation of the results obtained with each of them may differ, they do not seem to show important discrepancies. Table 4.1 shows the estimated hazard ratios by each of the models regarding death. Some of the variables that appeared significant the most is the levels of bilirubin, where the highest the greater the hazard functions' estimations. Also, the etiology of cirrhosis has appeared in most models, especially the cryptogenic has pretty high estimates in most models. However, these results have to be read with caution since, as it has been seen in the descriptive analysis of the data

(3.1), the frequency of this category is not specially large. Another variable that looks to be associated with higher hazards in most models is the INR. Finally, the treatment (mostly the albumin one) has also appeared significant in most models. In contrast, the estimated hazard ratios for the albumin levels were generally $<$ 1, meaning that the higher the levels of albumin, the less the risk. This contradiction may be due to the fact that the indicator of the treatment may actually be capturing the fact that those subjects receiving it could be those who were already worse. This should be further explored.

In this same line, it has to be mentioned that all the models have been fitted with the same covariates. The number of covariates might be a little too large in proportion with the number of observations and this should be taken into account. This has been done in order to not favour any of the models but in case we decided to further explore any of them we should choose which are the most relevant variables for the model and just keep those. This way we could also include interactions and, for exemple, further explore the relationship of the treatment variables with the others.

Future work

As just mentioned, the first step to continue with this project would be to adjust the variables included in the chosen model(s).

Although some very interesting models have been introduced through this project, there are more options to fit this type of data. For instance, two of the models introduced: landmarking and multi-state models could be used in the same analysis by building a landmarking multi-state super-model. Another option could be using joint modeling of longitudinal and survival data instead of focusing on survival analysis. Or, inside survival analysis, the dataset could be considered to be interval-censored instead of right-censored and therefore a whole different set of techniques should be applied. Another option would be using frailty models, which can also be used to model recurrent events because they quantify the correlation within individuals and allow easy predictions by updating the frailty distribution given the history of a patient.

In a different line, after improving the models built and assessing the survival of the patients and the associated risk factors, the next step would be to identify whether urinary biomarkers of tubular damage are able to predict response to treatment in patients with hepatorenal syndrome acute kidney injury. This way, we would want to establish the ability of investigated biomarkers (urinary NGAL and quinolinic acid) in predicting the reversal of HRS after treatment with vasopressorts and albumin and to evaluate the ability of these biomarkers in predicting hospital mortality, 28-day mortality and 90-day mortality in patients of HRS.

Table 4.1: Hazard ratios for all the variables in all the models fitted considering death as the endpoint. Statistically significant (at a 0.05 level) terms in bold.

	Basal variables		Time-dependent variables		Landmark models		Multi-state models	
	Sub-distribution	Cause-specific	Sub-distribution	Cause-specific	Super-model 1	Super-model 2	From non-responding	From responding
Age (yr)	1	**1.04**	1.01	1.02	0.99	1	**1.04**	0.96
Albumin (g/dL)	**0.73**	**0.69**	0.9	0.76	1.25	1.25	**0.64**	1.19
Ascites	1.51	1.71	1.58	**2.09**	1.29	1.3	**2.99**	1.52
Total Bilirubin (mg/dL)	1.03	**1.05**	1.02	**1.05**	**1.06**	**1.06**	**1.07**	1
Bacterial infection	0.88	1.09	0.65	0.74	1.44	1.49	0.94	0.75
Creatinine (mg/dL)	1.05	1.13	1.18	1.18	0.76	0.74	1.12	**29.03**
Etiology of cirrhosis - Alcohol	1.41	1.15	2.06	**2.13**	2.66	2.41	**2.96**	4.51
Etiology of cirrhosis - Cryptogenic	**3.14**	2.74	**4.79**	**5.96**	4.27	4.03	**9.86**	**10.27**
Etiology of cirrhosis - Hepatitis B virus	1.65	1.1	1.78	0.96	**5.21**	4.65	0.7	3.34
Etiology of cirrhosis - Hepatitis C virus	1.79	1.9	2.16	**2.37**	3.1	3.09	2.6	**5.38**
Etiology of cirrhosis - NAFLD/NASH	**2.06**	1.36	**2.62**	**2.14**	3.08	2.82	**2.86**	3.66
Etiology of cirrhosis - Other	1.57	1.19	2.05	1.89	1.33	1.19	3.04	0
Gastrointestinal bleeding	1.53	1.43	0.87	1.07	0.71	0.72	1.05	0.34
Hepatic encephalopathy	1.2	1.54	1.14	1.41	2.16	2.12	0.94	**4.83**
Hemoglobin (g/dL)	1.06	1.08	0.97	1.02	0.85	0.85	1.04	0.71
Heart rate (bpm)	1	1	1	1.01	1.01	1.01	1.01	0.99
INR	1.03	1.15	**1.23**	**1.24**	**1.41**	**1.38**	1.17	**2.76**
MAP (mmHg)	1	0.99	1.01	1	0.98	0.98	0.99	1.01
Sodium (mEq/L)	1.01	1.02	1.02	1.01	1	1.01	1.01	0.98
Response to treatment (creat < 1.5 mg/dL)			1.06	0.57	0.46	0.51		
Female sex	1.05	0.94	1.11	1.03	0.5	0.48	1.38	0.41
Treatment with albumin	**3.86**	**4.53**	**2.13**	2	**6.97**	**6.91**	2.72	0.71
Treatment with vasopressors	0.93	0.87	1.49	**1.69**	0.65	0.68	**2.2**	2.05
Leucocyte ($\times 10^9$/L)	0.98	0.99	0.98	0.99	0.95	0.95	1.01	0.92

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